Drug Development & Delivery

May 2024 Vol 24 No 4 www.drug-dev.com

Next-Generation Injections

The Science & Business of Pharmaceutical and Biological Drug Development

John Merhige
Collaboration Between a Device Supplier & Equipment Manufacturer to Meet the Needs of Patients, End-Users & Pharma Manufacturers

Nila Murali
Integration of siRNA, Nanoparticles & Capsule Endoscopy for Treatment of Inflammatory Bowel Disease

Cindy H. Dubin
Prefilled Syringes & Parenteral Delivery: Next-Gen Injections Feature Technology & Reconstitution

IN THIS ISSUE

INTERVIEW WITH

ADARE PHARMA SOLUTIONS'

CEO

TOM SELLIG

ASCENDIA PHARMA

Start your project within weeks; not months.

From pre-formulation to Phase III and commercial supply, Ascendia is the CDMO Partner of Choice for your most challenging projects.

Ascendia Pharma's combination of proprietary nanotechnologies and their BEST culture philosophy makes us a Partner of Choice for people with projects from complex formulations to commercial supply needs.

Technical Services from Ascendia:

- Rapid Early-stage Development Services
- Poorly Soluble & Low Bioavailability Drug Formulations
- LNP's for Vaccines, mRNA & Gene Therapy.
- cGMP Sterile & Non-sterile Clinical Trial Materials
- Sophisticated Formulations (Biologics & Small Molecules)
- 505(b)(2) Product Development

Contact Ascendia to find out how we can ***Make the Impossible Possible*** for you!

ASCENDIA PHARMA

732-658-4267

bd@ascendiapharma.com

www.ascendiapharma.com

UniSafe® Platform

Delivering the future with safety and simplicity

Developed around UniSafe®, our platform meets the needs of you, our partner, and your varying patients' needs both now and in the future.

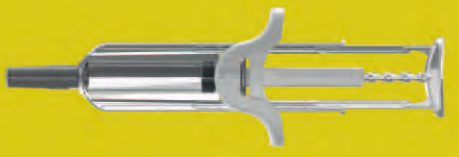
UniSafe® 1mL

A spring-free, passive safety device for 1mL pre-filled syringes, designed for simple assembly and use.

Proven, on market, in patient use

UniSafe® 2.25mL

A spring-free, passive safety device for 2.25mL pre-filled syringes, designed for simple assembly and use.



Fully industrialised and ready to supply

UniSafe® 1mL
Auto-injector

A reusable companion auto-injector for UniSafe® 1mL.

Coming soon

UniSafe® 1mL
Connected Auto-injector

A reusable connected companion auto-injector for UniSafe® 1mL.

Coming soon

Want to know more?

Visit **ompharmaservices.com/ddd-may2024** or email **pharmaservices@owenmumford.com**

OWEN MUMFORD
Pharmaceutical Services

Drug Development & Delivery

May 2024 Vol 24 No 4

Corporate/Editorial Office
170 Changebridge Road, Suite C5-4, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drug-dev.com


CREDENCE
MEDSYSTEMS
SLEEK
Preferred by users
Reduces wasted materials
Clean and classic award-winning design
SMART
Prevents premature activation
Enables dual sourcing & barrel flexibility
Integrated safety streamlines operations
SAFE
Biotech-friendly: Glue/Steel/Tungsten-FREE options
Automatic needle retraction
End-of-dose cues
THE CREDENCE
COMPANION
Innovation Without Change Has Arrived
Credence MedSystems, Inc. - +1-844-263-3797 - www.CredenceMed.com
This product has not yet been evaluated by FDA

Next-Generation Injections

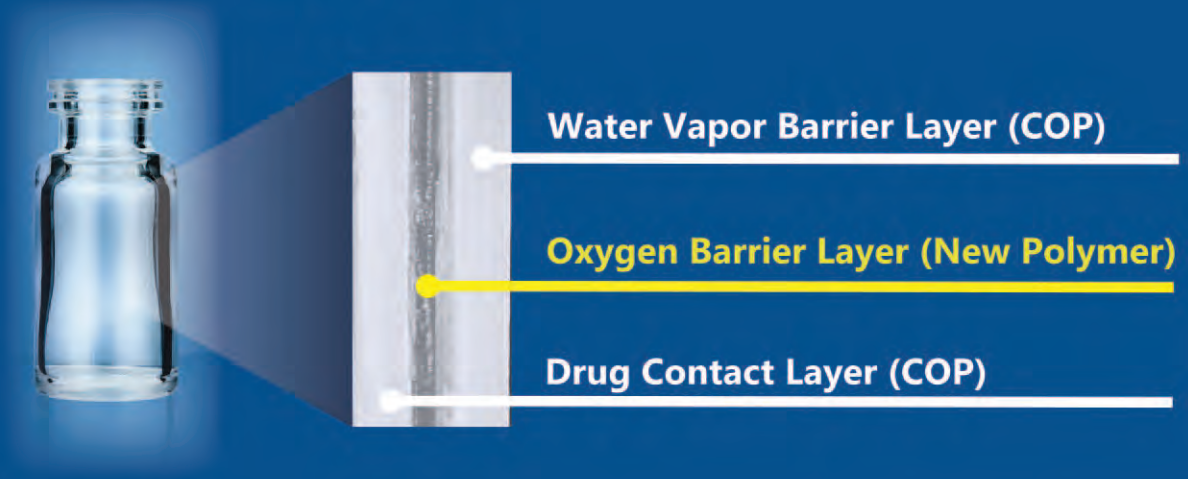
"With the market for parenteral combination products evolving over the last couple of decades, connecting devices have become almost critical. Wearable technology has become valuable for managing patient conditions, ensuring compliance, and gathering real-time data. Now, the global connected drug delivery device market is predicted to grow 23.4% and reach $25.6 billion by 2030."

p.38

Table of Contents

OXYCAPT™ Multilayer Plastic Vial

Multilayer Structure



- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Gamma-sterilized Vial
- For Biologics & Gene/Cell Therapy
- Customizable

2, 6, 10, 20mL Vial

Nest & Tub for Vial

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical Company, Inc.
https://www.mgc.co.jp/eng/products/abd/oxycapt.html
Mitsubishi Gas Chemical America, Inc.
http://www.mgc-a.com
Mitsubishi Gas Chemical Europe GmbH
https://www.mgc-europe.de

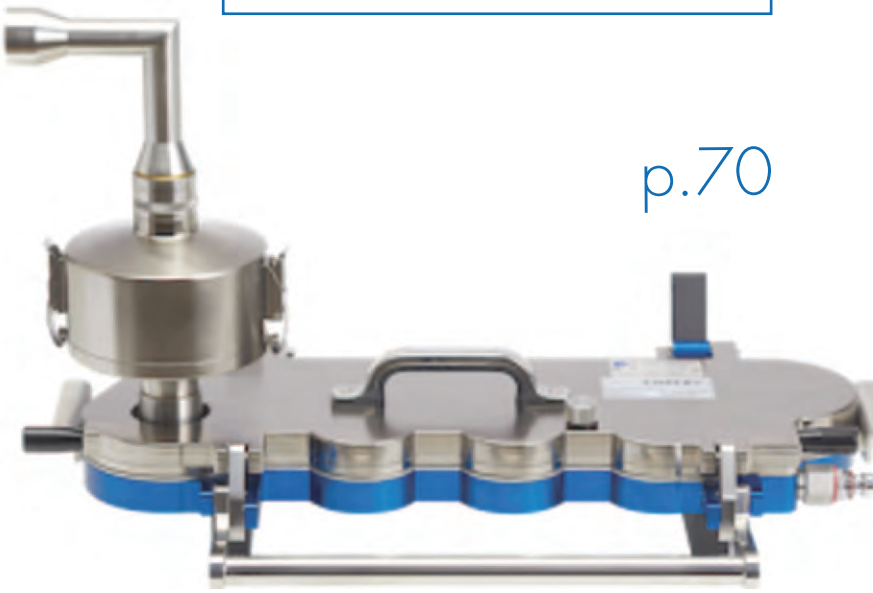
Table of Contents

Inhaled Therapeutics

"The global increase in respiratory diseases, as well as the potential to deliver drugs systemically, has led to increased interest and a shifting landscape within inhaled drug delivery. An alternative to pressurised metered dose inhalers (pMDIs), dry powder inhaler (DPI) formulations have the potential to meet the evolving market trends and deliver the next generation of inhaled therapeutics."

Departments

p.70



Nemera
we put patients first

Safe'n'Sound®

Robust and ergonomic passive safety system designed for user safety.

To know more about our global Parenteral offering

Abzena Launches Next-Generation Immunogenicity Tool for De-Risking the Development of Complex Biologics & Bioconjugates

Abzena recently announced the launch of its enhanced bioassay platform EpiScreen® 2.0, a comprehensive suite of assays that predict and evaluate potential risks of preclinical immunogenicity in protein, antibody, and gene therapy therapeutics. The next- generation tool provides a better immunogenic assessment that is highly sensitive, multi-parametric, and data-rich, which ultimately improves candidate selection and de-risks early phase development.

Abzena launched its first generation EpiScreen platform over 20 years ago and are considered to be innovators in the field of immunogenicity. The newly enhanced EpiScreen 2.0 builds upon the original platform by delivering a more advanced set of immune response measurements with the required sensitivity, plus detailed information on specificity and mechanism-of-action (MoA) to better inform the nature of immunogenicity risk and how to mitigate this through protein engineering and formulation.

Using flow cytometry, EpiScreen 2.0's Time Course Assay delivers levels of sensitivity comparable to traditional assays using [3H]-thymidine as a readout for proliferation and allows characterization of the responding immune cells by multiplexing the readout with cell activation markers. Beyond the standard assessment of CD4+ T cells, the platform can evaluate the responses of other immune cells, including CD8+ T-cells, giving insight into the MoA, which can be useful for gene therapy, where evaluation of the endogenous antigen processing pathway is more relevant.

These data-rich assays can support an array of drug types including biologics, bioconjugates, and gene therapies, and can be delivered as a platform method or customized to each program to provide the necessary information needed to select the best candidate for clinical evaluation.

Dr. Campbell Bunce, CSO of Abzena, said "Understanding a lead drug candidate's immunogenicity risk profile and how we can mitigate it is a key step in advancing new drugs from discovery to clinical trials. We developed EpiScreen 2.0 because we understand that there are many factors that contribute to the immunogenicity risk of a drug, especially with the next-generation therapeutics being developed like Antibody-drug conjugates (ADCs). I'm not aware of any other service provider that offers such an extensive set of immunogenicity assessment capabilities covering bioinformatics, proteomics, and ex vivo human immune cell assays underpinned by a high-throughput, high-quality infrastructure for blood processing and storage. Our EpiScreen 2.0 platform allows drug developers to be better informed and more confident in progressing to later stage development with a better chance of success in patients."

Abzena is the leading end-to-end bioconjugate and complex biologics CDMO + CRO. From discovery through commercial launch, we support customers with fully integrated programs or individual services designed to de-risk and streamline the development of new treatments for patients in need. With the ability to tailor its strategy and customer experience to each project, Abzena develops and implements innovative solutions that enable biotech and biopharma companies to realize the full potential of their molecule and move medicines forward faster.

Biolojic Design Announces Nektar Therapeutics Has Exercised its License Option to Develop an AI-Designed Agonistic Antibody Targeting TNFR2 for the Treatment of Autoimmune Diseases

Biolojic Design recently announced Nektar Therapeutics exercised its license option to develop a program resulting from the companies' research collaboration initiated in 2021. The research collaboration was established to design and test agonistic antibodies targeting tumor necrosis factor receptor type II (TNFR2), a novel, biologically validated disease target implicated in a wide range of autoimmune diseases that has been difficult to drug with conventional medicines.

The antibody program selected for development (now known as NKTR-0165) is designed to modulate the TNFR2 pathway in order to agonize – or activate – T regulatory cells and other anti-inflammatory cell populations, making this a promising approach to stimulating the immune system in ulcerative colitis, multiple sclerosis, vitiligo, and other autoimmune disease states. Under the 2021 research agreement, Nektar has tested antibodies computationally designed by Biolojic Design to precisely agonize the TNFR2 receptor.

Following successful preclinical in vitro and in vivo studies, Nektar decided to exercise the license option and has been advancing the program through IND enabling studies since late December, 2023. If the NKTR-0165 candidate proceeds through clinical development, Biolojic Design is entitled to development milestones and sales royalties.

Yanay Ofran, PhD, CEO, and founder of Biolojic Design, said "The unique agonist antibodies directed at TNFR2 are yet another demonstration of the power of Biolojic's AI platform for antibody design. Not only are these antibodies able to functionally activate TNFR2, they do so in a highly unique fashion. We look forward to seeing Nektar advance this promising molecule through clinical development for the potential benefit of the many patients who suffer from autoimmune disease."

Jonathan Zalevsky, Chief Research and Development Officer of Nektar, added "We're excited to be advancing NKTR-0165 through IND-enabling studies in 2024, with the goal of filing an IND in the first half of 2025."

Biolojic Design transforms antibodies into intelligent medicinal solutions through AI and computational design. Biolojic's platform generated the first AI-designed antibody to enter the clinic, which is now in Phase 2 clinical trials. Biolojic's platform turns human antibodies into programmable switches with a specific function: agonism, antagonism, and conditional binding. The platform can generate multi-specific antibodies that act as logic gates executing "and" or "xor" function. Biolojic's pipeline focuses on autoimmune and immuno-oncology, unlocking validated pathways that address large unmet needs. For more information, visit https://biolojic.com/.

Cellares & Bristol Myers Squibb Announce $380-M Worldwide Capacity Reservation & Supply Agreement

Cellares & Bristol Myers Squibb recently announced a worldwide capacity reservation and supply agreement for the manufacture of CAR T cell therapies in a transaction valued up to $380 M in upfront and milestone payments. As part of the agreement, Cellares will optimize, automate, and tech-transfer select Bristol Myers Squibb CAR T cell therapies onto its automated and high-throughput manufacturing platform, the Cell Shuttle. Cellares will dedicate multiple Cell Shuttle and Cell Q systems with fully automated, high-throughput quality control for Bristol Myers Squibb's exclusive use. The Cell Shuttles and Cell Qs will be deployed in Cellares' Smart Factories in the US, EU, and Japan.

Manufacturing cell therapies is both operationally and technically complex. Because cell therapies are rapidly transforming the way many different diseases are treated, the demand for these treatments is increasing significantly. This collaboration enables Bristol Myers Squibb to expand its manufacturing capacity, meeting the growing demand for its diverse range of cell therapies through a platform that is scalable and has the potential to improve turnaround time, bringing the promise of cell therapies to more patients faster.

"The agreement with Cellares is our latest step forward in support of our comprehensive strategy to unlock the full potential of CAR T therapy to deliver transformative treatments to as many patients as possible, as quickly as possible," said Lynelle B. Hoch, President, Cell Therapy Organization, Bristol Myers Squibb. "Our collaboration with Cellares strengthens our existing internal manufacturing capabilities for CAR T cell therapies by giving us access to the first end-to-end fully automated cell therapy manufacturing platform, to help ensure we meet the high demand for these differentiated treatments, now and in the future."

This agreement expands upon the existing collaborations between Bristol Myers Squibb and Cellares. In August 2023, Bristol Myers Squibb participated in Cellares' Series C financing to launch the first IDMO Smart Factory in an effort to meet the demand for cell therapies globally. That same month, Bristol Myers Squibb joined Cellares' Technology Adoption Partnership (TAP) Program to evaluate the Cell Shuttle's automated manufacturing capabilities.

"This agreement with Bristol Myers Squibb is aligned with our strategy of establishing a global network of high-throughput, automated Smart Factories to meet the growing and worldwide demand for cell therapies," said Fabian Gerlinghaus, CEO and co-founder of Cellares. "We look forward to demonstrating how our innovative technology's emphasis on standardization will accelerate commercial-scale manufacturing and worldwide deployment. Our collaboration with Bristol Myers Squibb and our collective expertise furthers our mission to accelerate access to life-saving cell therapies for patients globally."

Cellares is the first Integrated Development and Manufacturing Organization (IDMO) and takes an Industry 4.0 approach to mass manufacturing the living drugs of the 21st century. The company is both developing and operating integrated technologies for cell therapy manufacturing to accelerate access to life-saving cell therapies. The company's Cell Shuttle integrates all the technologies required for the entire manufacturing process in a flexible and high-throughput platform that delivers true walk-away, end-to-end automation. Cell Shuttles will be deployed in Cellares' Smart Factories around the world to meet total patient demand for cell therapies at global scale. Partnering with Cellares enables academics, biotechs, and pharma companies to accelerate drug development and scale out manufacturing, lower process failure rates, lower manufacturing costs, and meet global patient demand.

Neurolentech Signs Technology Access Partnership With Kaerus Bioscience

Neurolentech recently announced a technology access partnership with Kaerus Bioscience, a biotechnology company committed to turning scientific advances into treatment realities for patients with rare genetic syndromes of neurodevelopment. The agreement enables Kaerus Bioscience to access Neurolentech's NDD Drug Discovery platform and leverage its proprietary cell models and assays for functional screens to drive advances in neurodevelopmental disorders research.

Built for NDD drug discovery, Neurolentech's Platform comprises a vast collection of human-derived neuronal cell lines from patients with monogenic and complex neurodevelopmental disorders. The Platform will enable Kaerus Bioscience to model the complex neural networks underlying clinical features of genetic NDDs at a cellular level, as well as to investigate the therapeutic potential of its small molecule pipeline for numerous genetic syndromes preclinically.

The partnership marks a significant milestone in Neurolentech's mission to advance drug discovery for NDDs, and further reinforces its NDD Drug Discovery platform as a valuable resource for both researchers and industry partners.

Fiona Nielsen, CEO of Neurolentech, said "We are excited to collaborate with Kaerus Bioscience in advancing their programs in the field of neurodevelopmental disorders. Our platform's unique capabilities offer unparalleled insights into disease mechanisms, facilitating the development of novel therapies."

Robert Ring, CEO of Kaerus Bioscience, added "Our partnership with Neurolentech underscores Kaerus' commitment to leveraging cutting-edge technology and innovative platform approaches to accelerating the discovery of treatments for patients with genetic disorders of neurodevelopment."

Neurolentech is a biotech startup doing drug discovery for epilepsy and related genetic neurodevelopmental disorders (NDDs). The Neurolentech drug discovery platform is built on a library of human-derived iPSCs and hIPSC-derived neuronal cell models from patients across the epilepsy and NDD spectrum. Neurolentech has developed unique proprietary assays for interrogating the molecular aspects and cellular functional mechanisms of disease. With the combination of patient-derived models and assays optimized for interrogating NDD related mechanisms, Neurolentech can discover novel targets for drug discovery and screen effectiveness of potential novel therapeutics across their unique library of patient-derived models. For more information, visit http://neurolentech.com.

Kaerus Bioscience Ltd is a biotechnology company committed to turning scientific advances into treatment realities for patients with rare genetic syndromes of neurodevelopment. Kaerus has developed a pipeline of targeted, small-molecule therapeutics that address an underlying ion channel dysfunction in Fragile X syndrome, the most common inherited cause of intellectual disability and autism globally. For more information, visit www.kaerusbio.com.

Kincell Bio & Imugene Announce Strategic Manufacturing & Process Development Partnership

Kincell Bio, LLC and Imugene, Ltd. recently announced a strategic manufacturing and process development partnership, which includes the sale of Imugene's North Carolina Current Good Manufacturing Practice (CGMP) manufacturing facility and the transfer of process and analytical development activities to Kincell.

Under the terms of an asset purchase agreement between Imugene and Kincell, Kincell will acquire Imugene's CGMP-compliant cell therapy manufacturing facility in North Carolina for a total consideration of up to $6M USD in upfront and milestone-driven payments. Both parties have entered into a manufacturing supply agreement whereby Kincell will manufacture Imugene's Azer-cel to support ongoing clinical trials. Imugene will also transfer process and analytical development of Azer-cel to Kincell to support process and method optimization for commercial readiness.

Leslie Chong, Managing Director and Chief Executive Officer of Imugene, said "We are delighted to have found a strong partner for the development and manufacturing of our CAR T Azer-cel program. We are confident that this strategic partnership with Kincell will enable Imugene to reach key upcoming data inflection points and extend the company's cash runway to 2026. Moreover, this partnership allows us to focus on our key capabilities, namely the development of novel cancer treatments. With the transaction, we look forward to continuing to work with many of our former manufacturing colleagues in a new relationship as our contract development and manufacturing organization partner."

Bruce Thompson, CEO of Kincell, added "The acquisition of this facility and experienced team, which is actively manufacturing CGMP-compliant products that can support late-stage and/or pivotal clinical trials, accelerates our ability to expand our service offerings for cell therapy developers. The facility's location in Research Triangle Park (RTP) will facilitate access to talent in a fast-growing and attractive biotech hub. Additionally, we're excited that the manufacturing supply agreement enables us to partner with Imugene, an innovative immunotherapy company, to optimize and progress an allogeneic CAR T product candidate into later-stage development for patients with significant unmet medical needs."

The 32,800-sq-ft, state-of-the-art, CGMP-compliant facility is designed with the flexibility to expand in capacity and scope to support the manufacture of cell-based therapies. Kincell intends to evolve the site capabilities while leveraging enterprise-wide expertise to manufacture a broad portfolio of autologous and allogeneic products.

Imugene is a clinical-stage immuno-oncology company developing a range of new and novel immunotherapies that seek to activate the immune system of cancer patients to treat and eradicate tumors. Our unique platform technologies seek to harness the body's immune system against tumors, potentially achieving a similar or greater effect than synthetically manufactured monoclonal antibody and other immunotherapies. Our pipeline includes an off-the-shelf (allogeneic) cell therapy CAR T drug azer-cel (azercabtagene zapreleucel), which targets CD19 to treat blood cancers. Our pipeline also includes multiple immunotherapy B-cell vaccine candidates and an oncolytic virotherapy (CF33) aimed at treating a variety of cancers in combination with standard of care drugs and emerging immunotherapies such as CAR T's for solid tumours.

Kincell Bio engineers cells into therapies. Headquartered in Gainesville, FL, Kincell is a technology-forward contract development and manufacturing organization (CDMO) formed to streamline analytical development, process development, CMC consulting and early-stage GMP cell therapy manufacturing. Kincell's initial focus is on manufacturing commercially viable immune cell therapies, including autologous and allogeneic CAR-T, CAR-NK and CAR-M programs.

Evaxion Announces Phase 2 Clinical Trial Update: First Patient Completed Dosing With Personalized Cancer Vaccine

Evaxion Biotech A/S recently announced the first patient in its EVX-01 Phase 2 trial in metastatic melanoma received the last vaccine dose in combination with KEYTRUDA (NCT05309421).

The company initiated its Phase 2 clinical study in September 2022 to assess the efficacy, safety, and ability to induce a tumor-specific immune response of the EVX-01 cancer vaccine in metastatic melanoma patients. The EVX-01 vaccine was designed using Evaxion's proprietary AI-Immunology platform and is an individualized therapy matching the unique tumor profile and characteristics of the patient's immune system. Each patient enrolled in the trial receives a unique vaccine designed and manufactured based on their individual biology. Patients are administered 10 EVX-01 doses over a period of 78 weeks in combination with the anti-PD-1 therapy, KEYTRUDA (pembrolizumab).

Birgitte Rønø, CSO of Evaxion, said "With the progress made in the Phase 2 study, we are one step closer to fulfilling our mission of saving and improving lives with AI-Immunology. We eagerly anticipate sharing the 1-year clinical readout in Q3 this year and look forward to being one step closer to market with a novel personalized cancer vaccine."

Professor Adnan Khattak at One Clinical Research, Hollywood Private Hospital, Western Australia, expressed enthusiasm, stating "We are now entering into the era of personalized cancer therapies, where we adopt a tailored approach against an individual patient's tumor. In other words, we are treating each patient with the right drug. As a physician, I firmly believe this is the future."

At the end of 2023, Evaxion reported initial EVX-01 Phase 2 data confirming the favorable safety profile and promising immunological data as observed in the previously successful Phase 1 clinical trial.

EVX-01 is Evaxion's lead clinical asset and constitutes a peptide-based personalized cancer vaccine. The Phase 2 clinical study is a self-sponsored open-label, single-arm, multi-center trial carried out in collaboration with Merck Sharp & Dohme LLC that, together with leading principal investigators and research centers from Italy and Australia, aims to evaluate the efficacy and safety of EVX-01 vaccination in combination with anti-PD1 therapy KEYTRUDA (pembrolizumab) in treatment-naive patients with metastatic or unresectable malignant stage III or IV melanoma. More information can be accessed under clinical trial ID NCT05309421.

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.

Palisade Bio Enters Strategic Collaboration With Strand Life Sciences to Advance Precision Medicine Approach

Palisade Bio, Inc. recently announced it has entered into a transformative strategic collaboration with Strand Life Sciences, a leading bioinformatics specialist, aimed at advancing precision medicine for ulcerative colitis (UC) therapy.

The collaboration with Strand Life Sciences provides Palisade Bio access to advanced bioinformatics tools vital for understanding complex disease pathways and predicting responses to PDE4 inhibitors. Leveraging data from over ten UC clinical studies, Palisade has curated a pipeline of 1600 UC patient samples, including transcriptomics and clinical outcomes. This curated dataset, analyzed using in-house tools, enables Palisade to identify biomarkers for selecting UC patient responders, utilizing machine learning to develop a precision medicine approach to patient selection.

"Our partnership with Strand Life Sciences signifies a pivotal advancement in our mission to revolutionize UC treatment," said Dr. Mitch Jones, CMO at Palisade Bio. "By harnessing the power of bioinformatics and leveraging extensive patient datasets, we are highly optimistic in our ability to deliver personalized therapies that offer new hope to patients living with UC. More immediately, the findings from this collaboration will provide valuable guidance and insight for our lead program, PALI-2108."

"We are thrilled to collaborate with Palisade Bio in this transformative endeavor toward advancing precision medicine for ulcerative colitis therapy," added Ramesh Hariharan, CEO at Strand Life Sciences. "Our expertise in bioinformatics, machine learning/AI and knowledge curation towards biomarker stratification, combined with Palisade's extensive patient datasets, holds immense promise in identifying predictive biomarkers and ultimately improving outcomes for UC patients."

Palisade Bio is committed to advancing precision medicine solutions for UC and other inflammatory indications. The Company is advancing its collaborative efforts with Strand Life Sciences and other partners to continue driving innovation and transforming the landscape of UC treatment.

Palisade Bio is a biopharmaceutical company focused on developing and advancing novel therapeutics for patients living with autoimmune, inflammatory, and fibrotic diseases. The company believes that by using a targeted approach with its novel therapeutics it will transform the treatment landscape. For more information, visit www.palisadebio.com.

Strand Life Sciences is a multiomics research and diagnostics company that combines a long track record in bioinformatics with cutting-edge, laboratory assays and a vast hospital partner network that enables omics-based biomarker discovery. Strand's customers include global instrument, diagnostic and pharmaceutical companies. For more information, visit us.strandls.com.

Formulation Forum

Prefilled Syringes: Overcoming the Challenges for Safe & Accurate Delivery of Drugs

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

Shaukat Ali, PhD
shaukat.ali@ascendiapharma.com

Jim Huang, PhD
j.huang@ascendiapharma.com

INTRODUCTION

As we continue to discover challenging molecules, the drug industry is open to adapt the innovative methods and technologies for delivery and packaging of new medicines, while keeping top priority in patient compliance, convenience, and easy accessibility to all with an affordable price. Prefilled packaging is a convenient way for precise dosing of parenteral medications. Prefilled syringes filled with liquid formulations, most specifically, offers a wider acceptability among children and aging patient population for self-administrative of small and large molecules for unmet medical needs and life cycle management.[1]

With continued rise in demand, the market is expected to grow rapidly for ready-to-administer (RTA) prefilled syringes with projected potential market share of $12.8 billion with CAGR of >12% in the next few years.[2] This growth is fueled by a surge in geriatric and diabetes populations coupled with increased demands for biologics to address the unmet medical needs requiring the self-injectable route of administration.[3] The main interest in prefilled syringes stems from the number of benefits, including patient accessibility and affordability, safety, reducing drug waste, and outweighing patient's benefit over risk for health providers and drug manufacturers.[4] For drug manufacturers, as an example, prefilled syringes can reduce 20%-30% overfilling by accurate and measured fillings, leading to controlled cost. As a matter of fact, prefilled syringes can deliver solution volumes between 0.25 ml and 5 ml; and hence, they are best suited for administering drugs by subcutaneous (SubQ), intramuscular (IM), and intradermal (ID) injections. Coupled with patient risk, safety, compliance, and demands, drug manufacturers are bound to develop in the future more products in prefilled syringes as opposed to traditional sterile vials for injectable medicines.[5]

The following is aimed to provide a better understanding about some of the advantages of prefilled syringes, methods for manufacturing, and the syringe types commercially available.

ADVANTAGES OF PREFILLED SYRINGES

Prefilled syringes are used due to their conveniences, accuracy, and sterility assurance, mitigating risks in overdosing of drugs, contamination, and dosing errors.[6]

Convenience

Prefilled syringes leverage convenience to patients and healthcare providers. Because they are a single-use device, they reduce concerns for contamination and overdosing. They allow patients to easily self-administer injection, which is beneficial to patient populations requiring frequent doctor's visit or requiring daily injection schedules.[7]

Accuracy

Prefilled syringes provides more accurate delivery of drugs than vial dosing and reduces risk for dosing errors. If dosing is not controlled, it could impact the efficacy of the treatment.[8] Yang et al found that prefilled medications for anesthesia, for example, pose far and fewer liability issues compared to self-filled syringes.[9]

Sterility

Preventing the formulation from microbial contamination is the highest priority in prefilled syringes. It is important to protect patients from undesired adverse effects and/or infections. As a result, the aseptic filling process is used for manufacturing of prefilled syringes for safety and regulatory compliances.[10] Once filled, the drug product is sealed off from cross-contamination and remains stable and sterile for 2 to 3 years

TABLE 1

Drug	Prefilled Syringe Formulation
Ardeparin	Hospital Lidocaine 1% w/v
Choriogonadotropin Alfa	Lidocaine Hydrochloride 2%
Dalteparin Injection	Nadroparin
Erythromycin Injection	Reviparin
Vasopressin Injection	Sodium Hyaluronate 1% w/v
Enoxaparin Sodium Injection	Tinzaparin
Diclofenac Sodium	Amiodarone
Ephedrine Sulfate Injection	Emerphed®
Tezepelumab Injection	Tezspire®
Omalizumab	Xolair®
Abatacept	Orencia®

Approved Drugs in Prefilled Syringes

of its shelf-life. Sterilization is typically done by autoclaving or ionizing radiation. Gamma radiation, usually carried out at 25-50 kGy, is more efficient as opposed to autoclaving. It is also effective for other components used in prefilled syringes, such as plungers and stoppers.[11]

Manufacturing Benefits

Key advantage for measured filling in prefilled syringes is to avoid excessive filling as is the case with vials and other ampules. For instance, 20%-25% overfill is required for vials or ampules to satisfy the USP recommendation for a typical 0.5-ml fill. In contrast, for prefilled syringes of 0.5-ml volume, only < 2% overfill is needed, as a result, producing 18%-23% more doses for filling PFS than that in vials. Manufacturing prefilled syringes may sound simple, but it could be complex considering the precise control of product viscosity, temperature, pressure, and equipment designs. For example, biologic or protein formulations are temperature sensitive and highly viscous, which could pose challenges in filling the prefilled syringes. Therefore, appropriate aseptic filling strategies are required for handling of these molecules at ambient or sub-zero temperatures without exposure to heat.[12]

Marketing Benefits

Prefilled syringes offer immediate marketing advantages due to their attractive packaging, less risk, dose accuracy, safety, and self-administrative nature. As a result, dug manufacturers prefer to develop these "ready-to-use" products even with slightly higher marketing premiums. This also leads to broader acceptability by end users, doctors, and healthcare providers. Table 1 shows the approved drugs in prefilled syringe.[12]

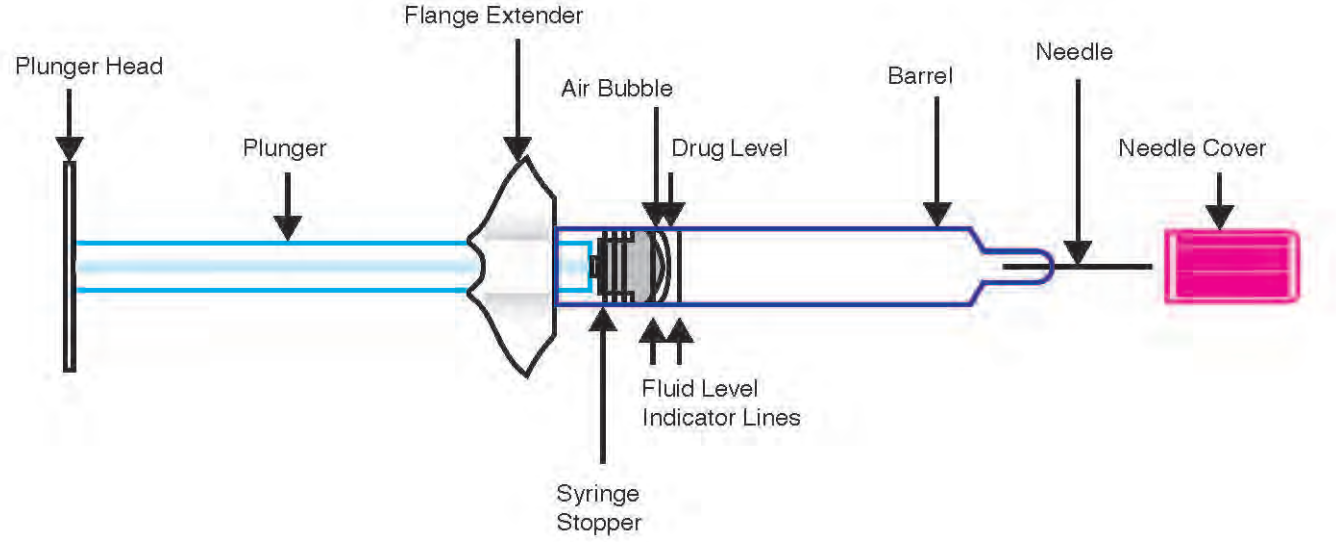
PRE-FILLED SYRINGE MANUFACTURING PROCESS

Materials & Components Used in Prefilled Syringes

Glass: It is derived from borosilicate glass of hydrolytic class I, stable at temperatures as high as 565°C, but is highly fragile so care must be exercised when used. This is used as a syringe barrel (non-reactive and stable during storage).

Plastics/Polymers: They produce robust, non-fragile devices compared to glass prefilled syringes with better durability, biocompatibility,

FIGURE 1



The Components of a Prefilled Syringe

TABLE 2

Component	Material
Barrel	Glass or Plastic
Piston	Elastomer
Tip Cap	Elastomer
Plunger Rod	Plastic
Lubricant	Silicone Oil
Needle	Stainless Steel
Needle Cover	Plastic
Lock Adapter	Plastic
Tamper Evident	Plastic
Finger Grip Extender	Plastic

Components of Prefilled Syringes

stability, and lighter weight. They should be free of leachables/extractables to avoid any adverse effects, such as carcinogenicity and immunogenic toxicity. Figure 1 illustrates the components of a prefilled syringe, while Table 2 shows the materials used to construct the prefilled syringe.

Glass filled syringes are of two categories, namely, oil siliconized syringes and baked-on silicone syringes. In oil siliconized syringe systems, there is direct contact of rubber with glass, which leads overtime to higher breakout forces and possible chances of contamination. In baked-on silicone syringe systems, however, there is a consistent coating of glass barrel, which leads to lowering of breakout forces during storage. As shown in Figure 2, where A denotes the higher breakout force (F) in oily siliconized syringes and lower breakout force (F) in baked-on silicone syringes.

In borosilicate glass prefilled syringes (USP Type I), there is a shift in pH as a result from the manufacturing of glass at higher temperature-processing conditions. Sodium borate ($Na_4B_4O_7$) formed evaporates at 800°C-1000°C, but on cooling to 580°C, sodium oxide remains in the glass on storage, and it releases sodium ions (Na^+) in water for injection (WFI) that leads to formation of NaOH and eventually change to alkaline pH in the prefilled syringe.[12]

In polymer based prefilled syringes, there are 2 types of materials used: Cyclo-olefin polymer (COP) and cyclo-olefin copolymer (COC). These low-density polymers provide high heat resistance, are autoclavable, break resistant, solvent and pH resistant, and transparent and eco-friendly.

There are two types of syringes available commercially. One type is the so-called staked needle syringe in which the needle is pre-attached, and the other type is like a Luer Cone/Luer Lock syringe in which the needle is free and can be attached with the prefilled syringe at the time of use.[13] The latter offers the patient advantage of selecting the required needle sizes. Table 3 shows the type of needles used in prefilled syringes for different routes of administrations.

Manufacturing of Prefilled syringes

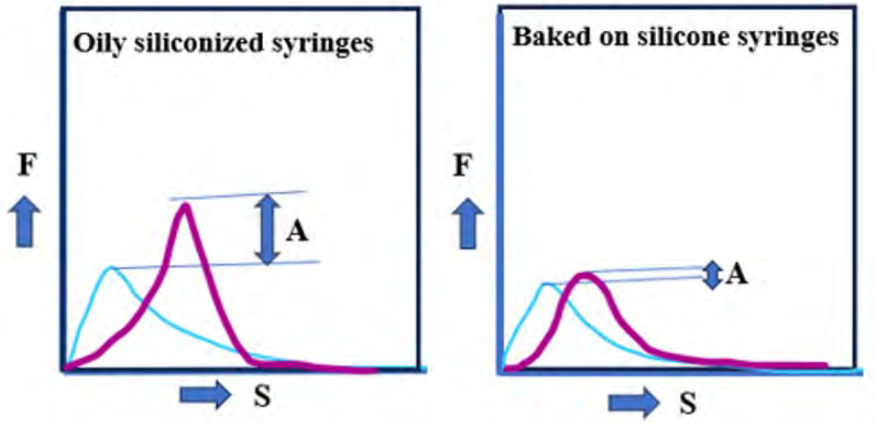
Conventional self-filling process requires filling of the syringe with solution and capping followed by sterilization. This filling process may lead to air bubbles. To alleviate these challenges, a bubble-free method is used that involves filling and capping under vacuum involving Hyaluron contract manufacturing technology. By eliminating the air bubbles, it improves the stability of drug from oxidative degradation of sensitive molecules. By placing the stoppers under vacuum, it provides a more accurate fitting in the prefilled syringes.[14]

Following the filling of syringes, other tests such as sterilization and labeling are required to establish the robustness of the prefilled process. As stated earlier, terminal sterilization is commonly used for sterilization. Autoclaving or steam sterilization is not a probable method as it can lead to package damage and is time consuming. Therefore, gamma radiation is highly preferred.[12]

SUMMARY & FUTURE PERSPECTIVES

The manufacturing of prefilled syringes involves identifying the components and processing of those materials, including cleaning and sterilizing the container, plunger, needle, and other components used in the

FIGURE 2



Oily Siliconized Syringe & Baked-On Silicone Syringe

TABLE 3

Injection Type	Needle Diameter (gauge)	Needle Diameter (mm OD)	Needle Length (inch)	Injection Angle (degree)
Subcutaneous (SubQ)	23-30	0.6-0.3	3/8-5/8	45-90
Intramuscular (IM)	18-25	1.2-0.5	5/8-1.5	90
Intradermal (ID)	25-27	0.5-0.4	3/8-5/8	5-15

Needle Geometries for Different Routes of Administrations

assembly process. Once the product is ready, it must be filled aseptically in a sterile clean room with Grade A or ISO 5 laminar flow environments to prevent product from contamination. This is typically done with specialized filling machines designed to control pressure and temperature. Filling is typically done in batches and must be strictly monitored to ensure accuracy. Because the fill and finish process must be conducted aseptically, several considerations must be factored, including use of correct environment and equipment to ensure sterility, maintenance of strict temperature controls, process validation, and environmental monitoring of non-viable and vial counts. It is critical the prefilled syringes are sterile and free of pyrogens. It is equally important the finished prefilled syringes should have complete labeling, packaging, and inspection by visual or automated systems. Improving shelf-life of prefilled syringes compared to traditionally self-filled syringes could help reduce stock losses and healthcare costs. Safety and regulatory compliances will play an important role in the marketing and launch of new prefilled syringes for innovative medicines – small and large molecules, polypeptides, and biologics.

Ascendia has installed a flexible aseptic filler for prefilled syringes, vials, and cartridges within its new state-of-the-art cGMP sterile manufacturing facilities that comply with regulatory standards. Coupled with rigorous testing and quality controls and testing, it is poised to tackle the molecules in the prefilled syringes with novel formulation and aseptic processes that improve a drug's bioavailability, efficacy, and stability over extended periods. Especially with the emergence of life-threatening diseases like high-stress critical situations or chronic dosing of CNS, oncology, and antivirus diseases, Ascendia is ready to manufacture prefilled syringes for immediate needs. Figure 3 shows Ascendia's flexible filler for batch size from a few units to up to 30,000 unit/batch. ◆

FIGURE 3

Ascendia's flexible filler for batch size from a few units to up to 30,000 unit/batch.

REFERENCES

1. E. N. Bukanova and H. Tunceroglu, Pre-filled syringes: reducing waste and improving patient safety, Anesthesiologist, 2018, 82, 16-17.
2. R. Soikes, Moving from vials to pre-filled syringe, Pharm. Technology, 2009 Supplement, Issue 5, 1-8.
3. P. Malik, Why utilization of ready to administer syringes during high stress situation is more important than ever, J. Infusion Nursing, 2022, 45, 27-36.
4. C. Dubin, Special Feature- Pre-filled syringes & parenteral manufacturing: Flexibility for faster development, Drug Dev. Delivery, 2019 May.
5. M. C. A. Whitaker and D. K. Whitaker, The impact of using pre-filled syringes on a standard operating procedure for preparing injectable medicines in clinical areas, Anesthesia, 2024, 79, 98-99.
6. S. N. Pagay, R. J. Bachorik, and T. L. Richard, Pre-filled syringe and pre-filled cartridge having actuating cylinder/plunger rod combination for reducing syringing force. Patent Storm: US Patent 5411489 - Pre-filled syringe and pre-filled cartridge, 1995.
7. A. T. Glenn, Prefillable syringes: Trends and growth strategies. Cedar cottage, Newtimber Place Lane, West Sussex, BN6 9BU, United Kingdom; ON drug delivery Ltd; 2006. Registered in England: No 05314696.
8. D. Beele. Increasing Popularity of Prefilled Syringes. Packazine, 2007, 1, 4-5.
9. Y. Yang, A. J. Rivera, C. R. Fortier, and J. H. Abernathy, A human factors engineering study of medication delivery process during an anesthetic pre-filled syringes versus self-filled syringes, Anesthesiology, 2016, 124, 795-803.
10. S. P. Jadhav, C. D. Patil, D. D. Sonawane, K. R. Jadhav and K. Salunkhe, Review on prefilled syringe as a modern technique for packaging and delivery of parenteral, Intern. J. Recent Scient. Res. 2020, 11, 11, 38301-38306.
11. P. Mudhar, Are Pre-Filled Syringes the Future? Asian Hospital and Healthcare Management. vol 23. Secunderabad, Andhra Pradesh, India: Ochre Media Pvt Ltd; 2011.
12. S. Makwana, B. Basu. Y. Makasana, and A. Dharamsi, Pre-filled syringes: an innovation in parenteral packaging, Int. J. Pharm. Invest., 2011, 1, 200-206.
13. V. Pironti, M. Raghunathan, and R. Hlodan, Pharmaceutical Online, White Paper, 1-4.
14. L. Danielle, Advanced innovations on a new generation of plastic prefilled syringes. Cedar cottage, Newtimber Place Lane, West Sussex, BN6 9BU, United Kingdom: ON drug delivery Ltd; 2010.

SCALING MANUFACTURING

Collaboration Between a Device Supplier & Equipment Manufacturer to Meet the Needs of Patients, End-Users & Pharma Manufacturers

By: John A. Merhige, MEM, and William Jaworski, MS, MBA

INTRODUCTION

Emerging trends in the pharmaceutical industry are posing greater challenges to the successful delivery of injectables than ever before. This requires innovation in drug delivery systems to address these challenges and meet the needs of pharmaceutical manufacturers, the drugs they are developing, and the end-users and patients that deliver them and benefit from them. But delivering innovation in drug delivery is hard. Robust controls must be demonstrated to address the understandable aversion to risk. Pipeline drug programs continue or are terminated based on clinical data and evolving corporate strategies, requiring flexibility. New device programs are not fully funded until clinical success is probable, demanding speed to market once green-lighted. These factors require delivery systems that solve a wide array of challenges with a breadth of variants, and a manufacturing capability with the flexibility to produce them.

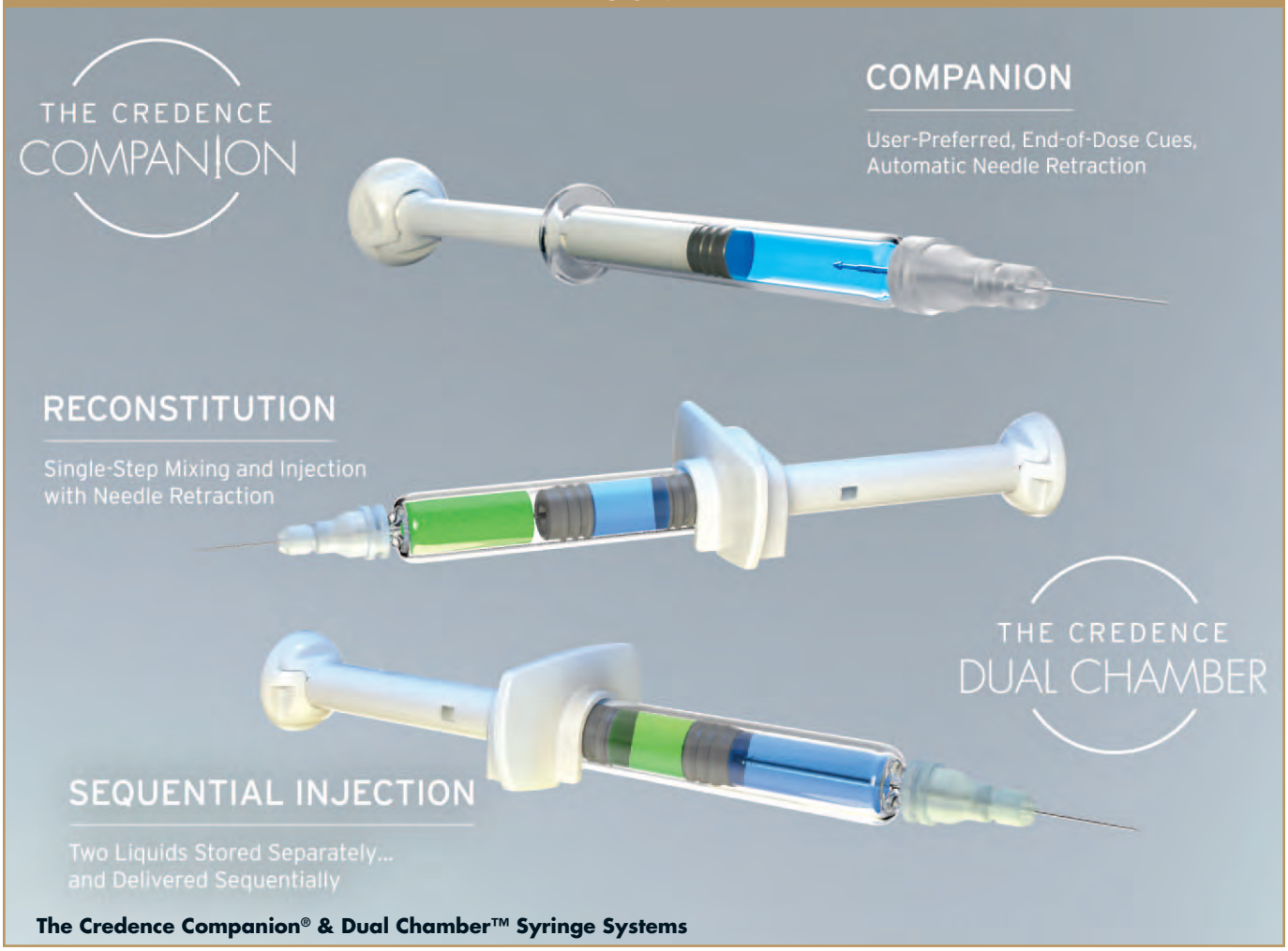
Credence MedSystems, an innovator of drug delivery systems, chose Mikron Automation, a leading partner for scalable and customized assembly solutions, to build an assembly system capable of producing over 150 variants of Credence's Companion® and Dual Chamber™ (DCS) Syringe Systems. The Flexible Clinical Line will operate under cGMP controls to support combination product development activities, such as device verification and validation, stability studies, and clinical trials. The following discusses the industry trends driving challenges in drug delivery, how the Credence products produced on the Flexible Clinical Line address those challenges, and how the Mikron MiniCell automation platform was leveraged to allow the flexibility and speed-to-market required to support Pharma's needs.

EMERGING TRENDS & THE RESULTING CHALLENGES

Healthcare in the home. Ongoing safety concerns. Sustainability's emergence as a priority. New formulations and combined therapies. Heightened regulatory scrutiny. Cost and efficiency pressures. These and other trends in our industry are driving new or intensified challenges in the delivery of injectable medications.

Chronic diseases are being treated with medications administered by self-injectors and their loved ones. Hospital-At-Home legislation, implemented to address pandemic-driven healthcare capacity constraints, is continuing to allow acute care to be delivered in the home under hospital-based requirements. As healthcare continues to move to the home, these injections are being performed by less experienced end-users with limited training and support. Concurrently, formulations are becoming more complex. With pharma extending dosing schedules, higher concentrations with higher viscosities are being injected in higher dose volumes. The difficulty of achieving liquid-stable solutions persists and pharma is moving toward combining multiple therapies in such areas as xRNA therapies, vaccines, and GLP-1s. This is driving increased development timelines and expense to target stable formulations or co-formulations, or alternatively, is causing pharma to compromise by launching therapies in inadequate

FIGURE 1



The Credence Companion® & Dual Chamber™ Syringe Systems

configurations that burden users and pose safety and efficacy risks during administration. Further, accidental needlestick injuries and syringe reuse continue to pose safety challenges. In short, drugs that are more difficult to administer are being administered by less-experienced users while requirements for safety, accurate dosing, and adherence are intensifying.

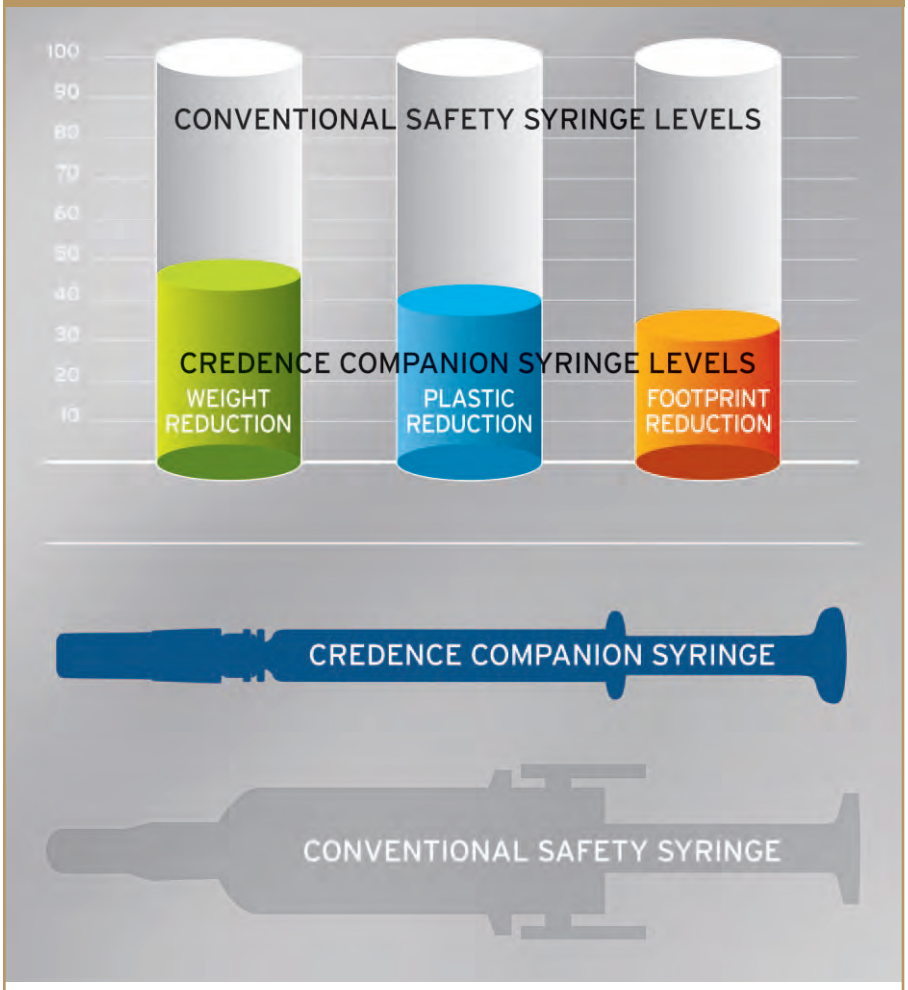
Additionally, the increased attention to sustainability, which seems to have finally arrived as an industry imperative, means that solutions to these challenges must come with reduced waste. And with intensified scrutiny on the performance of injection systems, devices must perform to heightened levels to drive complaints down. All of this must be achieved under the specter of ongoing pressures for cost and expense containment.

SOLUTIONS TO THESE CHALLENGES VIA INNOVATION

New trends create new challenges, and new challenges require innovative solutions. First considering the patient and end-user, a preferred delivery system can promote proper use and support adherence, which is linked to improved outcomes. Antalfy et al cite a series of studies showing that poor medication adherence worsens outcomes.[1] The Credence Companion, which has numerous usability advantages designed to promote adherence, has been demonstrated as preferred by self-injectors as well as HCP's.[2] Key preferred elements include the ease-of-use, ease-of-safety activation, and the end-of-dose cues in the form of a tactile and audible click at the end of injection when the needle automatically retracts into the plunger rod. The melding of user cues, passive integrated safety, and reuse prevention can promote adherence while addressing the continuing safety and economic risks associated with accidental needlestick and syringe reuse.

While the Dual Chamber Syringe (DCS) includes the same usability and safety advantages seen in Companion, it further incorporates simplified administration of drugs requiring separation of constituents during storage due to stability or co-formulation challenges. The DCS platform includes two variants; the Reconstitution DCS allows transfer of the diluent from the rear chamber into the front chamber to mix with the lyo cake, powder, or liquid before injection, while the Sequential DCS allows injection of two liq-

FIGURE 2



Sustainability Advantages of the Credence Companion

uids in sequence. This simplified usability is vital to enabling delivery of medication in the home, where users ranging from naïve self-injectors to HCPs will administer the medication. Further, the prefilled nature of the DCS and the elimination of numerous user steps reduce the risk of mis-dosing and the wasted dead volume (estimated at 20%-30%) associated with conventional vial kits. Risk of contamination and time to administer are also reduced (Figure 1).

It is relatively straightforward to connect enhanced usability with adherence, or to see how enhanced safety protects users and improves the overall cost of healthcare by reducing downstream expense resulting from accidental needlestick or syringe reuse. Less obvious, perhaps, is that solving usability and adherence challenges can lead to significant savings in development time and expense for drugs requiring separation during storage. As the usability and dose accuracy of dual chamber systems approach those of conventional single-chamber prefilled syringe presentations, new drug candidates can be introduced to the market faster because users can successfully use them. Reduced speed to market means the potential for market leadership and increased revenue, as well as significantly lower development cost that were traditionally directed at achieving stable formulations.

As the industry addresses the economic challenges associated with drug delivery, both sustainability and cost of ownership should be discussed together. With elderly population growth and increased prevalence of chronic disease, along with the vast amounts of disposables consumed by our industry, sustainability for sustainability's sake should be enough to make it an imperative. But too often, sustainability and cost savings are presented as mutually exclusive propositions. When innovation allows sustainability advantages to be a driver of cost savings, rather than of increased cost, sustainability becomes an imperative that is much more implementable.

The Credence Companion, with its integrated safety mechanism, has been evaluated against the conventional safety device, an add-on that wraps around the syringe barrel.[3] In that study comparing the 1-mL Long format, Companion was shown to reduce the weight of added components by 54%, utilize 40% of the plastic, occupy 47% of the volume pre-use, and occupy 33% of the volume post-use (Figure 2).

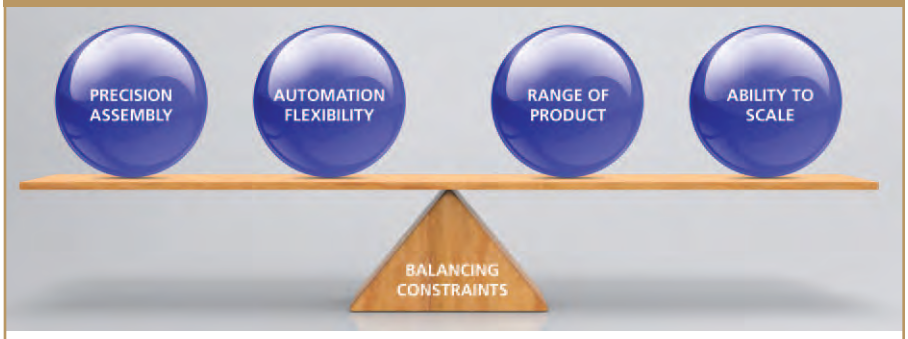
Each of these has obvious connections to an improved sustainability profile and has direct connections to cost savings. Large pharma manufacturers are paying for credits to offset their plastic waste. In addition to the cost, some experts believe this approach is less effective in reducing plastic pollution, and the only way to do so is to reduce plastic consumption, which Companion does.[4] Reducing weight translates to reduced cost of shipping throughout the supply chain. Smaller footprint means smaller secondary packaging, which translates to lower cost of materials, further reduced waste, and more effective use of shelf space – the latter being especially impactful in drugs requiring cold-chain storage. These significant improvements will be notably enhanced in a 2.25-ml format in which the larger add-

on device drives even more plastic, weight, and footprint while Companion has minimal change.

Companion's cost-of-ownership advantages extend beyond those linked directly to sustainability. The conventional add-on device requires dedicated equipment to mount the safety mechanism on an already-filled syringe. That capital expenditure is not needed with Companion. Additionally, ongoing operational savings also result from the following:

- Any build-up of scrap associated with the add-on assembly machine includes an already filled syringe. The disposal or rework of that scrap, which includes the drug product, is costly. This expense is eliminated with Companion.
- For every pallet of syringes that will be paired with an add-on device, there will be an additional pallet of add-on devices. The expenses associated with the storage and material transport of the additional pallets are eliminated.
- When the add-on safety mechanism prematurely activates during transit or preparation, the medication cannot be injected, which is the ultimate failure of a drug delivery device. The cost of these complaints and associated customer dissatisfaction is eliminated with Companion because its mechanism of action dictates the needle cannot retract until the plunger rod has reached the bottom of the barrel.

FIGURE 3



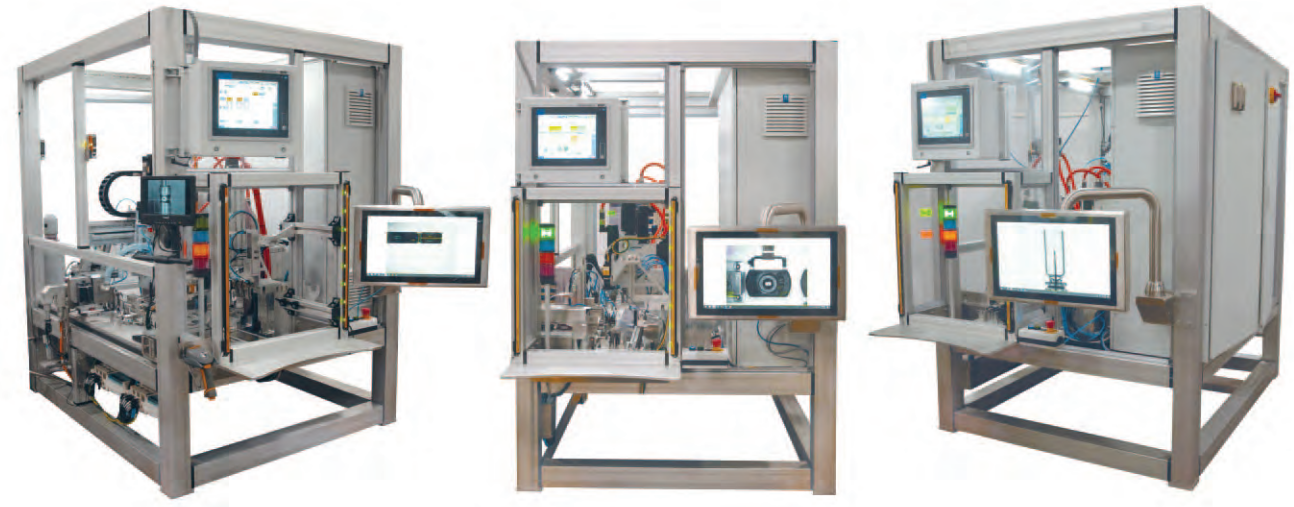
The Manufacturing Strategy's Balance of Constraints

INNOVATION EXTENDS BEYOND PRODUCT & INTO MANUFACTURING

With breakthrough products that will positively impact the drug delivery ecosystem, a robust manufacturing strategy is also required to support the production. The manufacturing strategy requires an ability to deliver a manufacturing solution that is optimized to what at times can be seen as conflicting requirements. Production of the Companion and Dual Chamber Syringe Systems requires the ability to assemble with extreme precision, allow for continued refinement of the medical device, have the ability to accommodate a wide range of variants, but be capable of manufacturing to scale. Credence partnered with Mikron, an industry innovator for scalable and customizable assembly solutions, for this unique challenge (Figure 3).

Mikron has extensive experience manufacturing bespoke automation for medical device and pharmaceutical clients. Mikron's automation philosophy de-risks and enables rapid deployment via

FIGURE 4



The Three Cells of the Flexible Clinical Line

FIGURE 5

The Flexible Clinical Line Installed in the Clean Room

the use of standard platforms and subsystem building blocks. This allows Mikron's engineers to focus more on specific critical aspects of the medical device and assembly process. This automation strategy helped rapidly deploy the lowest possible risk automation solution for Credence – the Flexible Clinical Line (Figures 4 & 5).

COLLABORATION SOLVES THE CHALLENGE OF CONFLICTING CONSTRAINTS

With heritage in the Swiss watch-making industry, developing robust and precision solutions is the norm for Mikron. Mikron has an extensive library of proven sub-system and design standards that can be leveraged to ensure the unique subcomponents of the Companion and Dual Chamber Syringe Systems are assembled and processed to their specifications to ensure patient safety and proper functionality. For the Credence products, this precision includes micro-component feeding, needle handling, precision welding, fine assembly, and vision inspection, just to name a few.

As speed to market is key for a novel product, Mikron needed to concurrently develop the automated manufacturing solutions, while Credence's design was being refined. This required tight collaboration between the two companies' engineering teams. As a benefit, some assembly techniques and device component designs were proven out on the Flexible Clinical Line as it was being assembled by Mikron. By utilizing the automation asset to provide real-time feedback, Credence was able to ensure a robust medical device design while Mikron was finalizing the automation.

The ability to accommodate a wide and varied range of products can run counter to automated manufacturing. However, one of Mikron Automation's standard platforms, the MiniCell, was developed specifically with this challenge in mind. This system provides not only the ability to rapidly deploy automation, but also the unique flexibility that Credence required to manufacture an extensive range of product variations. Credence's Flexible Clinical Line is a truly unique piece of automation in its ability to produce more than 150 product variants (Figure 6).

With the understanding that the Flexible Clinical Line is one of multiple important steps in Credence's product manufacturing journey, the two partners are using their experience to influence the design of a future high-volume system to support commercial adoption. This consists of using as many of the processes as

FIGURE 6

Products	Credence Companion® Syringe System Credence Dual Chamber™ Syringe System
Syringe Barrel Sizes	1mL Long 2.25mL 3mL 5mL Other barrel sizes can be implemented
Syringe Manufacturers and Treatments	Various manufacturers and siliconization treatments
Needle Lengths	8mm 1/2" 5/8" 1"
Needle Gauges	25G 27G 29G With thin wall options

Summary of Variants Produced on the Flexible Clinical Line

possible from the Flexible Clinical Line and leveraging the concept of process equivalency to reduce validation overhead and burden. The teams are also working together to evaluate and refine the manufacturing processes as they look toward the eventual high-speed assembly solution. Through developing subsequent process range capabilities studies and proof-of-principle experiments, Credence and Mikron are together developing the lowest-risk high-volume assembly system that can be deployed rapidly.

SUMMARY

Formulations are becoming more complex, and requirements for the performance and efficiency of delivery systems are becoming more stringent. But the great news is that more effective therapies treating more and more diseases are being delivered in settings that allow patients more comfort. Innovation and collaboration across the supply chain are required to meet the needs of patients and healthcare providers. Credence and Mikron have worked closely together, using creative manufacturing strategies to produce a wide array of problem-solving drug delivery systems. This has been demonstrated with the Flexible Clinical Line's completion of Factory Acceptance Testing at Mikron and its subsequent delivery to its final destination, where it is undergoing validations required to supply GMP product to Credence's pharmaceutical customers. ◆

REFERENCES

1. Antalfy A, Berman K, Everitt C, Alten R, Latymer M, Godfrey CM. The Adherence and Outcomes Benefits of Using a Connected, Reusable Auto-Injector for Self-Injecting Biologics: A Narrative Review. Adv Ther. 2023 Nov;40(11):4758-4776. doi: 10.1007/s12325-023-02671-2. Epub 2023 Sep 21. PMID: 37733212; PMCID: PMC10567963.
2. Companion Staked Syringe Formative Comparative HF Study (CD-003).
3. Credence Engineering Report #: ENG-0141.
4. https://time.com/collection/time-co2-futures/6691961/companies-offsetting-plastic-waste/.

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

BIOGRAPHIES

John A. Merhige is Chief Commercial Officer at Credence MedSystems. Previously, he was Vice President, Market Development at Sanofi, having joined Sanofi upon its acquisition of Pluromed. Pluromed developed and commercialized rapid transition polymers delivered from prefilled syringes for use in surgical procedures. Prior, he founded Prelude Devices to identify early stage medtech ventures and gained general management and leadership experience at Ford and Avery Dennison. He graduated from Dartmouth College with a Mechanical Engineering degree and returned to Dartmouth for a Masters in Engineering Management from the Thayer School of Engineering and the Tuck School of Business.

William ("Bill") Jaworski is the Sales Director and a member of the executive leadership team at Mikron Corporation Denver. Working at the intersection of healthcare, medical device, and manufacturing technology for 20+ years, he has explored market needs and developed solutions to meet those needs as Product Manager, Segment Marketing Manager, Global Marketing Director with GE Healthcare, and as a Business Development Director at ATS Life Sciences. He earned his BS in Mechanical Engineering and graduate degrees (MS in Mechatronics Engineering and a MS in Global Engineering Management) from the Northern Institute of Technology of Hamburg-Harburg, Germany, as well as an MBA from Marquette University.

Drug Development
EXECUTIVE

Tom Sellig

CEO

Adare Pharma Solutions

ADARE®
PHARMA SOLUTIONS

Expanding Capabilities to Exceed Customer Expectations

It's been more than two years since Tom Sellig took the reins as CEO of Adare Pharma Solutions. When we spoke with him shortly after he began his tenure, he shared his goals of positioning Adare in a competitive market to address complex formulation and development challenges and expand the company's customer relationships. We recently sat down with Mr. Sellig again to find how he has realized these achievements, and to learn more about the company's focus on addressing special needs in the market, its global expansion, and where he expects to take the company in the future.

Q: What are some of the challenges you're witnessing in the CDMO space?

A: The broader CDMO market includes drug substance, drug product, small molecule, and large molecule segments. There are regional players and global players in each segment, and each of those segments faces slightly different challenges.

When I think about small-molecule drug product – which is primarily where Adare's interests lie – one of the main issues continues to be supply chain challenges regarding API, especially controlled substance API. The DEA has changed the methodology for how it allocates quotas, and this is creating several issues for 2024, such as impacting how manufacturers like Adare produce products. There are mandated quotas for the API providers, and of course we can't manufacture products until we have the API, so scheduling of controlled substance manufacturing has gotten challenging. Luckily, we have a great logistics team that works closely with the DEA, with API providers, and with our customers to help minimize delays.

Q: We've talked about the challenges of the current marketplace. What are some of the opportunities available for CDMOs, and how is Adare taking advantage of them?

A: The CDMO landscape is one of rapid advancements, so companies that invest wisely and stay adaptable will always find opportunities to stay ahead of the curve and seize arising market opportunities. I continue to be really excited about the opportunities in the marketplace. Q1 2024 was very significant in terms of biotech funding, which means more companies can fund more development. That means more innovation and more opportunities for CDMOs, specifically Adare.

I also think companies that have great technology solutions are going to be in significant demand, and an unparalleled emphasis on technology is one way that Adare differentiates its offering. We're always evaluating new technologies to see if they can improve the development and manufacturing journey for our customers. The evaluation process requires time and resources that not every CDMO wants to commit, but at Adare we think it's worth the effort to discover technologies that power innovation for our customers.

Finally, there is a sense that many companies are looking to bring work back to the US that was previously outsourced or is being executed in other countries, which will be a boom for US-based companies.

Add all that up and it's really driving some great growth for the industry at large, and specifically for Adare. Our development pipeline is full of new opportunities. We have had record proposal volume in Q1 and we're seeing significant new opportunities. We are also looking at some growth from existing products. I came to this company two-and-a-half years ago believing firmly that there's significant opportunity for sustainable growth and we're seeing that growth today.

Q: You mentioned technology as a differentiator. What new technologies do you think have the potential to benefit the CDMO industry?

A: Two technologies come to mind immediately, technologies that might not just help grow the industry but even disrupt it in exciting ways. These are AI and 3D printing, both of which have already shown incredible boosts in efficiency and quality when implemented thoughtfully.

Adare has deployed AI very recently for advanced scanning capabilities, allowing us to look at a molecule in a very different way than we could previously. We are also using AI to predict how formulations and molecules will perform in the clinic. This is a really exciting breakthrough because it allows us to zero in on a formulation much faster and give us a higher probability that a particular formula will be successful in clinical studies, saving the sponsor time and money.

We recently installed a development-scale 3D printing capability in one of our Italian sites. This allows us to produce products in a very different way, and we think this will be great for several products in the global pipeline today.

We will be making more announcements about both of these technologies later in the year, so stay tuned.

Q: The continued growth of highly potent products is another major story in the pharmaceutical industry at the moment. How can CDMOs take advantage of this growth?

A: High potency has become an increasingly important part of pharmaceutical development. In fact, about half the drugs in development are highly potent compounds. The main driver is the oncology sector's domination of new drug development. I've seen estimates that 40%-50% of drugs in development are cancer drugs. And of those, 75% are high potency.

So, there are a lot of opportunities out there for CDMOs who want to get involved with high potency, but companies need to exercise abundant caution when doing so. Highly potent compounds require containment and infrastructure, and they take investment to support. You need to be vigilant about cross contamination and employee safety.

Because of these concerns, customers are hesitant to work with companies who are new to high potency. They demand CDMOs with deep experience handling highly potent products. That's where a company like Adare comes in. We have a long history of working with high potency, and we have facilities already in place that have been handling highly potent compounds for years.

In 2024 and beyond, we're leveraging that experience to further expand our high potency capabilities at most of the sites in our network. This will allow us to serve a broader range of the market by addressing high potency needs for additional steps in the manufacturing process and at different scales. For example, we will soon be offering wet and dry granulation that can support both clinical and commercial scale. With these expansions we will be able to serve more customers at more stages in their commercialization journey and ultimately help them get important products into the hands of patients faster.

Q: Pediatric formulations are a hot topic in the industry right now. This is one of Adare's specialties, so can you speak to the current landscape and how the company approaches pediatric development?

A: Pediatrics continues to be a growing portion of the market and you're right, there is quite a bit of focus on it at the moment. For example, there was legislation not too long ago that provides additional patent exclusivity for pediatric products. There's a greater awareness in the industry that pediatric products require different formulations for different metabolism in the body. Simply put, pediatric formulations are no longer a "nice to have." Companies must have a dedicated pediatric strategy in place to see their product live up to its full potential.

There are a lot of interesting challenges to overcome in pediatric development. If you've ever tried to get your child to take medicine, you know that it has to be convenient and easy to dose. It can't be hard to swallow, and it can't be bitter. Our formulators and scientific teams are well-versed in the needs of pediatric patients, and we deploy various strategies and technologies to meet those needs. We're the experts at taste masking bitter API via our Microcaps® encapsulation technology, and we provide customized release and other dosing options so that children ideally don't have to take as many doses. We also offer creative dosing formats that make medications easier to take, like powders that can be sprinkled on food and a solid dosage form that turns into an applesauce-like texture when you add a little bit of water to it.

Q: How do your high potency and pediatric offerings position the company in a competitive marketplace serving these special needs?

A: We want to be considered a leader in these spaces. We differentiate ourselves through our advanced technologies and capabilities, and through our focus on oral solid development for small molecules. We have a portfolio of technologies to deploy that can solve complex formulation and manufacturing challenges. We have a very deep toolbox that allows us to create a wide range of solutions to meet the demands of today's pharmaceutical global pipeline.

In summary, Adare is a full-service firm, able to offer solutions from the earliest phases of development and at every step all the way through to commercial manufacturing and beyond, including packaging.

Q: How has Adare adjusted its business model to become this full-service offering?

A: In many ways, we had to go back to basics. We acquired Frontida BioPharm in December 2021, around the time I joined Adare. Our leadership team assessed our priorities and the culture we wanted to build. To do that, we had to think internally about how we operate, how we are structured, and how we go to market.

It starts with having a client-centric mentality across the entire organization. As a company, we are wired to do everything necessary to ensure our clients are successful. Our leadership team personally takes ownership for ensuring the success of client projects, whether it's a smaller client or Big Pharma.

Q: What's Adare's business strategy on the world stage?

A: Adare is a global CDMO, and our business strategy is to constantly make significant investments in new equipment and capabilities for our global network to support more customers around the world. As one example, we recently upgraded our Pessano site in Milan, Italy to include expanded warehousing and a dedicated facility for packaging. In Europe, they prefer blister packs rather than bottles for oral solids, so we are installing blistering equipment to support those clients. The Pessano site is also part of our high potency expansion plan, allowing us to offer those services in Europe and beyond.

Q: We last spoke just over two years ago. Where do you see Adare in the next two years?

A: We want to continue on the successful path that we have started. We are going to see our internal investment projects through to fruition. We will continue to prioritize our customer-focused culture, and find creative ways to be cost-effective, faster, safer, and more efficient for our customer's projects. Most importantly, we will remain committed to our continuous improvement mentality of getting 1% better every day. ◆

KEEPING YOU CONNECTED TO YOUR TARGET AUDIENCE.

For more than 20 years, Drug Development & Delivery has successfully connected technology and service providers with R&D scientists, business development professionals and corporate managers working at pharmaceutical and biotechnology companies.

Marketing your technologies, services and products with Drug Development & Delivery keeps you engaged with your key audience.

Call us today or visit us at drug-dev.com and let us show you how.

- Print & Digital Editions
- Website Marketing
- Email Campaigns
- Videos
- Exclusive Whitepaper & Webinar Marketing
- Online Company Profile
- eBooks
- eNewsletters

John Kiesewetter: 541-338-0022
jkiesewetter@drug-dev.com

Amy Nicklaus: 862-274-5872
anicklaus@drug-dev.com

Ralph Vitaro: 973-263-5476
rvitaro@drug-dev.com

drug-dev.com

CELL & GENE THERAPY

It's Time to Build Infrastructure to Handle the Coming Surge

By: Fran Gregory, PharmD

INTRODUCTION

Cell and gene therapies are being developed faster than ever before, and they represent some of the most exciting developments in all of medicine. Cell and gene therapies are personalized medicines designed specifically to an individual patient. Although often grouped together because of their extraordinary impact and place on the cutting edge of medical tech, they're quite different.

Cell therapies modify existing human cells from a patient or donor and infuse them back into the patient. The cells become therapeutic, and they're designed to attack specific targets or diseases like multiple myeloma or leukemia. On the other hand, gene therapies directly impact a gene that is causing a condition or disease. These therapies can correct, eliminate, or even replace a targeted gene using vectors to deliver new genetic material. Gene therapies can treat complex and rare diseases like hemophilia or spinal muscular atrophy. Cell and gene therapies can even be used in conjunction and combined into a single therapy.

These treatments are saving lives and giving second chances to patients who once thought they had no other options. Called "living drugs," they are not only our best chance at finding treatments for rare genetic diseases that currently have no cure, but also offer greater potential to treat widespread diseases like cancer, rheumatoid arthritis, or heart disease.

The complexities and innovations associated with the production of cell and gene therapies also necessitates a shift in infrastructure, which will affect manufacturers, distributors, and providers. From development, manufacturing, storage, and delivery to patients; each step in the process requires forging a new path.

THE TRAJECTORY

Since their introduction, cell and gene therapies have been among the fastest evolving therapies in medicine. Early CAR-T cell therapies saved the lives of children with late-stage pediatric acute lymphocytic leukemia. Additionally, the US Food and Drug Administration (FDA) approved a gene therapy to treat hemophilia, a welcome advancement for patients who have historically faced a high risk of complications and who required ongoing treatment with very expensive medications.

These therapies significantly improve patient outcomes and reduce the ongoing burden of care. More than 6,000 diseases could potentially be treated by cell and gene therapies, affecting more than 350 million people worldwide.[1]

Today, only a small number of these therapies have been approved by the FDA, but a flood of new treatments is coming. More than 3,000 new therapies are in development globally, indicating a sign of their clinical potential.[2] In 2021, the US cell and gene therapy market was valued at around $5 billion. By 2027, it's expected to grow to about $37 billion, an increase of nearly 640%.[3]

When we look at the future of cell and gene therapies, clinical trials can give us a good idea of what may come next. Phase 3 trials are underway for therapies aimed at treating pulmonary hypertension, diabetic neuropathy, Parkinson's disease, chronic heart failure, vision loss disorders, and some cancers. Although not yet approved, trials across such a broad range of conditions

are proof of their potential to have a critical impact on the standard of patient care.

These treatments have the potential to save untold lives; however, this potential is paired with some significant challenges.

THE CHALLENGE

Patients will only benefit from treatments if they have access to them. Patient access to cell and gene therapies is limited for many reasons, beginning with product development.

Cell and gene therapies are often developed to treat very rare conditions. It is challenging to identify specific conditions likely to be responsive to these therapies and then to find enough patients suitable for participation in clinical trials from among some of the smallest patient populations in the world. Not only do manufacturers of these therapies need to design and enroll patients in clinical trials from among small groups of medically fragile patients, but they must also find the right sites and clinicians to administer these treatments.

The necessary patient-by-patient manufacturing process for cell and gene therapies is yet another barrier. These therapies are among the most complex specialty medications available; they require tailored manufacturing processes that create a completely individualized product for a single patient's treatment. After manufacturing, the product is volatile and must be handled with extreme care. This requires very sophisticated logistics, storage and tracking capabilities.

Cell and gene therapies are often stored at extremely cold temperatures, with temperature requirements as low as negative 190 degrees Celsius or below. These temperatures necessitate special handling and safety precautions for the logistical and clinical teams handling them, with delivery and on-site storage being particularly complex. Most provider sites are not currently equipped with cold chain storage for these products.

Upon receiving the product, providers administer it to a specific patient according to stringent processes and carefully choreographed timing. Once administered, tracking patient response and outcomes over time is extremely important in building the body of knowledge in this emerging field. This requires sophisticated chain of identity and custody solutions.

Upon completion of the requisite clinical trials, the process of securing FDA approval is lengthy, expensive, and complex. However, regulatory agencies are already working to improve these efforts.

In 2019, FDA Commissioner Scott Gottlieb acknowledged the upcoming surge in these therapies, and predicted that by 2025, the department would be approving 10 to 20 cell and gene therapies per year. Even then, he seemed to understand that changes would be necessary to meet the coming demand.

"We're working to expand our review group dedicated to the evaluation of these applications to keep pace with the rapid expansion in new product development," he said at the time. "Our eventual goal is to add about 50 additional clinical reviewers to the group charged with overseeing the clinical investigation, development, and review of these products. The activity reflects a turning point in the development of these technologies and their application to human health. It's like the period marking an acceleration in the development of antibody drugs in the late 1990s, and the mainstreaming of monoclonal antibodies as the backbone of modern treatment regimens."

This expansion is a welcome development in our fight to save and improve lives, but a major challenge remains.

Cell and gene therapies are very expensive — in fact, they're some of the most expensive treatments available. The

average cost is around $1.5 million per dose, with some treatment costs rising into the multimillions. In instances in which a therapy is administered a single time, this may be lower than the cost of ongoing lifetime care.[4] But for most patients and payors, the cost of these treatments may be prohibitive and could limit their availability to the patients who need them most. This is a challenge we must address if we want to expand access to these treatments.

In addition to all the logistical and costly expenses, there are also a variety of challenges in the development and availability of these therapies.

The first challenge starts at the beginning of the process with the identification of patients. It's challenging to identify a very small population of people with a very rare disease, which can be an issue when that population is the target demographic for many of the cell and gene therapies that are on the market today. Manufacturers of these therapies need to design and enroll patients in clinical trials, and identifying patients for those trials is a significant lift.

Also, the necessary patient-by-patient manufacturing process for cell and gene therapies represents another barrier to broader patient reach, requiring single-dose preparation and extreme diligence to produce.

THE FIXES

At Cardinal Health, we work to widen access to life-saving treatments like cell and gene therapies, and we're doing everything we can to move the industry forward. We have been working to build advanced infrastructure to support the development, manufacturing, distribution, and delivery of these products.

As the leading provider of comprehensive services for cell and gene therapies, we are proud of the clinical, regulatory, logistical, and patient-focused value we offer to healthcare providers and pharmaceutical manufacturers. We have been here from the field's inception, supporting the first CAR-T products, providing expertise in regulatory support, and consulting for more than 40 advanced therapies in 12 therapeutic areas. To date, we've processed thousands of cell and gene therapy orders.

We also have a partnership with TrakCel, the first provider of integrated cell and gene therapy software solutions for the precise management, control, and tracking of cell and gene therapy products. Our partnership with TrakCel allows us to have information on chain of identity, chain of custody, location, and patient journey throughout the process of product delivery and administration. As partners, Cardinal Health and TrakCel offer industry-leading visibility and transparency to healthcare providers, manufacturers, and case managers working with these important medications. However, we can't stop there.

Evidence-based medicine is critical to the delivery of better patient care. In the case of treatments that can cost millions of dollars, tracking and demonstrating the impact of these treatments on patient outcomes is key to increasing access. We must improve data collection before and after the patient receives treatment, which can be especially difficult when tracking patients from cell and gene clinical studies. Patients are located all over the world, but the treatment centers providing these therapies are often limited to centers of excellence or large hospital systems, often in urban or populated areas. This makes long-term patient evaluation difficult and data collection inconsistent or incomplete. Because of this challenge, it's difficult to create a complete data set around patient outcomes.

At Cardinal Health, we recognize these challenges, and we see them as opportunities. Opportunities to partner with treatment centers, providers, and pharmaceutical manufacturers to do better every day for patients. We continue to innovate beyond what we believe is possible, and we will strive to build a sustainable foundation upon which cell and gene therapies can thrive. We are committed to providing cell and gene therapy services that meet the needs of all stakeholders that will ultimately lead to better patient outcomes. ◆

REFERENCES

1. https://med.stanford.edu/cdcm/CGT.
2. https://pubmed.ncbi.nlm.nih.gov/ 37927037/.
3. https://www.businesswire.com/news/home/20220201006057/en/36.92-Billion-Cell-Gene-Therapy-Market---Global-Outlook-Forecasts-2022-2027---ResearchAndMarkets.com.
4. https://icer.org/wp-content/uploads/2020/11/ICER-Gene-Therapy-White-Paper-030317.pdf.

BIOGRAPHY

Fran Gregory is responsible for cell & gene therapies and biosimilars at Cardinal Health. Her background includes extensive clinical, health economics and outcomes research, trade and commercial experience in the payer/ PBM, specialty pharmacy and biotech manufacturer spaces. Her career reflects a consistent focus on complex, innovative, high-value pharmaceuticals and a passion for breaking down barriers to access and care.

DRUG & DEVICE DEVELOPMENT

Integration of siRNA, Nanoparticles & Capsule Endoscopy for Treatment of Inflammatory Bowel Disease

By: Nila Murali, Leia Jiang, and Ravali Bhavaraju

INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease (IBD) is a chronic condition of the gastrointestinal tract that affects approximately 3.1 million adults in the US, representing 1.3% of the adult population.[1] There is currently no cure for this disease, and treatment options prioritize the management of symptoms. Typical manifestations of IBD include diarrhea, abdominal discomfort, rectal bleeding, and reduced body weight. The range and severity of these symptoms can vary, and patients often experience periods of remission and active disease flares.[2] IBD can be further divided into two subcategories: ulcerative colitis and Crohn's disease, which are both characterized by abnormal immunological responses in the gastrointestinal (GI) tract and the bacterial microbiome. Ulcerative colitis (UC) affects a continuous region of the colon and rectum, which experiences inflammation and excessive ulcers on the outermost mucosal layer of the GI tract. Crohn's Disease involves inflammation and ulcers across all regions and layers of the gastrointestinal tract, with affected regions presenting in patches.

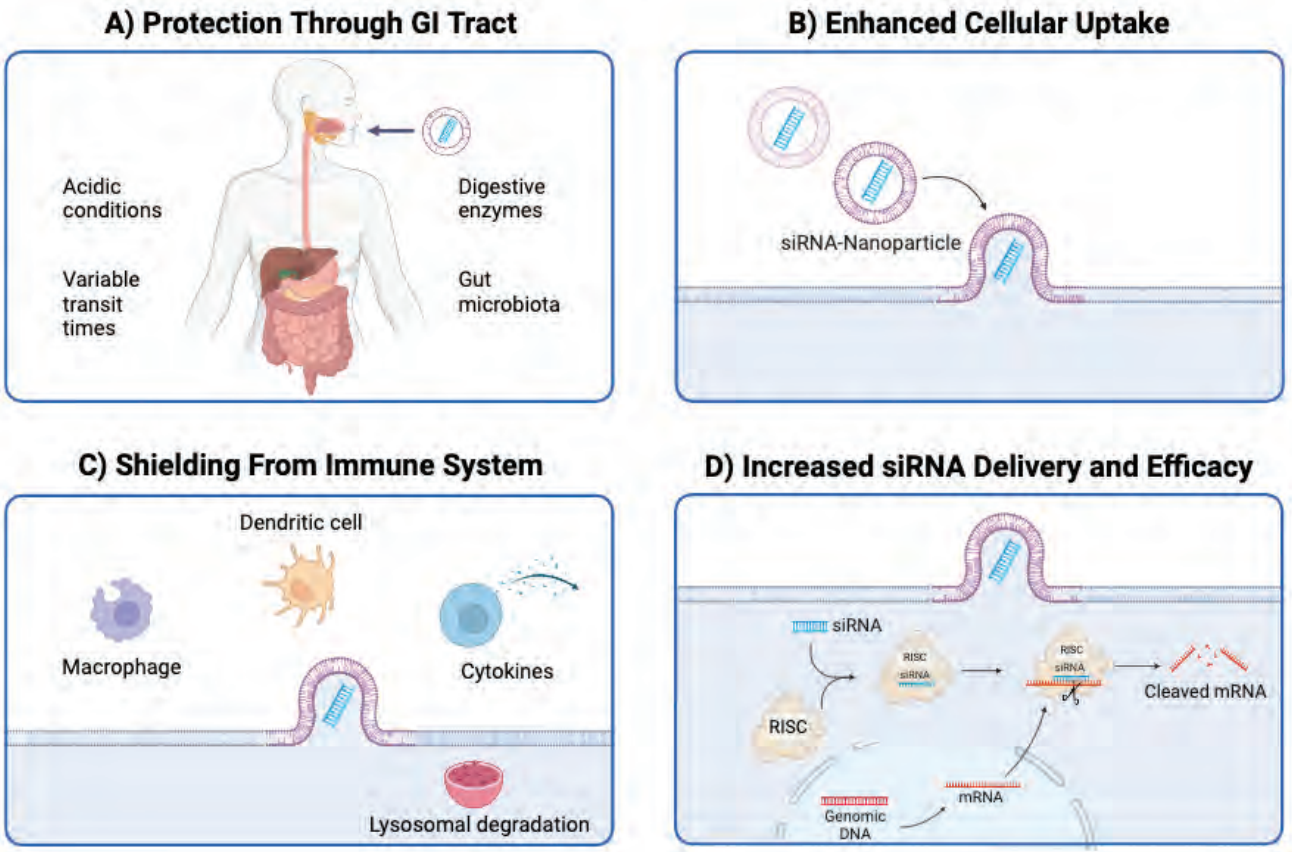
While many established treatments exist to manage symptoms, each has its disadvantages. Aminosalicylates have limited efficacy in severe cases and can cause gastrointestinal discomfort. Corticosteroids are efficacious at providing short-term relief but are not recommended for prolonged use due to side effects, which include osteoporosis, myopathy, diabetes, and hypertension. Immunomodulators lower inflammation through immune response suppression, which increases infection susceptibility and liver toxicity. While biologics are more potent and targeted in their inhibition of inflammation, they increase the risk of infections, are high in cost, and have lowered patient compliance due to the route of administration.[2] Overall, current IBD therapeutics are reactionary because they work to inhibit or modulate active inflammatory responses. Therefore, there is a necessity for preventative treatments that offer a high degree of specificity and target the root cause of inflammation.

CAPSULE ENDOSCOPY

IBD is most commonly diagnosed via endoscopic procedures, such as a colonoscopy. Though they are effective, colonoscopies are expensive and inconvenient, requiring patients to empty their bowels, follow strict liquid diets for 24 hours, and undergo temporary sedation during the procedure.[3] They are also limited to imaging within the colon due to length, size, and flexibility restrictions of the endoscope instrument. As an alternative, researchers have developed capsule endoscopy systems, which involves an ingestible pill with an embedded camera that can take images of the entire GI tract, including the esophagus and stomach, at a lower cost and without requiring a complex procedure.[4]

Capsule endoscopy devices are currently used for the detection and diagnosis of IBD and have laid the groundwork for a novel area of research in the treatment of gastrointestinal dis-

FIGURE 1



Nanoparticles enable improved delivery of orally administered siRNA by overcoming biological barriers. A) Nanoparticles protect encapsulated siRNA through the harsh conditions of the gastrointestinal tract. B) Nanoparticles bind with the cellular membrane and enhance endosomal uptake. C) Nanoparticles shield siRNA from immune cells in systemic circulation and degradation within the cell. D) By overcoming these barriers, nanoparticles increase delivery into the cell, where siRNA cleaves the target mRNA. Created with Biorender.com.

eases. Many medical device companies, such as Olympus, Jinshan, and Biocam, have introduced capsule endoscopes to the market. The PillCam™, developed by Medtronic, is the most well-known, and features a pill-shaped design enclosing a wireless camera. The PillCam SB model, once ingested, takes high-resolution images over a period of 8-12 hours and transmits its data wirelessly.[5] More recently, Medtronic developed the PillCam COLON2™, which captures panoramic images of the gut and uses artificial intelligence (AI) to dictate image-capturing frequency.[6]

The accessibility, image-capturing capabilities, ingestible size, and AI technologies of PillCam devices are compelling reasons to continue studying capsule endoscopy for IBD treatment. However, despite the diagnostic abilities of the current PillCam devices, they are not commonly used after initial disease identification, and very few are under development specifically for drug delivery applications.

NANOPARTICLE-MEDIATED SIRNA DELIVERY FOR IBD

Small interfering RNA (siRNA) treats IBD by targeting and silencing specific genes involved in inflammatory and immune responses. siRNA molecules selectively down-regulate genes associated with diseases by cleaving mRNA sequences. For IBD, siRNA knocks down genes that code for inflammatory mediators, such as TNF-α, integrins, and inflammatory interleukins. This targeted gene silencing directly addresses the root causes of inflammation in IBD, offering a precise method to mitigate the disease's effects. However, there are several barriers to targeted siRNA delivery. The negative charge, hydrophilicity, and large molecular weight of siRNA hinder its cell membrane penetration. Furthermore, while oral administration is often preferable due to increased patient compliance and ease of administration, it exposes siRNA to the GI tract's acidic conditions and digestive enzymes.[7]

Nanoparticles have emerged as a promising solution for siRNA delivery.

Nanoparticles are materials on the nanoscale that can be engineered to overcome biological barriers, including the harsh conditions of the GI tract, cellular binding and uptake, and the immune response in circulation and within the cell, and enable targeted delivery (Figure 1). The most common are administered orally and deliver siRNA that targets TNF-α, CD98, and Map4k4. Several nanoparticle carriers have shown efficacy in preclinical studies, including liposomes with hyaluronan and Dipalmitoyl Phosphatidylethanolamine (DPPE), polyethyleneimine-derived nanoparticles, calcium phosphate and Poly lactic-co-glycolic acid (PLGA) nanoparticles, chitosan-derived nanoparticles, and poly(amino acid) nanoparticles.[8]

Despite the potential of nanoparticle-mediated siRNA delivery to down-regulate inflammatory genes, it cannot precisely distinguish between diseased and healthy regions of the gut. Thus, targeted delivery to highly inflamed regions of the GI tract is difficult, and off-target effects may occur. Achieving precise delivery is challenging and is compounded by the lack of detection tools used in conjunction with treatment. Overcoming these hurdles is crucial for the successful use of siRNA therapies for the treatment of IBD.

INTEGRATION OF SIRNA DELIVERY & CAPSULE ENDOSCOPY

Capsule endoscopes and siRNA nanoparticle therapies have widely different application purposes for the diagnosis and treatment of IBD patients. Capsule endoscopy records real-time imaging data of the gastrointestinal tract, and the siRNA-nanoparticle therapies treat the root cause of inflammation in IBD. However, both have drawbacks that limit their individual utility. Currently, most capsule endoscopes with real-time imaging are not used after initial diagnosis as they are not engineered for therapeutic delivery. siRNA-nanoparticle therapies cannot precisely distinguish and target damaged regions and cells, resulting in off-target effects, material wastage, heightened immune responses, and tissue damage when used for prolonged periods. An integrated siRNA and capsule endoscopy system can address the pitfalls of each stand-alone technology and provide patients with a more effective therapy option. In this integrated system, the capsule endoscope will send imaging data to external software that triggers siRNA nanoparticle release based on the detection of swelling, ulceration, and strictures (Figure 2).

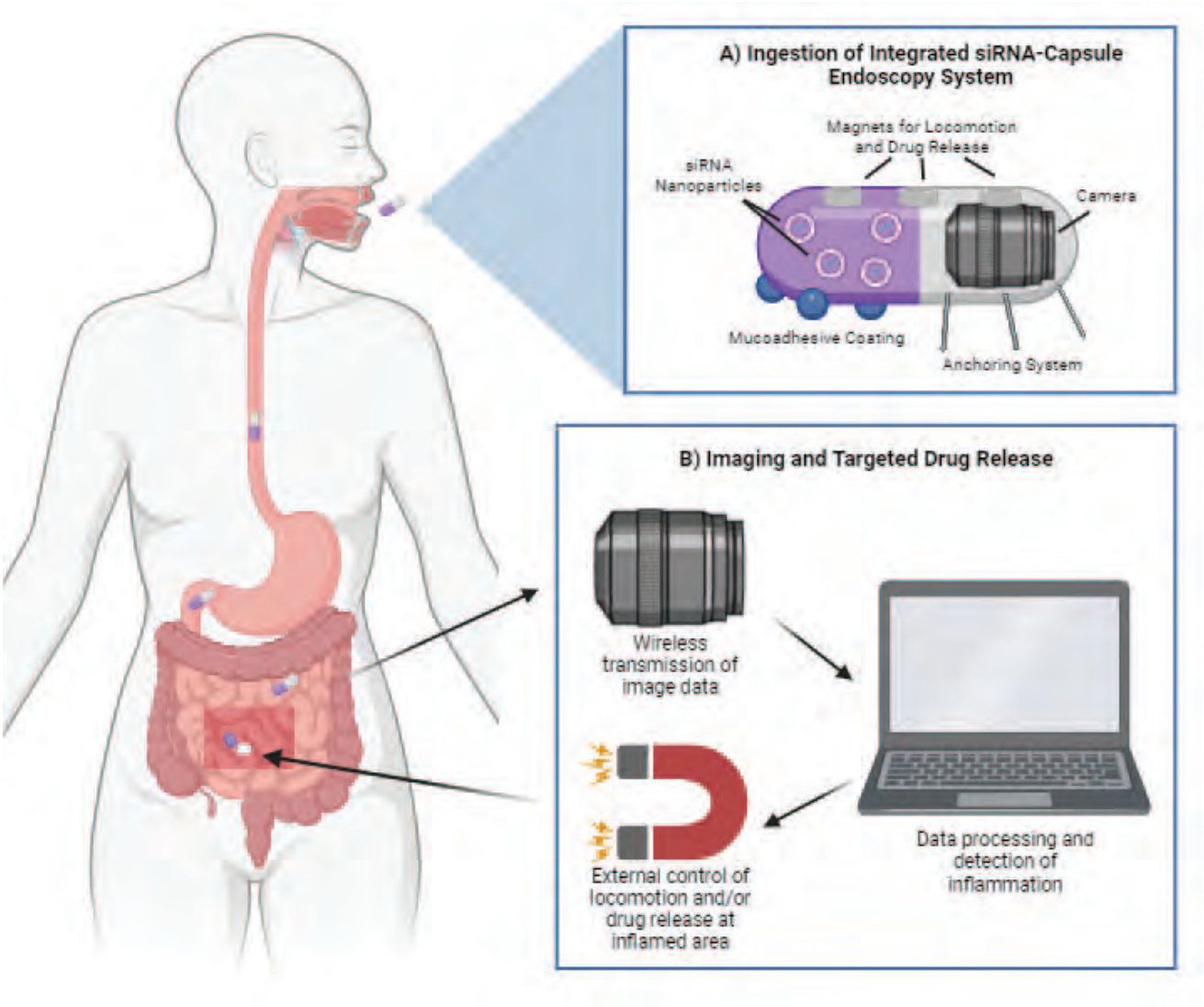
Due to the variable environment of the GI tract, several factors must be considered to develop an effective integrated capsule endoscopy drug delivery system. For example, the diameter of the GI tract and the presence of fluid vary significantly by patient. Therefore, integrated systems should fit within certain size constraints, include highly controlled drug-release mechanisms, and feature anchoring systems to attach to specific regions within the GI tract.[9]

The drug-release mechanism of a capsule endoscope needs to be strictly controlled to ensure that a precise drug dose is delivered at specific sites. In recent years, many different smart pill and capsule endoscope manufacturers have experimented with different active and passive release mechanisms of drugs for delivery to the GI tract. Three important examples are the RaniPill™, InteliSite®, and Enterion™ capsules. RaniPill uses a passive release mechanism in which the drug is encapsulated by a hydroxypropyl methylcellulose capsule in an enteric coating. This coating does not dissolve in low pH values found in gastric acid but dissolves and inflates a balloon when in the higher pH region found in the intestines. The balloon then exposes a biodegradable needle for direct deposition of the drug into the gastrointestinal wall. InteliSite contains a liquid drug in a 0.3-mL reservoir that is sealed with a thin layer of lubricant. The drug is released through a pre-programmed code on an external computer that provides activation energy. The system then uses a screw-pump release that delivers the drug in a passive, slow manner. Finally, the Enterion uses a radio-frequency transmitter to trigger a spring mechanism using magnetic impulses. The drug reservoir holds 1 mL of the drug and when triggered by an internal heating element, a piston rapidly releases the drug.[10]

Drug-release mechanisms for capsule endoscopes are still an active area of research. Uniquely, Lee et. al have developed a capsule endoscopy system that relies on magnets for locomotion and drug release, though it is not currently available on the market. Specifically, they created a system that captures images of the GI tract and actively delivers biodegradable therapeutic patches to target lesions via a robot-assisted magnetic actuator. The actuator controls a lid, capable of opening and closing to deliver multiple doses whenever an inflamed region is detected. Furthermore, embedded neodymium magnets allow the device to be precisely controlled with an external magnetic field, improving the accuracy of drug delivery.[11]

Traditionally, capsule endoscopy relies

FIGURE 2



Integrated siRNA-Capsule Endoscopy systems allow for targeted drug release post-ingestion. A) Features of an integrated siRNA-Capsule Endoscopy system can include cameras, anchoring systems, mucoadhesive coatings, and magnets. The system is ingested by the patient. B) Images taken by the embedded camera are wirelessly transmitted to a computer, where image data is processed to detect specific areas of inflammation. Based on the data, the locomotion and drug release of the system at target areas are externally controlled. Created with Biorender.com.

on the natural peristalsis of the GI tract for movement. To target specific areas of interest, anchoring systems that can resist peristalsis are required. Tethered legs or hooks are common anchoring systems that function by attaching to the intestinal wall while images are captured. Similarly, mucoadhesive patches or coatings can stick to the intestinal wall, and often biodegrade after use. Moreover, motors and actuators are frequently used for precise navigation and anchoring. Mechanical actuators often use tethered legs, rolling treads, and propellers for locomotion. The main limitation of mechanical actuators are their large size, which is primarily due to bulky mechanical locomotion devices and a need for energy storage. Magnetic actuation involves embedding a magnet in the capsule and orienting it through a magnetic field gradient external to the patient. Magnetic actuation emerged as a human-controlled mechanism but is now commonly completely computer-controlled.[12]

Many different release and anchoring mechanisms for smart capsule drug delivery in the GI tract are actively being researched today. By providing targeted and preventitive treatment, the combination of smart capsule endoscopy and siRNA delivery will change the landscape of IBD treatment.

FUTURE OUTLOOK

As new technologies emerge, an integrated capsule endoscopy and siRNA delivery system can be engineered with increasingly effective imaging systems, release mechanisms, locomotion machinery, dosing regimens, and anchoring systems. For example, artificial intelligence and machine learning are rapidly gaining traction in pharmaceutical and medical applications. They can play crucial roles in the identification of inflammation and the successful delivery of siRNA to that inflamed region. Another promising area for future work is the attachment of IBD-specific biomarkers to the capsule surface for chemical recognition and release of siRNA nanoparticles. Furthermore, the imaging capabilities of existing capsule designs can be improved with the use of blue and green light, which can increase the visibility of inflammation.[13] Many other innovations are in development for nanoparticle-mediated siRNA delivery and capsule endoscopy, and the application of such technologies in an integrated system is key.

This article highlights a promising technology that can change the way Inflammatory Bowel Disease is treated. Current imaging technology can successfully identify inflammation, and current treatments can address active inflammation and manage symptoms. There remains a need for technology that can address the reactive nature and systemic effects of current treatments. The combination of siRNA nanoparticles, which target the root cause of inflammation, and capsule endoscopy, which enables targeted delivery, will be a significant step forward for patient care. ◆

ACKNOWLEDGMENTS

The authors would like to express their gratitude to Dr. Nicholas A. Peppas, whose expertise and guidance have been invaluable throughout the research process. This paper would not have been possible without his support.

REFERENCES

1. Xu, F.; Dahlhamer, J. M.; Zammitti, E. P.; Wheaton, A. G.; Croft, J. B. Health-Risk Behaviors and Chronic Conditions Among Adults with Inflammatory Bowel Disease — United States, 2015 and 2016. Morb. Mortal. Wkly. Rep. 2018, 67 (6), 190–195. https://doi.org/10.15585/mmwr.mm6706a4.
2. Cai, Z.; Wang, S.; Li, J. Treatment of Inflammatory Bowel Disease: A Comprehensive Review. Front. Med. 2021, 8.
3. Diagnosing Inflammatory Bowel Disease. https://nyulangone.org/conditions/inflammatory-bowel-disease/diagnosis (accessed 2023-11-27).
4. Iddan, G.; Meron, G.; Glukhovsky, A.; Swain, P. Wireless Capsule Endoscopy. Nature 2000, 405 (6785), 417–417. https://doi.org/10.1038/35013140.
5. Validation of SmartPill® wireless motility capsule for gastrointestinal transit time: Intra–subject variability, software accuracy and comparison with video capsule endoscopy - Diaz Tartera - 2017 - Neurogastroenterology & Motility - Wiley Online Library. https://onlinelibrary.wiley.com/doi/abs/10.1111/nmo.13107?casa_token=0qYEM6K2xloAAAAA%3APog03mHb3pivCj7Bd267mG7mg4z1A3YE0CZ4BqGhaue_gLMH-8HVkGyeiAsJcxiJX1BW5GVuvpkuSfYI (accessed 2024-03-30).
6. PillCam COLON capsule endoscopy: recent advances and new insights - Samuel N. Adler, Yoav C. Metzger, 2011. https://journals.sagepub.com/doi/10.1177/1756283X11401645 (accessed 2024-03-30).
7. Tokatlian, T.; Segura, T. siRNA Applications in Nanomedicine. WIREs Nanomedicine Nanobiotechnology 2010, 2 (3), 305–315. https://doi.org/10.1002/wnan.81.
8. Mitchell, M. J.; Billingsley, M. M.; Haley, R. M.; Wechsler, M. E.; Peppas, N. A.; Langer, R. Engineering Precision Nanoparticles for Drug Delivery. Nat. Rev. Drug Discov. 2021, 20 (2), 101–124. https://doi.org/10.1038/s41573-020-0090-8.
9. Scott, R.; Enns, R. Advances in Capsule Endoscopy. Gastroenterol. Hepatol. 2015, 11 (9), 612–617.
10. Cortegoso Valdivia, P.; Robertson, A. R.; De Boer, N. K. H.; Marlicz, W.; Koulaouzidis, A. An Overview of Robotic Capsules for Drug Delivery to the Gastrointestinal Tract. J. Clin. Med. 2021, 10 (24), 5791. https://doi.org/10.3390/jcm10245791.
11. Active Capsule System for Multiple Therapeutic Patch Delivery: Preclinical Evaluation | IEEE Conference Publication | IEEE Xplore. https://ieeexplore-ieee-org.ezproxy.lib.utexas.edu/abstract/document/10341491 (accessed 2024-03-20).
12. Slawinski, P. R.; Obstein, K. L.; Valdastri, P. Capsule Endoscopy of the Future: What’s on the Horizon? World J. Gastroenterol. 2015, 21 (37), 10528–10541. https://doi.org/10.3748/wjg.v21.i37.10528.
13. Muto, M.; Horimatsu, T.; Ezoe, Y.; Hori, K.; Yukawa, Y.; Morita, S.; Miyamoto, S.; Chiba, T. Narrow-Band Imaging of the Gastrointestinal Tract. J. Gastroenterol. 2009, 44 (1), 13–25. https://doi.org/10.1007/s00535-008-2291-5.

BIOGRAPHIES

Nila Murali is a Chemical and Biomolecular Engineer from The Georgia Institute of Technology, where she collaborated on research with Dr. Anant Paravastu on the synthesis and modeling of Alzheimer's beta-amyloid self-assemblies. She has previously worked at Somerset Therapeutics, Regeneron Pharmaceuticals, and Bristol Myers Squibb as a Process Development Engineer. Currently, she is working toward her PhD in Molecular Pharmaceutics and Drug Delivery at The University of Texas at Austin, focusing on inhalation drug delivery for chronic lung infection caused by *Pseudomonas Aeruginosa*.

Ravali Bhavaraju is a Biomedical Engineer from The University of Texas at Austin. She has worked in numerous aspects of drug delivery and has done extensive research with Prof. Nicholas A. Peppas in the biomedical engineering and pharmaceutical departments of The University of Texas at Austin. She has previously worked for Eli Lilly and Company and Stryker. Her research focus is on physiologically based pharmacokinetic modeling and drug delivery of siRNA for Inflammatory Bowel Disease.

Leia Jiang is a Biomedical Engineer from The University of Texas at Austin. She is continuing her studies with a PhD in Biomedical Engineering at Carnegie Mellon University, focusing on Tissue Engineering and Regenerative Medicine. She collaborated with Dr. Miguel Flores-Bellver at the University of Colorado School of Medicine on extracellular vesicles for therapeutic delivery in the eye. She also worked with Dr. Tyrone Porter at The University of Texas at Austin, on *in vitro* modeling of the blood-brain barrier.

Why PharmaCircle?

Since 2003, PharmaCircle has been providing clients with the integrated data, powerful analysis tools and industry knowledge needed to solve complex, real world challenges in product development and innovation.

PHARMACIRCLE™

www.pharmacircle.com

Pipeline & Products Intelligence

Business Intelligence & Prospecting Tools

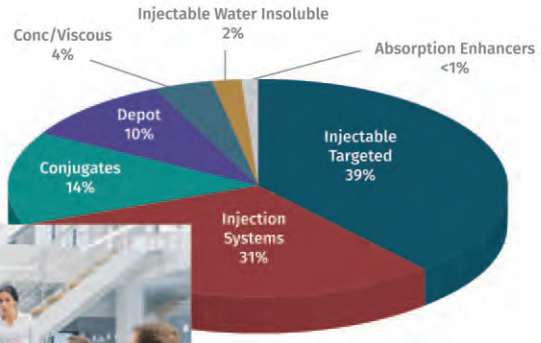
Research & Development Analysis Tools

Regulatory Databases & Documents

View Formulation and Component Details

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



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities

Assess Development Pipelines and The Competitive Landscape

PHARMACIRCLE™

Schedule Your Demo

PharmaCircle serves commercial and emerging stage life sciences companies and suppliers from around the world. See how we can help you.

www.pharmacircle.com

Special Feature

Prefilled Syringes & Parenteral Delivery: Next-Gen Injections Feature Technology & Reconstitution

By: Cindy H. Dubin, Contributor

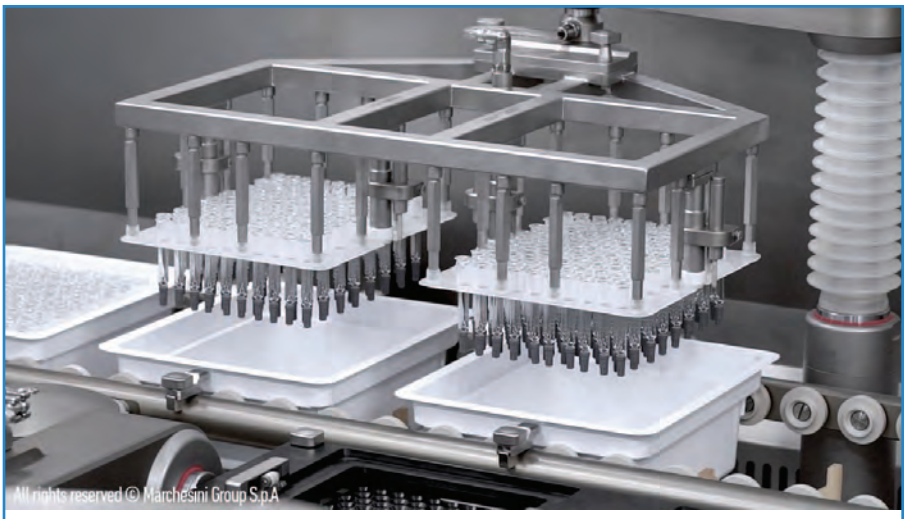
The 2023 winners of the Parenteral Drug Association (PDA) Drug Delivery Innovation Award is a good indication of the current status of the parenteral and prefilled syringe (PFS) sectors and how innovation is moving it forward. The Innovation Award went to Merck KGaA for the Digital Platform for Enhanced Adherence Tracing. The innovation is a secure and scalable ecosystem helping to monitor real-time data received from autoinjectors. With the market for parenteral combination products evolving over the last couple of decades, connecting devices have become almost critical. Wearable technology has become valuable for managing patient conditions, ensuring compliance, and gathering real-time data. Now, the global connected drug delivery device market is predicted to grow 23.4% and reach $25.6 billion by 2030.[1]

Another interesting segment of the market to watch is lyophilized injectables. This segment represents a crucial intersection of innovation, patient care, and market dynamics. Surging demand for more stable and longer-lasting formulations and the rising prevalence of chronic diseases necessitates the development of more effective and convenient drug delivery systems, thus driving demand for lyophilized injectables.[2] In 2022, the market was valued at around $280 billion; by 2032, analysts expect it to soar to $988 billion.[3] Advancements in biotechnology and pharmaceutical manufacturing techniques are enhancing the efficiency and scalability of lyophilization processes, opening new avenues for growth.[2]

In this area, PDA presented the Partnership Innovation Award to Stevanato Group, Bayer US LLC, and Vetter Pharma-Fertigung for the Diluent PFS for reconstitution and administration of a lyophilized biologic. According to PDA, the goals of this partnership were to solve a potential compatibility issue with the diluent PFS and biologic drug product and reduce the gliding forces of the diluent PFS during drug product reconstitution.

Mitsubishi Gas Chemical's OXYCAPT Multilayer Plastic Vial Carbon Dioxide Barrier of OXYCAPT Vial (Mitsubishi Gas Chemical Company, Inc.)

This exclusive, annual *Drug Development & Delivery* report highlights other innovations from key players in parenteral delivery and prefilled syringes, with focuses on: safety; meeting regulatory requirements; cost; fill/finish; and dosing.



Huge investments for the fill and finish of prefilled syringes at Aenova (Photo: Marchesini).

Aenova: Investing in a Comprehensive Fill/Finish Portfolio

Aenova, a leading international CDMO, has a long tradition in sterile manufacturing at its Latina site. Over the past two years, more than $20 million have been invested in Latina to offer customers modern, Annex 1-compliant, aseptic filling technology for sterile dosage forms, especially vials and PFS. This new manufacturing area has already been approved by the Italian authority (AIFA). Aenova is further investing along the entire process of manufacturing infrastructure, analytical capabilities, and cold chain warehouse, offering customers a comprehensive portfolio in the fill/finish area.

"At the Aenova Site Latina, we offer manufacturing services to a global market, with high levels of expertise, for both clinical trials material manufacturing and commercial supply," says Paolo Abbate, Managing Director at Aenova's Latina site. "Our new filling line can support batches from 10L to 1,500L in size, working with both disposable and stainless-steel equipment trains. Our line is a RABS line, enabling increased flexibility and easier process customization."

Technology transfer activities and the PPQ strategy are established in agreement with customers and are fully compliant with cGMP guidelines. Quality control supports in-process control, product release, and stability testing, while also providing a comprehensive service for microbiological and chemical testing.

"Aenova prides itself on its flexibility in finding solutions and has available space for further facility expansion," says Mr. Abbate.

ApiJect: Helping to Open New Markets & Reduce Costs for Injectables

"The market needs an affordable, environmentally sustainable, and easy-to-use prefilled injector that can expand access to safe injections for all people in all markets," says Bo Kowalczyk, Chief Commercial Officer at ApiJect. In addition, there is need for a more efficient and environmentally friendly sterile fill/finish process capable of meeting the demand for prefilled injectables in western markets, yet be cost-effective for global health markets, and scalable to meet the need for surge capacity in times of crisis (like another epidemic/pandemic).

"ApiJect is transforming drug delivery by making it possible for more injectables to reach more markets in a cost-efficient prefilled format," he says.

The ApiJect Prefilled Platform uses a device design and manufacturing process that combines temperature-controlled Blow-Fill-Seal (BFS) aseptic fill/finish with attachable plastic component design. "BFS is an efficient, advanced aseptic process that is highly automated with a compact, simple supply chain, and can scale up to 15 million units per machine per month," says Mr. Kowalczyk. Additionally, ApiJect devices can be equipped with safety features like needle shields and auto-disable mechanisms, as well as single-dose packaging to enhance convenience.

Patient convenience, ease of use, and safety are key benefits of prefilled formats. The need for self-injection is becoming more of a necessity and is not limited to remote patient monitoring. Healthcare systems are striving to reduce costs, resulting in a shift from hospital to clinics, outpatient services, pharmacies, and at-home self-injections. "This trend requires a user-friendly, simple, and uncomplicated device," he says. "And, patients prefer a device that is easy to use and has a straightforward disposal process."

The growing adoption of environmental, social, and governance (ESG) considerations are causing an increased focus on waste management reduction

The Prefilled ApiJect Injector.

and more eco-friendly materials and technologies. He says: "While eco-friendly adoption is important, companies also need to keep affordability, sustainability, and accessibility in mind when evaluating device compliance. The ApiJect Drug Delivery Platform can both deliver on ESG goals while also meeting the world's growing need for safe, injectable formats."

He explains that BFS is eco-friendly due to its reduced material waste, lower energy consumption, reduced carbon footprint, and elimination of terminal sterilization. And when ApiJect converts that BFS container into a prefilled injector, it does so with a manufacturing process that is as price-efficient and scalable as the standard vial-plus-syringe format – with the safety of a prefilled, single-use device, he adds. This technology can allow for a shift from glass vials/PFS to plastic-based prefilled formats, resulting in much less energy for manufacturing, transportation, and incineration.

ApiJect's first prefilled injector made on the Prefilled ApiJect Platform has not yet received regulatory approval; FDA approval for its first combination product is expected in early 2025. "Today, we are working with several pharma partners to achieve global market acceptance via a scalable, cost-effective, prefilled injection device that, when combined with their drug or vaccine, could increase vaccine uptake and meet the requirements of global health authorities and markets," says Mr. Kowalczyk. Key stakeholders from multiple global health markets have been actively engaged and support submission when ready.

Aptar Pharma: Helping Pharma Manufacturers Meet New Annex 1 Requirements

In the pharmaceutical sector, ensuring the safety and effectiveness of injectable medications is of utmost importance. Particulate and microbial contaminations are among the main cause for FDA recalls as they can put patients at risk. The increasing quality expectations of the industry are accompanied by a tightening of regulatory requirements, which intensifies the pressure for manufacturers to guarantee the purity and safety of their drugs. Additionally, the growing focus on biologics and biosimilars within research and development is accompanied by a need to minimize development risk. "Choosing the right partners throughout drug development journeys is crucial to accelerate market access and ensure patient safety," says Estelle Verger, Business Development Senior Manager at Aptar Pharma.

These observations align with the latest update of Annex 1 by the European Medicines Agency's Good Manufacturing Practices (EMA GMP), which emphasizes the criticality of contamination risk mitigation. This update requires manufacturers of sterile products to implement a comprehensive contamination control strategy, not just within their own operations, but also throughout their upstream supply chain.

Aptar Pharma, a leading manufacturer of primary packaging solutions, offers solutions that can help pharma manufacturers meet new Annex 1 requirements and take their contamination control strategy to the next level, she says. "When working with primary packaging components, microbial and particulate contamination could come from the components themselves, their packaging or be accidentally introduced on the filling line during aseptic transfer," Ms. Verger says.

To address the first situation, Aptar Pharma developed PremiumFill®, an improved manufacturing process for elastomeric closure components that leverages robotization and clean rooms to reduce the risk of contamination during production. She explains: "This improved process enables improved specifications on key contamination criteria (i.e., fibers, embedded particles, loose particles, biological contamination) as listed in the Annex 1 revision. PremiumFill components use the same rubber formulations and designs as standard products, allowing manufacturers to easily upgrade their operations, without requiring regulatory reapproval."

As of Annex 1 revision, sterile drug manufacturers must be able to demonstrate and check the sterility of their primary packaging. To answer this need, Aptar Pharma offers Ready-To-Use gamma sterilized vial stoppers and syringe plungers, a validated and market-proven sterilization method offering all the required guarantees and certificates.

"The proprietary process for RTU components demonstrates integrity at the point of use, as required by Annex 1, and avoid the use of Tyvek material, which is a potential source of fiber contamination," she says.

To further minimize risks of introducing extrinsic contaminants during the transfer of components on aseptic filling lines, Annex 1 highly recommends using isolators or RABS. Aptar Pharma aligned with this recommendation by offering components packaged in a large variety of Rapid Transfer Port bags to connect directly to the manufacturers' filling lines,

therefore, helping to limit the risk of accidental contamination.

Ms. Verger adds: "Though the Annex 1 revision imposes stricter guidelines to manufacturers, solutions are already commercially available on the market to help them implement their contamination control strategies, while improving their operational efficiency."

Artcraft Health: Onboarding Technology Prevents User Errors

Artcraft Health is a demonstration and training device company serving the injectables market, where there is an ongoing and critical need to ensure successful patient onboarding for new drug delivery systems. To meet this need, Artcraft Health provides training devices and patient onboarding programs for the full spectrum of injectables — from prefilled syringes and autoinjectors to electromechanical on-body devices. "With expertise in patient-centered engineering and educational design, Artcraft Health focuses on errorless device training for the parenteral drug delivery market," explains Marty Mason, Senior Director of Demonstration and Training Devices, Artcraft Health.

Within this market, a key concern for delivery device development and training is environmental sustainability. As companies aim to reduce their carbon footprint and protect the environment, many are developing methods to either reuse syringes or create eco-friendly disposable syringes. "Reusable prefilled syringes are significantly more expensive than disposable syringes, making cheaper, readily available disposable syringes a strong alternative," he says. "However, strategies that focus on patient training could help ensure prefilled syringes remain cost-effective and compatible with current sustainability goals."

For example, Artcraft Health has developed a device-onboarding technology called accuDemo™ for reusable delivery devices such as prefilled syringes. The accuDemo technology is designed to prevent 100% of user errors in every onboarding session, thereby helping to reduce the cost associated with prefilled syringes and increase the likelihood of compliance with therapy. "As the parenteral market shifts toward connected devices and remote patient monitoring, technologies like this could increase the effectiveness of reusable prefilled syringes and help address the ongoing industry challenge of patient adherence," Mr. Mason says.

The strategic use of technology and training can greatly accelerate the success of parenteral programs. For instance, a pharmaceutical client tasked Artcraft with creating a demonstration device and training program for a cutting-edge on-body injection device that could be programmed to deliver the right dose of medication at a specific time without the need for an in-person visit. Specifically, Artcraft Health had to engineer a demonstration unit that would simulate for patients the full 27-hour drug administration experience in a greatly condensed time frame.

"To achieve this, our team reverse engineered the complex commercial device to create a fully functional, fully reusable demonstration unit that used solid-state electronics instead of liquid to simulate the entire 27-hour drug administration experience in just 3 to 7 minutes," Mr. Mason explains. "The ability to use technology to 'collapse time' and deliver an accurate training experience was critical to the success of this parenteral program."

Although building a demonstration unit is a critical piece of the puzzle, knowing how to simplify and ensure successful patient use is the key to making it effective. For the parenteral market, this is a principle that Artcraft Health calls "Certainty of Use."

"Simplifying complex delivery methods and packaging them into easy-to-understand educational tools and technologies guides patients to comply with dosing and administration for injectables," Mr. Mason says. "Taking a truly ho-

AccuDemo™ is designed to prevent 100% of user errors in every onboarding session.

listic approach to demonstration device development and training not only provides the highest quality training but also aids in the launch strategy for commercial teams in the parenteral market."

BD Medical-Pharmaceutical Systems: Integrating Plunger Stoppers Into Combination Products

BD Medical-Pharmaceutical Systems provides a broad portfolio of parenteral drug delivery systems, including glass and plastic prefillable syringes, safety and shielding systems, and advanced drug delivery systems including pens, autoinjectors, wearable and on-body injectors. The company also offers a range of combination product development testing services.

One of BD's latest innovations is the expansion of the BD SCF™ PremiumCoat® plunger stoppers to include 1-3mL sizes, in addition to the 1mL format that is already available. "This allows us to strengthen our BD Neopak™ Glass Prefillable syringe product portfolio by offering a differentiated system solution with the prefillable syringe, plus the stopper, which addresses the needs of pharmaceutical and biotech companies for the development of complex biologics in larger dose volumes," says Benjamin Roussel Senior Marketing Manager, BD Medical-Pharmaceutical Systems.

BD SCF PremiumCoat supports a higher predictable system injection performance due to reduced glide force and glide force variability (by up to 51% and 73% respectively for the 1-3mL). This helps to reduce injection time and reduce injection time variability.

In addition, BD SCF PremiumCoat is designed to enable improved container closure integrity with a three-rib design and BD guarantees that all stopper ribs touch inside of the prefilled syringe barrel.

BD SCF™ PremiumCoat® 1-3mL with BD Neopak™ Glass Prefillable Syringe.

BD also offers a robust system data package to support the integration of the BD SCF PremiumCoat into combination products, such as with a prefillable syringe with or without an autoinjector or safety device. Mr. Roussel says: "This ensures higher PFS system functionality and to get timely availability of the needed information for design, quality assurance or regulatory purpose across the system. Ultimately, it is a way to secure drug-combination performance and, therefore, to support pharmaceutical and biotech companies to deliver their drugs on time."

As BD looks toward future innovations, sustainability criteria has become increasingly important. When deciding which initiatives to launch, BD Medical-Pharmaceutical Systems uses a tool producing science-based results and Environmental Footprint (EF) data – the product lifecycle assessment (LCA). The study was subcontracted to ERM4 on BD prefilled syringes systems to identify hotspots throughout the full combination product lifecycle end-to-end (including device manufacturing, filling, usage, and end-of-life, but excluding drug manufacturing). The analysis covers the direct and indirect emissions of BD suppliers, manufacturing plants, and customers, and provides a global overview on where efforts should be made all along the PFS.

"The LCA identified priority areas and what we could do in-house with our suppliers and customers," he explains. Based on these results, the team developed a road map towards real-world sustainability improvements, such as regionalizing suppliers to limit air freight; replicating manufacturing on a global scale; increasing the use of renewable energy; reducing energy consumption and waste; introducing recycled content; and integrating ecodesign into new product development and continuous improvement.

"Sustainability criteria has become instrumental in the portfolio management of the pharmaceutical industry to ensure that new product development and the management of legacy products' lifecycle are aligned with market needs, thus ensuring long-term commercial success," Mr. Roussel says.

Credence: Addressing At-Home Administration & Sustainability

Treatment in certain therapeutic areas like chronic illness and diabetes management/weight loss management involves frequent dosing regimen – some of them daily, weekly or monthly. This implies use of multiple injectable devices by a patient

Credence's Companion® with proprietary integrated automatic needle retraction technology.

repetitively over a short- or long-term basis, depending on the disease state. Therefore, an enormous amount of used plastic needs to be incinerated or moved to landfill, which leads to environmental challenges.

"With the industry trend of injectable delivery moving from formal healthcare settings to administration-at-home and heightened sustainability imperatives, injectable device aspects like simplicity, usability, reusability, reliability, and sustainability are becoming key enabling product differentiators in the crowded device market," says Laxman Halleppanavar, Head of Portfolio Strategy and Management at Credence.

Credence's Companion® and Dual Chamber™ Syringe Systems both include proprietary integrated automatic needle retraction technology that provides inherent usability enhancements like end-of-dose and safety cues, reduced RNS removal force, and elimination of premature safety activation "by design." He says: "These injection systems offer superior environmental footprint via reduced quantity of plastic, the use of high quality environmental-friendly plastics, reduced weight, and reduced footprint. The inherent device design allows for a range of customization possibilities to suit various drug characteristics. This is enabling our pharma partners to open new drug candidates that are difficult to co-formulate, promoting simplified and faster combination product development cycles."

Observing the trends like administration-at-home and heightened sustainability targets, Credence identified an opportunity to maximize the sustainability advantage of its injection systems by enabling use of its delivery systems with a platform of compatible reusable autoinjectors. Credence is collaborating with various industry players with the goal of providing substantial reduction in Total Cost of Ownership and improvement to sustainability profiles for its customers and across the entire supply chain – all the way to end users, says Mr. Halleppanavar.

Curia: Supporting Clients Through Scale-Up & Manufacturing

Curia provides end-to-end services for developing, scaling, and commercializing parenteral therapeutics and vaccines. Its two clinical manufacturing facilities are outfitted to support formulation, lyophilization, and analytical development needs across both large- and small-molecule modalities, as well as clinical batch manufacturing into vials, prefilled syringes, and cartridges. Curia's commercial manufacturing sites also offer capabilities and capacity to scale-up and validate commercial manufacturing processes into all three formats utilizing in-process engineering to support clients' product needs. The sites have supported numerous commercial launches and hold strong regulatory track records.

"As a product progresses through clinical trials, more often than not, drug development companies will focus on manufacture of their product into a vial format given the lower cost," says Ronald A. Aungst Jr., Vice President, Business Unit Operations, Drug Product at Curia. "These drug products are then administered via sterile disposable syringes to patients, however, in latter stages of clinical trials, many companies will focus on opportunities to move to a prefilled syringe or cartridge (for autoinjectors) as the primary packaging of the drug products due to the ease of use for administration by the end user. This aids in the clinician's and/or patient's ability to safely administer therapies/vaccines with little need for manipulation of the product."

Curia has supported several clinical programs that ultimately have resulted in a PFS format. "However, as one example, due to the highly viscous nature of one of our client's products, even the early-phase clinical trial materials were manufactured into a PFS out of necessity," says Mr. Aungst. "The viscosity of this extended-release product made it nearly impossible to extract the material sufficiently into a disposable syringe from a vial for administration in early-phase clinical trials."

Matthew Codd, Vice President of Sales, Drug Product at Curia, says: "Successfully developing the process for filling the product into a PFS became essential. Curia's network of facilities across its business platform continue to support the suc-

cessful commercialization of this very impactful product for our client's patients."

Gerresheimer: Customizable RTF Syringes Meet Customers' Needs

Gerresheimer specializes in manufacturing primary packaging such as prefillable syringes tailored to the injectables/parenteral market. The company offers a diverse range of glass and Cyclic Olefin Polymer (COP) products designed to address specific needs within the healthcare industry. If a particular product is not part of its existing portfolio, customizations and product developments are offered to meet a client's unique requirements.

One example of Gerresheimer's product/service benefiting a pharmaceutical client involved the development of a customized ready-to-fill syringe for specific applications. "Additionally, we assisted in refining and optimizing manufacturing processes, enabling the establishment of commercial production across multiple international locations," says Stefan Verheyden, Global Vice President Sales, Pharma & Biopharma Solutions, Injectables, Gerresheimer. "This comprehensive approach ensured the successful implementation of their prefilled syringe/parenteral program, enhancing both efficiency and market competitiveness."

Prefilled syringes may be a bit more expensive than vials and disposable syringe solutions, but they offer a range of benefits, such as less overfilling requirements, reduced packaging materials, and minimized risks of handling errors during administration. "This makes prefilled syringes for expensive drugs a more economically reasonable packaging choice," says Maximilian Vogl, Head of Global Product Management, Syringes, Gerresheimer. "This shift from vial to syringe translates into enhanced efficiency and safety, contributing to overall cost-effectiveness in the long run."

Lifecore Biomedical: Helping Clients Evolve From Syringe to Autoinjector

To address increased capacity needs, safety requirements, and industry trends, Lifecore Biomedical is working with well-established vendors to leverage modern technologies. Currently, the company is expanding fill/finish capacity with recent investments in two new Groninger filling systems with SKAN isolators.

"With GMP-readiness of one system in the coming months, and installation of the second system thereafter, customers will benefit from the innovative technology for vial, syringe, and cartridge programs," says Jessica Miller, Director of Business Development for Lifecore.

In addition to safety improvements from isolator containment, these systems have capabilities such as independent fill-head operation, enabling in-process control (IPC) and adjustment of fill volume for each individual unit of product. Plus, the new technology incorporates a variety of mechanisms that enable higher yields, maximizing return on investment of precious, often high-value, APIs.

Beyond fill/finish equipment, Lifecore is responding to industry trends influenced by patients. "Many of the new syringe programs involve an eventual path toward an autoinjector format," comments Ms. Miller. "Autoinjectors are growing due to increases in chronic diseases and the desire for greater patient convenience, as well as benefits related to drug compliance (i.e., better dosing control). Also, from a payer perspective, self-administration removes costs associated with injection in a healthcare setting."

To help create awareness of high-quality options for our clients, Lifecore has entered into a non-exclusive co-marketing partnership agreement with SHL Medical. SHL Medical is a leader in the design, development, and manufacture of autoinjectors, pen injectors, and drug delivery devices. Ms. Miller says: "The relationship with SHL gives us direct access to experts who can advise on important considerations when a client wants to move from a vial or syringe to a self-injection system. Bringing in that expertise at the start helps set up the program for success in areas like sourcing and analytical testing, which can differ significantly compared to programs without autoinjectors."

Mitsubishi Gas Chemical Company: 3-Layer Vial Protects Biologics, Gene/Cell Therapies

Mitsubishi Gas Chemical Company, Inc. provides multilayer plastic vials called OXYCAPT for biologics and gene/cell therapies stored at low or ultralow temperature. OXYCAPT consists of three layers: the drug contact layer; an outer layer made of COP; and an oxygen barrier layer made of a novel polyester.

"OXYCAPT can offer a number of advantageous qualities as a primary drug container, such as excellent oxygen, carbon dioxide and ultraviolet (UV) light barrier, strong water vapor barrier, very low extractables, high pH stability, low protein adsorption and aggregation, high transparency, high break resistance, lightweight, etc.," says Tomohiro Suzuki, Associate General Manager, New Business Development Department, Mitsubishi Gas Chemical Company, Inc.

He adds that OXYCAPT has excellent CO_2 and O_2 barrier, which contributes to stabilizing the gene and cell therapies. "These drugs are mainly stored and transported with dry ice emitting CO_2 gasses, so a CO_2 barrier is necessary to prevent CO_2 ingress into the vials," says Mr. Suzuki. "According to our internal study, CO_2 barrier of OXYCAPT is about 20 times better than the COPs. Also, no CO_2 permeation was observed at container closure integrity testing at -75°C."

Safe'n'Sound 1mL (Nemera)

Safe'n'Sound 2.25mL (Nemera)

Nemera: Platforms Enhance Patient Safety

Nemera's products offer a comprehensive solution for the evolving demands of the injectables market, addressing the critical needs of increasing biologics and biosimilars pipelines, mainly used in the treatment of chronic diseases and the growing trend of home and self-administration of biologics bolus injections.

"Our injectables platform, ranging from Safe'n'Sound®, a safety system device for prefilled syringes, to Symbioze™, our reusable large-volume body injector, are all designed to enhance patient safety and support them along their treatment journey," says Cécile Gross, Marketing Category Manager – Parenteral, Nemera. "To best meet market and patients' needs, Nemera offers a range of services from research to define design customization requirements, and human factor study to drug-device assembly."

Indeed, the increase in remote patient monitoring has positively influenced the demand for self-injection, particularly autoinjectors, in several key ways. She says: "The development of remote monitoring has had a main impact on patients' quality of life, allowing them to manage their conditions more effectively from the comfort of their homes."

In turn, this has reduced the burden of disease, particularly in the case of chronic or life-long diseases, while playing a role in reassuring patients when administering medication in the homecare setting. To facilitate remote monitoring, the development of connectivity devices allows close monitoring of patient adherence and compliance for their treatments and to adjust injection devices, offering more tailored and effective treatment to patients.

Ms. Gross says that while it is important to consider the cost difference between prefilled syringes and disposable syringes, noting that the higher cost of a PFS is justified by their different use. "Prefilled syringes can accommodate biologics and complex formulations, particularly in the treatment of chronic or severe diseases

as in oncology and immunology therapeutic areas," she says. "In contrast, disposable syringes may not be suitable for such applications due to their limitations in terms of drug compatibility or interaction that may affect the stability and efficacy of sensitive drugs."

In addition, she says PFS offer advantages in terms of patient safety, enabling integration into the reusable and safety devices that are specifically and ergonomically designed for self-injection. "As a result, while disposable syringes may be a less expensive alternative, they may not always be the most appropriate or effective option for administering certain medications, particularly those requiring special formulations or safe home administration," she says.

Noxilizer, Inc.: NO_2 Sterilization Offers a Variety of Advantages to Prefilled Syringes

Noxilizer offers nitrogen dioxide (NO_2) sterilization to pharmaceutical, biotech, and medical device companies. NO_2 is a leading alternative to sterilization methods, like ethylene oxide (EO) and vaporized hydrogen dioxide (VHP). Companies choose NO_2 to sterilize their single-use prefilled syringes or delivery systems because of the ultra-low temperature (10°C-30°C) sterilization process that may extend shelf life, low to no ingress maintaining drug integrity, minimal vacuum option to prevent/minimize stopper movement, and simple and safe to bring in house to reduce total manufacturing time, explains Maura O. Kahn, Senior Vice President, Commercial, Noxilizer, Inc. Noxilizer customers have purchased sterilizers and installed them in their own manufacturing facility or installed at their contract manufacturing organization (CMO). There is also contract sterilization available in the US and Europe.

Noxilizer's 1-Pallet NO_2 Production Sterilizer

As Noxilizer's customers consider a variety of prefilled syringe designs, she says there has been continued growth of polymer syringes. As an example, one global biotech company approached Noxilizer to evaluate three different syringe designs (polymer and glass syringe barrels). At the same time, the biotech company was evaluating other sterilization methods with these designs. The company's first choice was the polymer syringe. Ms. Kahn says this was due to the favorable benefits that the polymer syringe brought to the drug product, patient, manufacturing, etc.

"Noxilizer conducted extensive feasibility testing on the designs, as well as provided the company with advice on backstop design, sterile barrier packaging, and process challenge devices," she says. "The benefits of NO_2 sterilization (specifically the ultra-low temperature sterilization process and maintenance of drug integrity due to low/no residuals) enabled the biotech company to move forward with their first choice, the polymer syringe."

PCI: Comprehensive Injectable Drug Delivery Solutions

PCI is a leading CDMO, providing integrated end-to-end sterile injectable drug development, manufacturing, device assembly, and advanced packaging solutions to increase product speed to market and opportunities for commercial success. Spanning the cycle from development to commercialization, PCI offer comprehensive injectable drug delivery solutions for large and small molecule life-changing therapies.

"Our integrated sterile drug manufacturing and injectable packaging solutions support biopharma companies in optimizing dosing and providing convenient, easy-to-use patient-centric therapies to patients," says Justin Schroeder, Vice President, Global Technical Services, PCI. "Our consultative approach and extensive experience provides a flexible and agile solution for our clients."

With remote patient monitoring through telehealth appointments or digital platforms, healthcare providers can remotely monitor patients' health conditions and adjust treatment plans as needed, removing the need for frequent patient visits to healthcare facilities. Mr. Schroeder says:

"These user-friendly drug-device combination products have revolutionized drug delivery, offering patients greater convenience, accuracy, and control over their treatment regimens. This accessibility contributes to the increased demand for autoinjectors."

As a device agnostic final assembly and packaging solution provider, PCI works with its clients to guide their choice of packaging utilizing state-of-the-art software to analyze sustainable factors down to individual components. By having a complete view of which specific elements of packaging are contributing most to a package's carbon footprint, clients can make more informed decisions.

"Sometimes small changes can have a compounding impact," says Mr. Schroeder. "For example, this software revealed that when changing from a plastic tray to a molded, paper fiber tray, global warming impact is reduced by 50%. Together with our clients, PCI work to develop the most appropriate solution that aligns to their ESG goals and budget."

With the industry evaluating ways to enable a closed loop system whereby they capture and recover used post-consumer devices, this likely will be a more impactful and a more immediate solution than the industry developing a delivery form made of recyclable materials, which then needs to be separated downstream as medical waste, he says.

"On the other hand, disposable syringes contribute to plastic waste, which has become a significant environmental concern," he says. "In response, manufacturers are exploring ways to develop disposable syringes using biodegradable or recyclable materials to minimize their environmental footprint. Additionally, efforts are underway to optimize packaging and disposal methods to further reduce environmental impact."

Prefilled syringes as a standalone configuration provide efficiency, eliminating the waste caused by overfilling vials. The design, components (including stopper), and functionality improve dosing control, thereby reducing drug product waste.

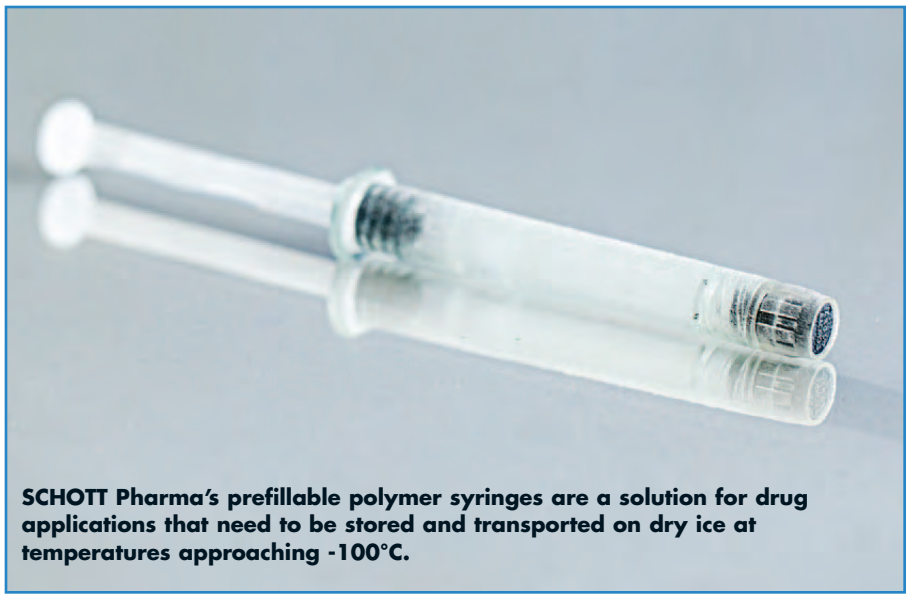
Disposable syringes may be cheaper, he adds, but cost is only one consideration and the flexibility of a prefilled syringe as a delivery format alongside benefits of patient-centricity compared to traditional vial and syringe drug delivery options, are driving significant growth of prefilled syringe usage. A prefilled syringe in an autoinjector provides a patient-centric device that supports a high acceptance of self-administration. While the unit cost may be higher, self-administration eliminates the cost of administration within a clinical setting, and removing the need to go to clinic also helps reduce carbon footprint.

"Providing a balance of accessibility/self-administration without the cost of an autoinjector, advances in needle safety devices such as needle guarding caps and retractable needle systems also aid in reducing stick injuries to those administering vaccines and other injectable treatments," says Mr. Schroeder. "Ultimately, safety, ease of use, and a positive patient experience leads to better adherence and better health outcomes, which in the long run leads to a more effective overall healthcare spend."

SCHOTT Pharma: Providing Products That Meet Myriad Industry Trends

As a drug containment and delivery system provider, SCHOTT Pharma is a one-stop-shop for pharma companies, CDMOs, and start-ups. Its portfolio includes prefillable polymer and glass syringes, cartridges, vials, and ampoules, and functional services.

Tom van Ginneken, Head of Product Management Polymer Solutions at SCHOTT Pharma, explains that the company's products ensure that medications reach the patient in a safe and timely manner, and thereby address major pharma trends, such as GLP-1, ADCs, mRNA, the shift from hospital to homecare, the shift from intravenous to subcutaneous, as well as the manufacturing transformation of pharma companies making use of ready-to-use products.



SCHOTT Pharma's prefillable polymer syringes are a solution for drug applications that need to be stored and transported on dry ice at temperatures approaching -100°C.

"We see a change in drug formulation that results in the route of administration shifting from intravenous to subcutaneous," he says. "This allows for patients to self-inject medications in the comfort of their home. This trend is driven by pharma companies that are manufacturing medications for chronic and lifestyle diseases and try to make the treatment as comfortable for patients as possible."

He adds that the drug delivery process needs to be as uncomplicated as possible with very few manual steps to ensure that the drug is administered safely and in the right dosage. This is where prefillable containers, such as syringes, come into play as they are prefilled with the exact drug dosage. SCHOTT Pharma supports several such products on the market today, such as autoinjectors with prefillable glass syringes (for small volumes of 0-3mL), wearable devices equipped with prefillable glass syringes or cartridges (for medium volumes of 3-10mL) or larger homecare infusion pumps combined with prefillable polymer syringes (for large volumes of 10-50mL).

"Prefillable syringes actually offer various advantages over disposable options," says Mr. van Ginneken. "These include a longer shelf life, safer and easier drug administration, the easier option for high-speed filling of medications, and no need for drug preparation steps, which results in lower risk of dosing errors, contamination or infections. On top of that, the total cost of ownership is lower compared to disposable options, making prefillable syringes a preferred choice to ensure a safe and easy drug administration."

One such example is the SCHOTT TOPPAC® freeze prefillable polymer syringe, which was designed to meet the growing needs of drugs that are stored and transported at low temperatures. The syringes can withstand extreme temperatures without compromising structural integrity or drug stability.

Scientist working in Selkirk Pharma's new APS-qualified manufacturing facility.

Selkirk Pharma: New Fill/Finish Facility Has Purpose-Built Design

US-based manufacturing is critical to alleviate growing demands and capacity constraints within the fill/finish industry. Recent acquisitions will likely continue to amplify those constraints until new reliable capacity becomes available. Selkirk Pharma is a new fill/finish facility providing state-of-the-art capacity. Its purpose-built design includes isolator technology, high-yield filling, software controlled unidirectional flow, and investment in Pharma 4.0 (digitization of operations) as critical technologies for best-in-class operations.

"We see investment in Annex 1-compliant technology and systems as a requirement for future production and a focus of pharmaceutical companies," says Tony Murray, Director, Commercial Operations, Selkirk Pharma. "Implementation of software-controlled systems for unidirectional flow prevents cross-contamination and is critical for Annex 1 compliance within a multi-product manufacturing facility. A comprehensive Pharma 4.0 strategy and computer system assurance approach is essential to ensure data integrity." Additionally, Selkirk has high-yield vial filling capability available for both clinical trial and commercial biologic products and has invested in two new syringe lines to support growing demand for syringe capacity.

He says the market for prefilled syringes and cartridge drug delivery looks very strong and is expected to grow. Self-administration and ease of use of administration in healthcare settings continue to drive the injectable drug market. Chronic conditions requiring regular administration for health issues including diabetes, heart disease, and cancer are at the forefront of the shift. In addition, simplification of delivery and increased safety moving from a multi-step administration to a one-step delivery, is preferred. "Every indication is that this trend will continue as more biologics are considering the use of prefilled syringe and cartridge platforms," Mr. Murray says.

Prefilled syringe manufacturing and packaging operations at Simtra's Bloomington, Indiana facility.

Simtra BioPharma: Committed to PFS Capacity

Simtra BioPharma Solutions (Simtra) is an independent CDMO specializing in partnering with leading pharmaceutical and biotech firms on injectable drug products. Simtra offers a wide range of manufacturing options for syringe sizes of 0.5–20mL. Its capabilities include rotary piston and peristaltic pump filling, insertion-rod stoppering, excess time-delay function and aseptic formulation.

"Simtra has experience with many different molecule types, such as expertise helping clients select the right container for their product and manufacture it efficiently to meet the demands of the market," says Benoite Angeline, Vice President, Head of Marketing at Simtra.

The COVID pandemic has accelerated market demand for self-treatment and remote physician consultations, with many patients now more willing to treat themselves and manage their conditions with fewer face-to-face interactions with healthcare professionals, she says.

"As prefilled syringes are ready to use and no manipulation is needed, they are the favored container system for self-administered drugs – not just for diabetes or weight loss, but also for asthma, migraine, multiple sclerosis, arthritis, osteoporosis, sexual dysfunction, and fertility treatments," says Ms. Angeline. "It's a big win for healthcare systems as patients don't need to go to a clinic or ask the pharmacy to reconstitute the drug. A PFS may be more expensive in terms of pricing, but significant savings can be made through eliminating the cost of healthcare overhead, whether that involves a clinic or a pharmacist, or having a nurse administer the product."

Simtra is making significant investments in increasing its PFS capacity. For example, the company has added a new high-speed syringe line at its Halle/Westfalen, Germany facility, which will be cGMP-ready in Q1 2025. It also recently announced a $250+ million investment to expand its sterile fill/finish manufacturing site in Bloomington, Indiana. A new, state-of-the-art 150,000-sq. ft. building will be constructed to house two high-speed automated isolator syringe fill lines and a new high-speed isolator vial line equipped with three 30-sq. meter lyophilizers. Each process suite in the new building will be fitted with dedicated formulation/compounding rooms.

Singota Solutions: PFS Are Low-Cost, Dose-Accurate Solutions

Singota Solutions is a US-based CDMO specializing in formulation development and aseptic fill/finish for injectable biotech projects through the development

Singota Solutions is a CDMO located in Bloomington, Indiana, focused on getting products to patients faster by being agile, accountable, and transparent.

and clinical-stage process. Singota utilizes state-of-the-art robotic aseptic filling technology operating within a completely gloveless work cell, ensuring highly repeatable and precise fills for small-batch manufacturing, ideal for the production of preclinical and clinical injectable products in prefilled syringe, vial, and cartridge formats with minimized line losses, explains Will Powers, Senior Director Business Development, Singota Solutions. The company works with proteins, biosimilars, peptides, oligonucleotides, other biologics, and small molecules, and has extended its support beyond manufacturing, offering stability studies, finishing (labeling and kitting), supply chain (storage and distribution), as well as transportation engineering and testing services.

Singota's development and manufacturing services have assisted several clients in their product development pipelines. Mr. Powers describes how Singota played a significant role for one of its clients in the development of an injectable peptide drug using a PFS format with indications for hematologic and various blood disorders. "Over a multi-year period, Singota provided formulation and analytical development and stability studies for multiple concentrations, placebo formulation, and engineering and clinical batches for Phases I, II, and III clinical trials for both US and European theaters," he says. "Singota also conducted process studies for lyophilization parameters. The product is currently in Phase III trials."

This case study illustrates the growing demand for PFS. There is also increasing demand for patient monitoring. Mr. Powers says self-injectable devices lower the cost of administration (no need for a clinician) and a use of a PFS or similar cartridge can facilitate the reality of an autoinjector. The injector can be fitted with data collection capabilities, and when coupled with WiFi, can be transmitted and then monitored by remote healthcare professionals.

The Alba® syringe – solution to silicone challenges (Stevanato Group)

"Technology advancements in parenteral presentations over the years have been driven by the need for improvements in quality, convenience, cost of administration, and data gathering," he says. "The benefits of using PFS are numerous. In the clinic, this format allows efficient, reliable, convenient methods for administration."

He adds that PFS eliminates the need to transfer product from a vial to a syringe, which reduces costs (no additional handling and disposal of a second container). "While the prefilled syringes themselves might appear to be a costly material item on their own, they provide a number of downstream cost saving, product quality, safety, efficiency and reliability benefits in providing an important means of administration to improve the lives of patients."

Finally, PFS reduces chances for dosing errors. Manufacturing of the PFS products ensures a sterile product and uniformity of the dose, and dosing errors are eliminated, he says.

Stevanto Group: Range of Integrated Solutions for Faster Market Entry

The growth of biologics is driving the need for new solutions in terms of primary containers, delivery devices, and technologies to rise to the challenge of critical issues such as protein aggregation, inorganic extractables, underdosing, and delamination. This is why Stevanato Group has developed the Alba® prefilled syringe

platform for high-value drugs. According to Enrico Barichello, Product Manager for the Syringe Platform at Stevanto Group, the Alba PFS significantly reduces development time, time to market, and the quality costs associated with any wastage of the drug product. "Alba is a breakthrough solution for silicone challenges, achieving minimized particle release and optimal drug product stability," he says. "It is designed for sensitive biologics – employing a plasma treatment on a standard silicone coating to create a barrier that ensures exceptional stability and resistance over time."

Another rapidly growing area in the healthcare industry is GLP-1 drugs, which are transforming the treatment of diabetes and obesity. A reliable container supply, smooth operation, and safe and easy self-administration are crucial for these new drugs, so Stevanato Group has developed the Nexa® high-performance syringe system. Mr. Barichello says: "Nexa syringes are optimized for integration in autoinjectors and give consistent gliding and injection force, with ultra-low tungsten and glue residuals, and enhanced cosmetic quality."

Additionally, the Aidaptus® autoinjector, a two-step, single-use autoinjector with a versatile design, can accommodate both 1mL and 2.25mL prefilled syringes in the same base device – so injections can be daily, weekly, monthly, or quarterly. "Aidaptus is at the forefront of bringing self-administration therapies into patients' homes due to its unique user-friendly and versatile features, making it ideal for GLP-1 and biologics," says Adam Stops, Head of Product Management for Drug Delivery Systems, Stevanato Group.

Innovation in moving therapy from hospital to home care is crucial to address the human and financial burdens of managing chronic conditions. Drug delivery systems play a crucial role by enabling complex therapies to be self-administered in a user-friendly way, in a home environment. "Stevanato Group offers innovative user-friendly devices that help ensure patients receive an accurate dose each and every time with minimal inconvenience," he says. Moreover, he says all devices are designed to minimize user steps and improve the overall patient experience. Each therapy requires a unique solution, which is why the company offers the Alina® pen injector, the Aidaptus autoinjector, and the Vertiva™ on-body delivery system platform.

"Stevanato Group offers a range of optional integrated solutions, including device customization, drug containment solutions, analytical services, and equipment for final assembly and packaging – offering an unprecedented set of integrated solutions for faster time to market and reduced total cost of ownership," he says. "Our unique approach as a one-stop-shop provider means it can cover the entire product lifecycle, from concept definition to industrial delivery and final packaging."

Ypsomed: Developing Next-Generation Pens & Autoinjectors

Ypsomed's comprehensive pen and autoinjector platform portfolio, including UnoPen and YpsoMate, is positioned to support the burgeoning demand for peptide hormones for treating Type 2 diabetes (T2D) and obesity. Ypsomed is building its global manufacturing footprint in Switzerland, Germany, and China, and manufacturing options in the US are currently being assessed. "Ypsomed has ongoing development projects based on UnoPen and YpsoMate with a range of companies active in the peptide hormone space and is developing next-generation pens and autoinjectors to better serve the needs of T2D and obesity patients," says Ian Thompson, Vice President, Account & Business Development, Ypsomed Delivery Systems.

Ypsomed's UnoPen and YpsoMate serve the GLP-1 market.

Disposable or prefilled pens and autoinjectors are still the devices of choice,

ensuring easy-to-use and safe self-injections. He says: "The huge demand for GLP-1 drugs for treating T2D and obesity, which are injected weekly, is increasing demand for both pens and autoinjectors. If the drug can be formulated in a pen containing four doses, the number of devices required per patient annually can be reduced significantly compared to single-use autoinjectors."

A pen injector design by Springboard, a Sanner Group Company.

Sanner Group: Finding Solutions Where Others Have Not

Springboard Pro provides device design and development expertise from new requirements to approved products for its parent company, Sanner GmbH, or to a third-party for manufacture. Sanner provides state-of-the-art primary syringe and drug container manufacturing, secondary packaging for autoinjectors, pen injectors, pumps, inhalers, and other devices, incorporating electronics, and offers sterilization concepts and box-built-logistic services. Sanner Group has developed devices from initial brief to manufacture, including projects that have faltered with other companies.

"Customers regularly ask us for help where their drug interacted with the syringe in an unacceptable way," explains Tom Oakley, Vice President of Design & Development, Springboard Pro Ltd. "For example, when the force required to complete an injection could be too high or too variable, or when the plunger exhibits "stick slip" where the injection is far from constant or stops entirely, or the drug could be damaged by its interaction with the syringe, needle, or plunger. Skilled engineers and scientists have been able to establish the root cause of the issues and work out robust solutions."

Demand for self-injection is driven by increased patient convenience through at-home administration, improved adherence by missing fewer appointments, reduced healthcare professionals' time, cost, and not needing facilities. This potentially reduces environmental impact by removing the need for patients to travel.

Additionally, disposing of an autoinjector has significant environmental impact and the options for disassembly and recycling are limited due to contamination. "But, the environmental impact of disposable emergency autoinjectors can be justified by preventing loss of life, and should be offset against the environmental impact of patients travelling to receive injections," he says. "Nevertheless, reusable autoinjectors have gained renewed interest as a way of minimizing environmental impact, and can incorporate disposable subassemblies containing the syringe and needle, but are largely reusable. They tend to require more user steps and be more expensive than disposables, and have a higher initial environmental impact. A reusable device has more scope for additional features such as electronics and connectivity, although these bring their own environmental burden."

He adds that modern disposable autoinjectors are easy to use and minimize administration errors. But, there may be some additional costs reflected in regulatory, quality, and development. "Factors such as sterilization, documentation, and high capital manufacturing lines are not discernable in the final product, but prefilled syringes need specific raw materials of extremely high purity, which are relatively expensive, and exquisite quality assurance," says Mr. Oakley. "A developer may also need to make significant i nvestments to perform necessary leachables and extractables and drug stability testing."

Novocol Pharma: Supporting Fill/Finish Demand for GLP1-RA Cartridge Injectables

Novocol Pharma is a CDMO specializing in sterile cartridge fill/finish, and supports both clinical phase and commercial customers with turnkey services from product development, tech transfer, fill/finish to final device assembly. In addition, through its Duoject Medical Systems device group, Novocol Pharma offers drug delivery design services and drug delivery solutions

including a portfolio of reconstitution, injection, and safety systems.

"Self-administration of injectable drug products via pen injector, autoinjector or prefilled syringe continues to be a growing market trend due to the prevalence of chronic diseases, advancing drug delivery innovations and new product development with the intention of reducing healthcare burden and improving patient convenience," says Eric Lee, Director, Business Development, Novocol Pharma. "This demand is being propelled by the recent boom in demand for GLP-1 RA weight-loss and diabetes treatments."

Novocol recently completed the installation of a new high speed aseptic cartridge filling line that is well-suited to produce GLP-1 RA drug products, which are commonly filled aseptically in 3mL glass cartridges and then assembled into a pen injector device. This new installation will provide additional capacity of over 50 million units to Novocol's existing cartridge manufacturing facility.

In addition, solutions from Duoject align with this growing trend of patient-centric drug delivery and reconstitution systems. The commercially marketed PenPrep EVO device, a cartridge-based reconstitution system, addresses administration challenges (including multiple steps and needlestick injuries) for lyophilized drug products that are typically supplied in a standard glass vial and allows for the patient to self-administer the admixture using commercially available cartridge-based pen injector devices.

"Duoject also supports customers with the design and development of all-in-one reconstitution and drug delivery systems to further simplify the patient user experience," says Mr. Lee. "These novel technologies use standard commercially available vials and cartridges without relying on specialty components such as dual chamber cartridges and syringes where supply and manufacturing capacity may be constrained." ◆

References

1. Connected drug delivery device development, by Michael Earl, Today's Medical Developments, Sept. 2023, https://www.todaysmedicaldevelopments.com/article/connected-drug-delivery-device-development-wearable-medical-manufacturing/.
2. Lyophilized Injectable Drugs Market: Charting Growth to 2032, by Ojas Panse, Apr. 17, 2024, https://www.linkedin.com/pulse/lyophilized-injectable-drugs-market-charting-growth-2032-ojas-panse-vaxhf/.
3. Lyophilized Injectable Drugs Market Size Global Forecast 2023-2032, Global Market Insights, July 2023, https://www.gminsights.com/industry-analysis/lyophilized-injectable-drugs-market.

SUPPLY CHAIN SOLUTIONS

From Lab to Life: Strategies for Unwavering Resilience in the Clinical Supply Chain

By: Nina Vas

INTRODUCTION

In today's complex and interconnected environment, the importance of a reliable supply chain has never been greater. Specialty supply chain companies are expanding healthcare's reach globally by investing in strategies that enhance supply chain resiliency, thereby delivering essential services where they are needed most.

As new innovative medical technologies and time-sensitive therapies continuously emerge, the effectiveness of logistics, storage, and distribution solutions are pivotal in disease prevention, treatment, and management. Recent years have tested the resilience of the pharmaceutical supply chain, highlighting its essential role in ensuring seamless drug delivery from manufacturer to patient. Despite disruptions, these supply chains have shown remarkable adaptability, innovating to enhance the transport of critical shipments and advanced therapies. Such challenges underscore the need for specialty logistics teams to build a flexible, anti-fragile supply chain capable of withstanding global uncertainties. The role of knowledgeable supply chain experts has never been more significant to ensure the uninterrupted flow of essential medicines worldwide.

CONTINGENCY PLANNING: ENHANCING SUPPLY CHAIN RESILIENCE WITH OPTIMIZED REGIONALIZATION STRATEGIES

Regionalization strategies are key in accelerating and safeguarding supply chain integrity. By diversifying production and procurement across various suppliers and geographical regions, supply chains become more robust, capable of overcoming challenges such as climate disasters, geopolitical instability, labor shortages, and regional resource scarcity. This contingency forecasting approach ensures if one facility or shipping lane faces disruption, alternative nodes in the network maintain the essential flow of medicines. Lessons from the pandemic have reinforced the value of geographically dispersed manufacturing and distribution networks, creating redundancy while managing risk to enhance supply chain flexibility.

Diversifying supply chain resources is crucial in forging resilience. It reduces over-reliance on single sources and eases pressure on specific regions, thereby mitigating the impact of localized disruptions. The regionalization of resources and manufacturing, a growing trend in recent years, continues to be instrumental in addressing global challenges. For instance, consider how the European Union's decision to phase out Russian fossil fuels impacted the availability of dry ice, essential for cold chain packaging.[1] This challenge prompted supply chains to innovate, expanding their supplier network and adopting self-manufacturing methods. Moreover, diversifying suppliers and exploring alternative transport routes has proven effective in distributing medications to hard-to-reach areas, as seen during the Ukraine conflict and the pandemic.

Another strategy is proactively streamlining regional regulatory processes to maximize supply chain agility. Marken's global trade compliance team ensures compliance with all regulatory requirements, local laws, and custom guidelines. Our Qualified Persons (QPs), pharmacists, and technical directors with diverse expertise in product types and dosage forms across all four re-

gions (NORAM, EMEA, LATAM, APAC) are personally dedicated to ensuring the quality of investigational medicinal products (IMPs) being released aligns with the specific clinical protocol. Through meticulously executed global supply chain audits, our QPs and pharmacists mitigate risk and confirm that only compliant products are released in support of QP declarations for import into the EU and their own regions respectively.

COLLABORATIVE COMMUNICATION DRIVES SYNERGISTIC SUCCESS IN SUPPLY CHAIN ORCHESTRATION

Another major consideration for building resiliency in the supply chain is end-to-end collaboration, extending beyond healthcare and pharma organizations to include suppliers as well. This approach fosters proactive insight sharing and joint contingency planning, enabling a unified response as situations evolve. While integrating technology to support stakeholder communication is essential, savvy operations leaders also prioritize establishing open communication channels. By embracing diversity and cultivating less transactional, more relationship-focused interactions, we enhance our ability to absorb disruptions and promote transparency, trust, and clear communication for the present and future.

These open channels are further strengthened by real-time data sharing from supply chain managers, suppliers, and manufacturers, which is crucial in proactively identifying potential disruptions. Working collaboratively, stakeholders develop best practices and optimized contingency strategies, allowing for a rapid, coordinated response to challenges. This minimizes the impact on supply chains and, most importantly, ensures an uninterrupted supply of products to patients. Such dynamic communication is invaluable for swiftly pivoting strategies, whether adjusting mid-trial for direct-to/from patient shipments or other decentralized services. A resilient supply chain, ready to adapt to any circumstance, relies heavily on robust communication and transparency throughout its network.

WHAT'S INSIDE THE BOX: REAL-TIME TRACKING FOR DATA-DRIVEN DECISION MAKING

Enhancing supply chain visibility and traceability is a key enabler for building a resilient supply chain able to overcome challenges and engrain the highest level of quality into processes. Recent accelerated research in new modalities of medicine, sponsors seek deeper, product-level visibility on shipments of advanced therapies — an "inside-the-box view" to securely monitor status throughout the journey.[2] This involves implementing cutting edge, end-to-end supply chain tracking systems with data analysis for real-time visibility into the condition and movement of goods from the production stage to the end-user. These systems are powered by limitless technological solutions like radio frequency identification tags, sensors, and barcodes, as well as digital platforms — covering every angle to provide granular data on the location and condition of biological samples and medical products.

Real-time data analytics empower operations teams to identify potential bottlenecks and disruptions early, enabling proactive management of inventory levels, transportation routes, and delivery schedules. This approach not only prevents drug shortages and delivery delays, but also maintains the integrity of temperature-sensitive materials and optimizes inventory.

Interoperability between teams, facilitated by integrated, cross-organizational platforms, is vital for achieving complete

transparency. Specialty supply chain resilience involves leveraging various technologies and digital tools to enhance supply chain transparency — key factors in building patient confidence and ensuring secure medication delivery.[3] At Marken, our proprietary Marken Maestro™ software provides patients and sponsors with a transparent view of the product's journey, offering secure, real-time updates on conditions and GPS tracking.

Regular assessments and stress testing evaluate the impact on supply chain resilience. Developing a comprehensive risk framework helps identify and prioritize potential disruptions, allowing for the implementation of effective mitigation plans. This process encompasses a wide range of factors, such as geopolitical events, natural disasters, transportation challenges, economic impacts, and regulatory changes. Successful strategies that consistently manage disruptions are integrated into our best practice framework, enhancing agility and ensuring patient access to life-saving medications.

Elevating visibility within the supply chain cultivates a culture of risk awareness and preparedness across the organization. It's imperative for leadership teams to embody and promote critical thinking in the face of disruptions, fostering a resilient supply chain culture. This involves every network level, from the C-suite to frontline employees, in identifying risks, conducting regular assessments, applying risk management principles, and integrating findings into decision-making. By nurturing a culture of risk awareness, organizations can effectively anticipate, respond to, and recover from disruptions, ensuring uninterrupted delivery of essential medicines.

REDEFINING SUPPLY CHAIN RESILIENCE THROUGH INNOVATIVE TECHNOLOGY SOLUTIONS

A flexible, ready-to-pivot supply chain requires the integration of groundbreaking digital technologies. The use of advanced tools like AI, data analysis, and industry cloud computing is revolutionizing the field. These technologies not only streamline operations, but also enhance data capture, leading to more intelligent decision-making. This evolution benefits patients and sponsors with reduced costs, faster turn-around-times, and refined inventory management (reducing the overage required).

AI and machine learning (ML) are particularly transformative, optimizing resources and predicting demand fluctuations with greater accuracy. AI algorithms utilize both current and historical data to sharpen demand forecasts. Meanwhile, ML minimizes the risks associated with inventory shortages or surplus. Additionally, AI and automation are pivotal in boosting productivity and minimizing human error. For instance, automated robotic systems efficiently handle repetitive tasks like medication picking and packing, enhancing accuracy and overall efficiency. The future of these technologies promises even more advanced capabilities, such as automated contingency responses, potentially meeting patient needs with unprecedented speed and resource optimization.

Effective communication technology is also vital in fostering collaboration and partnerships within the pharmaceutical supply chain. The industry's shift toward integrated, industry-cloud solutions demonstrates a growing recognition of the value these technologies bring. They are instrumental in enhancing collaborative projects, allowing for the efficient sharing of information, best practices, and resources. This collective approach addresses common challenges and significantly improves supply chain performance.[4]

Leveraging AI for smart shipment management, including location GPS data, will provide further predictive capacity with live insights and in-depth analysis of various external factors, including labor shortages, conflict zones, adverse weather conditions, and congested or hazardous road conditions – in addition to other ongoing global disruptions.

For instance, consider Marken's Monarch, an innovative, efficient and sustainable packaging solution for transporting and safeguarding temperature-critical clinical pharmaceuticals across the globe. With temperature-range capabilities from ambient to deep frozen (-80°C), it goes beyond the dimensions of performance with internal and external sensors that monitor real-time container performance, ensuring we grasp a holistic view of the shipment's environment and can make proactive data-driven decisions.

A recent example involved an unexpected FDA hold on a Marken Monarch shipment. While such unforeseen disruptions can be catastrophic, we were able to actively monitor the shipment performance throughout the 3-day delay to ensure the packaging upheld temp conditions. Receiving this live data and vigilant oversight was key – we were able to make the strategic decision to then distribute the shipment in a temperature-controlled vehicle (TCV) to its final destination, which confirmed adherence to the strict time and temp requirements.

This approach embodies proactive

forecasting and heightened situational awareness where we don't just track data; we harness it, leveraging real-time analytics to inform and drive our decisions. Looking forward, as technology continues to evolve, we anticipate a future in which these critical decisions are executed autonomously, ensuring even swifter resolutions without the need for human intervention. These advantages are revolutionary for clients and patients alike, with levels of oversight, efficiency, and foresight we have not seen before.

SUMMARY

Building a resilient pharmaceutical supply chain requires a comprehensive approach that includes diversification planning, advanced technology investment, collaboration, and enhanced visibility. By diversifying supply sources, improving visibility, prioritizing risk management, and leveraging digital technologies, pharmaceutical companies forge a supply chain that is both robust and flexible, capable of withstanding disruptions and ensuring continuous access to essential medicines.

In light of recent challenges, innovation and adaptation have become imperative for bolstering supply chain resilience. As the pharmaceutical industry evolves, so too must our supply chain management strategies. Embracing change and adapting to new trends are necessary to maintaining the security and efficiency of our supply chains.

By embracing change and mitigating disruption, Marken is able to offer an agile and limitless supply chain network that improves healthcare accessibility and equity globally. Marken's robust global network, combined with cutting-edge digital tools and a patient-centric mindset, optimizes logistics efficiency and flexibility to ensure the distribution of innovative drugs, treatments, and other clinical products to those who need it most. Where there is a need, Marken makes it happen. ◆

REFERENCES

1. Council of the European Union. (2023, June). Impact of Russia's invasion of Ukraine on the markets: EU response. Retrieved from consilium.europa.eu.
2. EY. (2023, October). EY report finds cracks in supply chain operations. Retrieved from ey.com
3. EY. (2023, October). Why digital supply chain visibility should be a pharma priority. Retrieved from ey.com
4. BMC Health Services Research. (2023, June). Exploring the role of ICT in pharmaceutical supply chain practices. Retrieved from bmchealthservres.biomedcentral.com

BIOGRAPHY

Nina Vas is the Vice President of Global Quality Assurance at Marken, where she is responsible for managing the quality and global GMP depot network of the company. With 25+ years' experience in the life science, supply chain and project management, her main focus is leading and driving the quality strategy as well as overseeing Marken's global GMP storage facilities, including Centres of Excellence for ultracold and cryogenic storage. Nina brings a wealth of experience in operational, quality, and process improvement, having managed the performance of the full supply chain to support the distribution of clinical trials to global destinations.

Drug Development
EXECUTIVE

Sam Lee, PhD
President & co-CEO
Cocrystal Pharma

COCRYSTAL PHARMA, INC.

Cocrystal Pharma: Utilizing Structure-Based Technologies to Provide First- & Best-In-Class Antiviral Drugs to Address Critically Unmet Medical Needs

Cocrystal Pharma, Inc. (Nasdaq: COCP) is a clinical-stage biotechnology company discovering and developing novel antiviral therapeutics that target the replication process of influenza viruses, coronaviruses (including SARS-CoV-2), and noroviruses. Cocrystal employs unique structure-based technologies and Nobel Prize-winning expertise to create first- and best-in-class antiviral drugs. Despite the numerous strains that may exist or emerge, these enzymes are required for viral replication and are essentially highly conserved across all strains. By targeting these highly conserved regions of the replication enzymes, our antiviral compounds are designed to exhibit a broad-spectrum activity and tested to be effective against resistant variants. *Drug Development & Delivery* recently interviewed Dr. Sam Lee, Cocrystal Pharma's President and co-CEO, to discuss the company's latest achievements in antiviral drug development.

Q: What is the approach you are currently taking to address the replication of viruses where we have seen current therapies fail??

A: Our unique structure-based drug discovery platform provides a 3-D structure of inhibitor complexes at near-atomic resolution and immediate insight to guide Structure Activity Relationships. This helps us identify novel binding sites and allows for a rapid turnaround of structural information through highly automated x-ray data processing and refinement. By targeting viral replication enzymes and protease, we believe it is possible to develop an effective treatment for all coronavirus diseases, including COVID-19, Severe Acute Respiratory Syndrome (SARS), and Middle East

Respiratory Syndrome (MERS), as well as other common viruses like influenza A and norovirus. Our main SARS-CoV-2 protease inhibitors showed potent in vitro pan-viral activity against common human coronaviruses, rhinoviruses, and respiratory enteroviruses that cause the common cold, as well as against noroviruses that is the leading cause symptoms of acute gastroenteritis.

Q: What have been the underlying issues with current treatments?

A: The fact is patients suffering from these acute and chronic viral infections have few effective treatments. Some available options have characteristics that limit their market potential such as pricing, poor tolerance, inconvenient administration, ineffectiveness against some viral subtypes and/or resistance. We are working to develop best-in-class antiviral therapies that are effective against all viral subtypes that cause disease and also address viral resistance.

Q: What are the unique advantages of your technology?

A: Our drug candidates are being designed to be effective on the broad range of viruses causing the disease. It is the different strains that emerge over time that help to develop treatment resistance, as well as vaccine resistance. This is one reason we see multiple generations of vaccines emerging to address the different variants emerging with SARS-CoV-2. Many antiviral drugs available today are effective only against certain strains of viruses and are less effective or not effective at all against other strains. Our drug candidates, in addition to addressing the virus itself, also specifically target those proteins involved in viral replication. Despite the viral strains, these replication enzymes are essentially identical (i.e., highly conserved) among all strains of a given virus. By targeting these conserved replication enzymes, we believe our antiviral compounds will show to be effective against major virus strains. Replication enzymes are generally conserved not only among subtypes of a given virus, but also among different viruses.

Q: Can you discuss your lead program with influenza A?

A: Each year, there are approximately 1 billion cases of seasonal influenza worldwide, with 3-5 million severe illnesses and up to 650,000 deaths, according to the World Health Organization. On average, about 8% of the US population contracts influenza each season. In addition to the health risk, influenza is responsible for approximately $10.4 billion in direct costs for hospitalizations and outpatient visits for adults in the US annually. As we've generally discussed, many antiviral treatments for influenza are only partially effective and prone to viral resistance. As the flu changes year by year, approved treatments like oseltamivir, zanamivir, and Xofluza®, are becoming less and less effective.

There are three types of influenza viruses: A, B, and C with the A and B viruses being the significant human respiratory pathogens that cause seasonal flu. Influenza A viruses are historically responsible for multiple major influenza pandemics worldwide. We have developed novel, broad-spectrum antivirals that are specifically designed to be effective against all significant pandemic and seasonal influenza strains, and to have a high barrier to resistance due to the way they target the virus' replication machinery.

CC-42344 inhibits the first step in influenza A's viral replication by binding to a highly conserved PB2 site of the influenza A polymerase complex and exhibits a novel mechanism of action that inhibits viral replication.

In vitro testing showed CC-42344's excellent antiviral activity against influenza A strains, including pandemic and seasonal strains, as well as against strains resistant to Tamiflu® and Xofluza, while also demonstrating favorable pharmacokinetic and safety profiles. We conducted a healthy volunteer Phase 1 study with oral CC-42344 in Australia and in late 2022, we reported favorable safety and tolerability results from that study.

Now we are conducting a randomized, double-blind, placebo-controlled influenza Phase 2a human challenge study in the United Kingdom to evaluate safety and viral and clinical measures in healthy volunteers who are challenged with influenza A. We expect to report topline results from the Phase 2a clinical study this year.

Q: How are you addressing norovirus?

A: Although norovirus is a worldwide public health problem, there are no effective treatments or vaccines. Norovirus afflicts an estimated 685 million people annually at an estimated societal cost of $60 billion. About 200 million cases are seen among children under 5 years old, leading to an estimated 50,000 child deaths every year, mostly in developing countries, according to the Centers for Disease Control and Prevention (CDC). CDI-988 *in vitro* studies showed potent broad-spectrum

antiviral activity against a panel of pandemic GII.4 norovirus proteases, which have caused the majority of norovirus outbreaks worldwide since 2002, and a favorable pharmacokinetic property targeting the gastrointestinal tract.

Our compound CDI-988 targets a highly conserved region in the active site of the main 3CL protease required for viral RNA replication for pandemic norovirus and coronaviruses, including SARS-CoV-2. CDI-988 is a breakthrough discovery of the first-in-class pan-coronavirus and pan-norovirus antiviral agent with potential efficacy in these two indications. It is currently being evaluated for safety and pharmacokinetics in a randomized, double-blinded, placebo-controlled Phase 1 study in healthy subjects being conducted in Australia.

Q: COVID continues to be an issue as well. Is the approach to addressing this similar?

A: We chose CDI-988 as our lead candidate for the treatment of coronaviruses, including SARS-CoV-2, the virus that causes COVID-19, as well as for noroviruses. CDI-988 was specifically designed and developed as a broad-spectrum antiviral inhibitor using our proprietary structure-based drug discovery platform technology to target a highly conserved region in the active site of coronaviruses, noroviruses, and other 3CL viral proteases. As I previously mentioned, we believe CDI-988 is a first-in-class pan-coronavirus and pan-norovirus antiviral agent with potential efficacy in both indications.

As you may know, COVID is a coronavirus. Coronaviruses (CoV) are a family of viruses that historically have been associated with a wide range of responses, from no symptoms to more severe disease that includes pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and death. The ability of someone with no symptoms to transmit infection to another person heightened the public health challenge of COVID. By targeting the viral protease, we believe it is possible to develop an effective treatment for all coronaviruses, including SARS-CoV-2 and its variants, SARS and MERS.

We see great promise with both of CC-42344 and CDI-988 drug candidates as potential effective easy to administer treatments for highly contagious, pandemic viruses, while also providing significant market opportunities for Cocrystal. Following a highly productive year in 2023, we expect to report topline data from our Phase 2a influenza and our Phase 1 CDI-988 studies this year. ◆

FORMULATION DEVELOPMENT

The Rising Need for an Integrated Approach to Small Molecules Drug Development

By: Julian Northen, PhD

INTRODUCTION

Small molecules as therapeutic agents have played a significant role in the improvement of human health and well-being since the discovery and commercialization of molecules, such as Aspirin and Salvarsan over a century ago.[1] They can broadly be defined as any organic compound with a low molecular weight (<1000 Daltons) and often have advantageous properties. These include the ability to be administered orally or to permeate via cell membranes to reach their intracellular targets, or not in the case of the blood-brain barrier where ingress may not be wanted.

Since the early days of drug development, the needs of the population have changed with regard to the medicines produced by the pharmaceutical industry. As the population ages, human behaviors shift and lifestyles change, so do the demands for effective treatments.

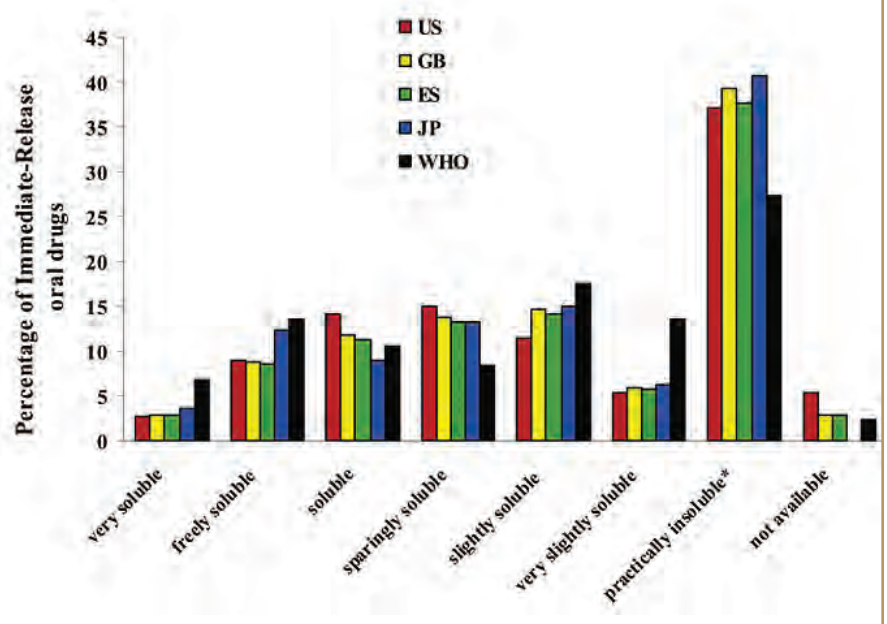
These changes pose a number of challenges. In living longer, we find that neurodegenerative conditions now pose an increased burden that requires effective treatment.[2] As the demands of a changing society evolve and continue to act as a driver for the identification of novel small molecules, the roles and diversity of the available medicines will also change.

TRENDS IMPACTING SMALL MOLECULE DRUG DEVELOPMENT

Historically, it has been estimated that approximately 90% of all marketed drugs are represented by small molecules, demonstrating the opportunities that these candidates have provided.[3] Advances in the technologies available to scientists have seen a rise in the application of biologics, such as antibody, cellular, and gene-based therapies.

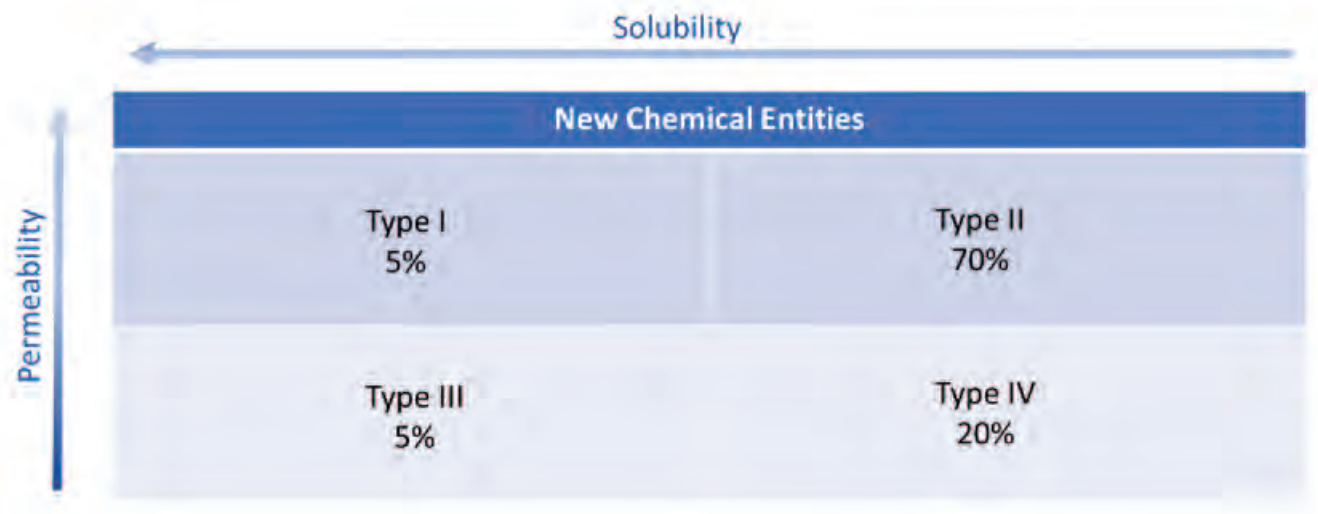
The generation of new leads in the small molecule field remains a highly attractive challenge and one that is being met by the combined use of in silico screening tools and artificial intelligence (AI). These machine learning algorithms

FIGURE 1



Percentage of immediate-release oral drugs by region vs. solubility.

FIGURE 2



BSC schematic of solubility vs. permeability relationships for Classes I-IV.

aim to significantly reduce the risk of failure and streamline the development process to provide structures of stable, druggable target molecules that are sensible from both a synthetic and a toxicological perspective.[4] Although this is an exciting advancement in the complex process of developing new medicines, the need for the integration of more traditional "medicinal chemistry expertise" remains.

Throughout the past 20 years, there has been a shift in the demographic of those companies taking small molecules into later-stage clinical development. There has been growth in the number of small- to medium-size companies that hold on to their assets after Phase 1. Whilst the risk of possible failure remains high, the rewards are also more significant.

Another trend has been a growth in the number of products that are on an accelerated development pathway, due to the needs of a particular patient group being unmet by current therapeutics. This accelerated trajectory toward the clinic poses a burden on those planning for success as a significant amount of data is required early in the development timeline to support safe and rapid progression.

AN INCREASE IN CHALLENGING SMALL MOLECULES IN THE PIPELINE

Despite the integration of in silico modelling and AI approaches to design, there are an increasing number of small molecules entering development that exhibit challenges to their progression. These most commonly manifest as sub-optimal physicochemical characteristics, particularly inadequate or very low solubility, poor permeability, and unacceptable powder handling properties.

A rather succinct representation of this trend was provided over a decade ago by Amidon, who presented a graphic of immediate-release oral drugs by region as a percentage set against solubility.[5] Most drugs for each region were those listed as practically insoluble (Figure 1).

Another graphic depicting the landscape for new chemical entities (NCEs) utilized by the biopharmaceutical classification system (BCS) to define the challenges being faced with at least 70 % of those NCE's falling within the BCS Class II category (Figure 2).[6]

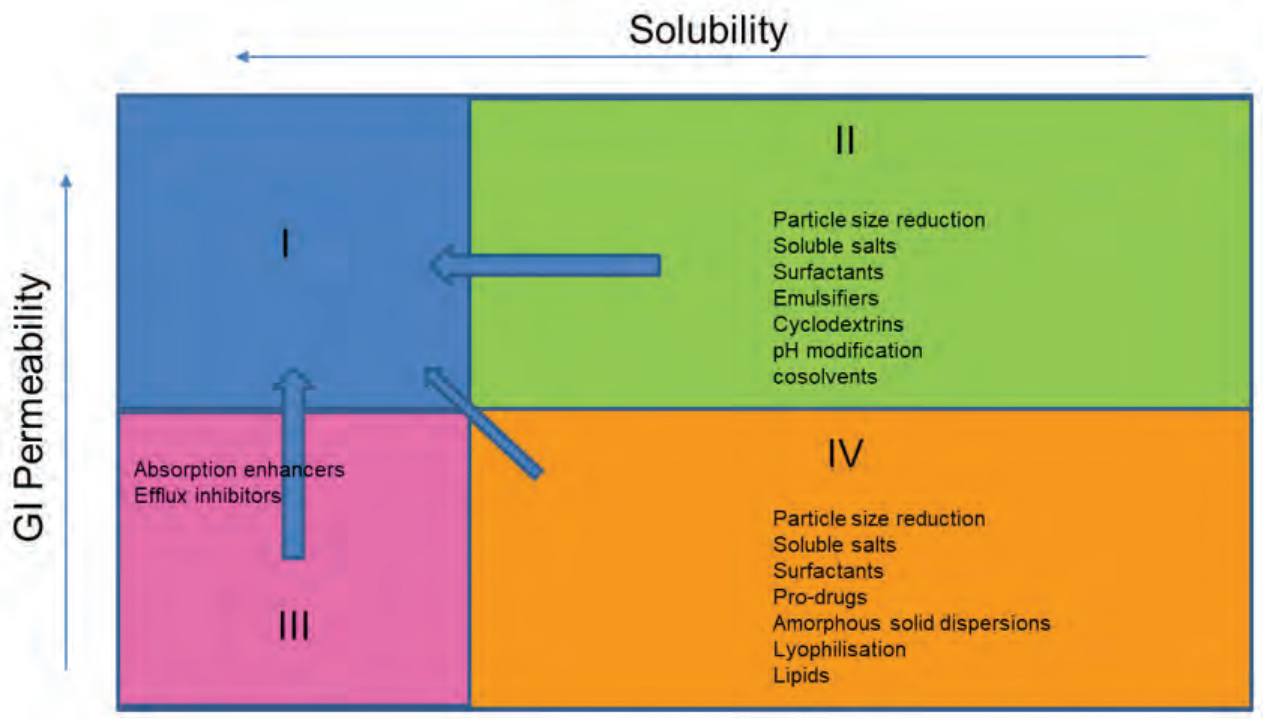
THE NEED FOR AN EFFECTIVE STRATEGY TO IMPROVE SOLUBILITY & PERMEABILITY

Medicinal chemists may utilize in silico screening and AI to aid in the design of new structures. The pharmaceutical chemist has access to AI and screening tools to help with the prediction of solvate formation, propensity toward polymorphism and the likelihood of forming salt or cocrystal versions.[7] AI and screening tools represent a growing part of the development toolbox and function to supplement the more traditional screening and manufacturing activities.

From a preformulation perspective, challenging molecules require a suitable strategy to be in place early in the drug substance's life cycle. A simplified example of a training tool used in-house that describes this approach (a schematic relative to the BCS) is illustrated in Figure 3.

Thorough characterization and performance evaluation of a molecule with the route of administration in mind should answer the question: "What are the critical quality attributes (CQAs) that the selected solid form should provide?"

FIGURE 3



Example of early preformulation considerations to optimize APIs within the separate BCS classes.

This question is continually challenged during development. For example, the acceptable and desirable attributes for a parenteral application may well differ significantly from that required for a respiratory indication.

A review of the approaches used to manipulate BCS Class II and IV candidates in Figure 3 illustrates that salt formation is a common route traditionally employed to improve many fundamental properties of a molecule. The well-cited reference – the Handbook of Pharmaceutical Salts – neatly defines that the selection of an optimal salt form for a novel drug candidate.[9] Such studies are commonplace and can be extended to consider the benefits relative to:

- Polymorphism footprint (salt vs free API polymorphism)
- Morphology and powder flow (impact on size reduction/capsule filling/blend uniformity)
- Crystallinity/thermal stability
- Excipient compatibility and stability
- Recrystallization – further potential to control CQAs

UNIQUE APIS REQUIRE AN INTEGRATED APPROACH

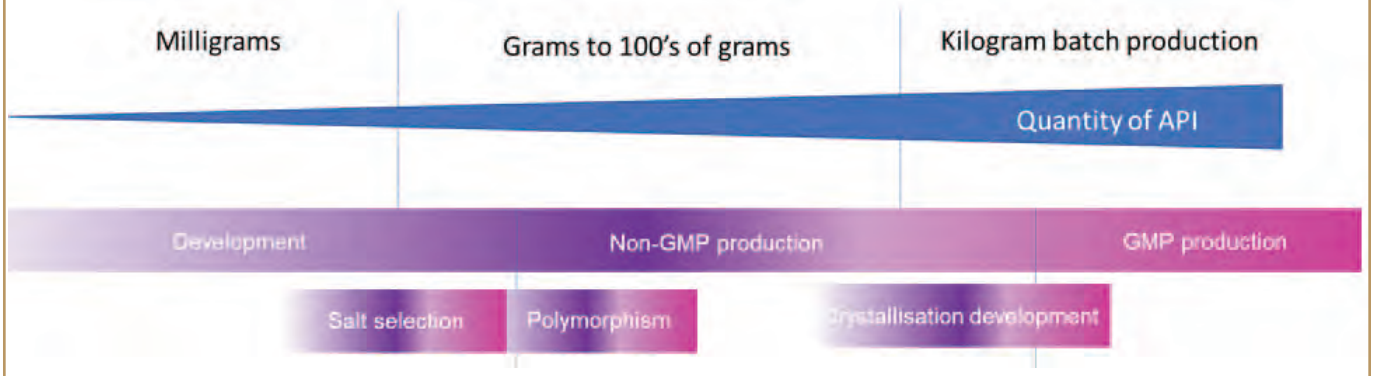
There is no one size fits all when it comes to development. Compounds should be developed on a material basis, as screening and selection should never be formulaic. The entire process must be both iterative and pragmatic when required, and the ability to integrate the various aspects of pharmaceutical development, especially in the early phases, is ideal. A schematic of a phased approach is provided in Figure 4.

Given the pace of early phase development and the challenging nature of many NCEs, having a team of synthetic chemists integrated and coordinating with solid state experts enables rapid and successful progression. Taking the time to understand what is important from the beginning allows the construction of tailored programs.

One of the critical benefits of integration is easy access to material. As a synthetic process is optimized the impurity profile changes, and not always subtly. If the composition of the final product is brought to the forefront of the initial interactions between the chemist and the solid state scientist, early batches can be profiled with only a few mg cost in terms of spent API.

Ideally, this work starts to build a data set correlating solubility characteristics with form and impurity profiles. Solubility is typically gathered in water and processes applicable solvents during early phase chemical development. Solid form characterization normally includes (but is not limited to) crystallographic profile by XRPD

FIGURE 4



Schematic of the development work-flow for chemistry overlaid with solid form development and available amounts of material.

and thermal properties.

For BCS class II and IV candidates, this solubility correlation can be of particular significance if an early amorphous batch was positioned toward the lower end of acceptable. Form change to a crystalline or to a more stable crystalline polymorph would likely reduce efficacy and require a more complex formulation strategy.

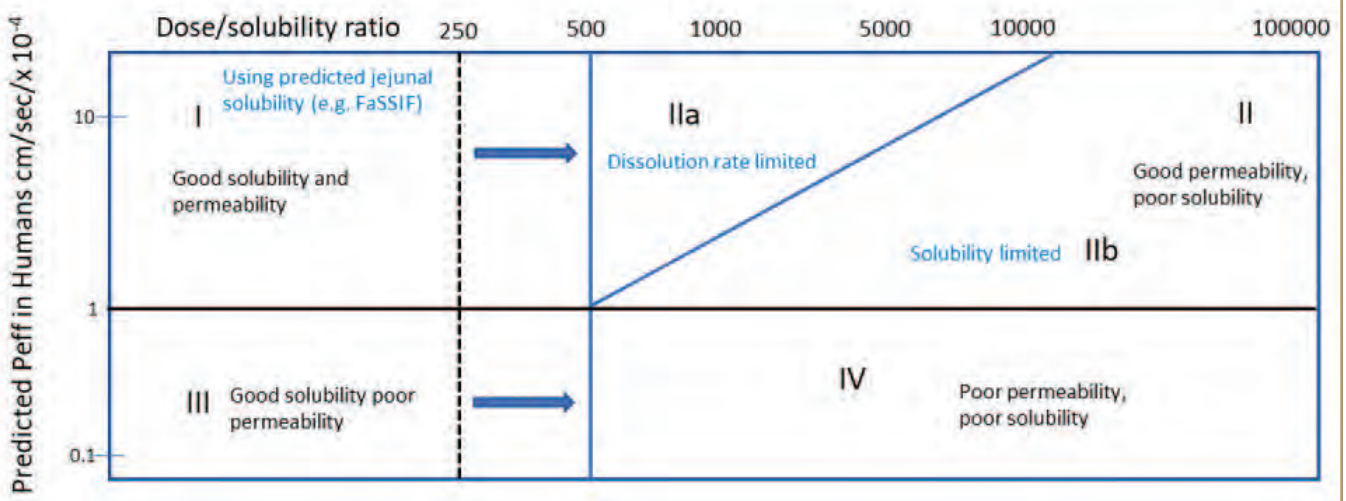
Another benefit of integration is the opportunity to profile each stage of the synthetic process. For highly insoluble molecules, it is likely that as you progress toward the final structure, solubility will drop, with work-up and isolation becoming more challenging. If this is combined with a propensity to polymorphism, control of the CQAs of intermediates, as well as the final product can be more than problematic.

Understanding form change throughout reduces the risk of failure at a later stage when more is at stake from a production perspective. Inorganic impurities that may become entrapped within the API and oligomers can be particularly troublesome. This is particularly evident during early phase batch isolation in which well-designed crystallizations are less common and precipitative methods are more often innocently applied before sufficient data is in hand.

This pragmatic approach to development should enable choices from an early stage and answer the question: "Will a salt be required, or is size reduction the initial option ahead of more complex strategies?" These decisions are critical and the integration of solid form with chemistry and early preformulation activities is a significant benefit to a risk-mitigating program.

Preformulation evaluations in particular are vital and more so in which a molecule has a pKa profile that makes salt formation likely but not without challenge. Having a well-characterized batch, solu-

FIGURE 5



Re-defining the BCS for developability, DCS put forth by Butler and Dressman.

bility data can make the choice of salt or parent less of a challenge and for very little material cost.

A very useful reference to consider is that of Butler and Dressman who derived a Developability Classification System (DCS). Figure 5 illustrates this system in a schematic for oral immediate-release compounds and addresses the question of whether dose/solubility ratio, dissolution rate, and/or permeability would limit oral absorption of a drug. It can be used to help derive strategies for formulation and in turn the identification of the CQAs of the drug substance that should be the target deliverables.[10] From the CDMO perspective, partnerships between internal working groups and the customer are essential.

BIOGRAPHY

Julian Northen graduated from the University of Newcastle upon Tyne with a 1st Class Honours degree and subsequently a PhD in Medicinal Chemistry and Anti-cancer Drug Design. This was followed by two post-doctoral positions, before a move from academia to Onyx. He has over 20 years of industrial experience in PR and D and is currently Solid State Manager at Onyx and is responsible for all solid form development, crystallization development, and preformulation activities.

THE FUTURE OF DRUG DEVELOPMENT RELIES ON AN INTEGRATED APPROACH

Small molecules continue to play a pivotal role in the supply of effective medicines to an ageing population and as tools to better understand the mechanism of interaction with their biological targets. Their complexity in terms of structure and material behavior makes development a continual challenge for those involved in deriving strategies that will deliver an effective drug product. Those molecules that are classified or predicted to sit within BCS class II and IV are of particular significance. However, realizing the benefits of integrating solid form and chemical development teams from an early phase, plus making use in silico and AI technology can provide a streamlined and risk-mitigating journey from the early phase to the clinic.◆

REFERENCES

1. Hartmut, B.; Harter, M.; Hab, B.; Schmeck, C.; Baerfacker, L.; Drug Discovery Today, v27, No6, 2022, 1560-1574.
2. Abbott, A.; Dementia: A problem for our age; Nature, 475, 2021, 52-54.
3. Ngo, H.X.; Garneau-Tsodikan, S.; Med.Chem. Comm., v9(5), 2018, 757-758.
4. Mullard, A.; Nature, v549, 2017, 445-447 / Gonzalez, M.G. et al.; Drug Discovery Today, v27, No6, 2022, 1661-1670
5. G.L.Amidon et al; Mol Pharm 2006 Nov-Dec;3(6):631-43
6. L.Benet, Pharm Res; 2005 Jan; 22(1):11-23
7. Heng, T. et al; ACS Omega, 6, 2021, 15543-15550.
8. Pharmaceutical Preformulation and Formulation, M.Gibson, Ed. Chapters 1-2; ISBN 1-57491-120-1
9. C.G. Wermuth and P.H. Stahl, "Introduction," in Handbook of Pharmaceutical Salts: Properties, Selection and Use, P.H. Stahl and C.G. Wermuth, Eds. (Wiley–VCH, Weinheim, Germany, 2002)
10. Butler, J.M; Dressman, J.B, J. Pharm. Sci.; Vol 99, 12, 2010

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

CLINICAL TRIALS

Enhancing Clinical Trials: A Strategic Framework for Positive Site-Sponsor Relationships

By: Matthew Jones and Julia Scanlon

INTRODUCTION

In today's challenging clinical trial landscape, the importance of building positive site experiences and fostering strong relationships between sponsors and sites cannot be overstated. As sponsors strive to secure sites and establish themselves as a sponsor of choice for projects, it is essential to address two fundamental questions: How can we best serve the needs of the sites? How can the sites best support our trial needs?

To answer these questions, we propose a framework of requirements that sponsors and contract research organizations (CROs) often struggle to address.

The following will delve into the key elements of such a framework, designed to cultivate positive site-sponsor relationships. By examining shifts in trial strategy and execution, we can pave the way for a collaborative, mutually beneficial environment, and a sustainable competitive advantage.

INTERACT WITH A SITE AS A SINGLE, ALIGNED & CONNECTED ORGANIZATION

To truly unlock the potential of a strong site-sponsor relationship, it is crucial to operate as a single, aligned, and connected organization when interacting with sites. This requires a shift in mindset in which we balance the prioritization of the organization and those of the individual studies. By adopting a portfolio planning approach, we can align our strategies with trial needs and objectives, creating a complete picture from top to bottom.

While portfolio planning is not a novel concept, many organizations struggle to move beyond study-centric operations. The symptoms of operating with an overemphasis on study-centric operations are evident in disconnected and repetitive site-sponsor interactions, leaving sites frustrated. The remedy lies in shifting the focus toward indication or portfolio planning and feasibility strategy.

Portfolio planning still considers the individual study objectives, but it establishes a collective understanding of all trials being planned across a therapeutic area, indication, region, or other grouping where sites may overlap. Then, it uses this appreciation to identify operational and strategic efficiencies across trials. Decisions are made collectively, with the primary objective of achieving the best outcome for both the sponsor and the sites.

With an understanding of requirements at a portfolio level, we can identify synergies and opportunities to operationalize multiple studies in parallel at the same site. The exercise also helps identify and elevate the most strategic sites across the sponsor enterprise. Effective portfolio planning provides numerous benefits, including:

- Maximizing internal resources by identifying and eliminating repetitive work
- Respecting site resources by considering site contributions strategically
- Streamlining operational aspects such as feasibility surveys and regulatory document requests

However, it's important to note that an effective strategy is only half of the equation. To truly realize the potential of portfolio planning and resource allocation, organizations must empower their teams with systems, technology, and data that enable them to be informed and connected. Without these tools, even the best strategies can fall short of expected outcomes.

REDESIGN DATA COLLECTION, ACCESS & GOVERNANCE FOR CONNECTED INTELLIGENCE

In the quest for a comprehensive and strategic approach to trial operations, connected intelligence plays a crucial role. Maintaining visibility and tracking progress requires data to be connected and easily accessible. One area where this connectivity is often lacking is in the collection and utilization of feasibility data.

Traditionally, feasibility assessments have been treated as transactional exercises, focusing solely on meeting the specific needs or endpoints of a particular study. This approach typically involves conducting a one-time survey using a general-purpose tool and saving the data in a siloed repository such as SharePoint. As a result, a proactive team that wants to access historical data would face the arduous task of manually searching through folders and files. Even if past feasibility assessments were found, their ability to provide a holistic understanding may be limited. To truly harness the potential of feasibility data, it must be treated as a valuable asset and supported by a process and system that respects its significance.

Let's delve into a feasibility system that considers the interconnectedness of people, processes, data, and technology. While the concept of treating feasibility assessments as an enterprise activity is not complex, the operational reality often sees teams working in silos with limited awareness of how data can be collected, standardized, and leveraged across assessments within a program or across multiple programs. To enable connected intelligence, it is essential to integrate feasibility data at the portfolio, study, and site level, creating a single asset that is centralized, connected, and indexed to a single source of truth.

Sites and sponsors can strengthen relationships and foster collaboration through early portfolio planning, supported by data management, to build a mutual understanding of each other's needs.

Looking at site data as a unified asset may seem complex due to the various ways it can be segmented. However, we present a framework that allows data to be collected at different levels for different use cases, each adding its own value:

- Profiles of investigators and facilities
- Questions aligned with specific indications or therapeutic specialties
- Questions aligned with particular studies or protocols
- Questions aligned with individual sites

While the concept of site and investigator profiles has been explored in the industry, its implementation is crucial. Without a plan to integrate this data into a single asset, its value remains limited. The strategy should encompass the full scope of site data as one unified asset. To ensure this asset can be effectively leveraged and maintained, several critical factors must be in place:

- Data should be standardized, centralized, and governed by robust data governance practices
- Data should be accessible, with clear categorization and indications attributed
- Data should be dynamic, allowing users to utilize scoring algorithms based on expected answers and historical data
- Data collection should primarily occur directly from investigators through a technology that enables features such as data refreshes and response prepopulation in order to establish a single source of truth

By redesigning data collection, access and governance for connected intelligence, organizations can unlock the full potential of feasibility data to facilitate informed decision-making, enhanced collaboration, and a deeper understanding of trial operations.

ESTABLISH A MUTUAL UNDERSTANDING BETWEEN THE SPONSOR & SITE

To build strong and effective relationships, it is essential to start with building a mutual understanding between sponsors

To develop a mutual trust and long-term relationships, sponsors must operate as a single, aligned and connected organization when interacting with sites.

and sites. Moving beyond transactional study/site interactions and striving for sponsor-site partnerships are key to achieving this goal. Partnerships begin by looking outside of what a site can do for the immediate need and asking two fundamental questions: How can we best serve this site's needs? How can this site best serve our short-term and long-term trial needs?

Characteristics of transactional relationships:

- Communication is one-way, initiated when study opportunities arise
- The focus is on finalizing site selection
- The primary driver of engagement is determining whether the site can meet the sponsor's needs

Characteristics of partnership relationships:

- Sponsors approach sites to understand and appreciate the unmet clinical needs of their patients
- Early engagement is sought to gather feedback on the study design
- The primary driver of engagement is determining how the sponsor can meet the site's needs

Partnership relationships built on a mutual understanding lead to multi-study engagements, prioritized patient recruitment, and ultimately improved treatment. By nurturing these relationships, sponsors and sites can work together more effectively, leading to improved outcomes.

So, how can we build strong and effective site experiences and relationships? The answer lies in acting as a single coordinated organization when interacting with a site. When this aspect is missing, it leaves sites frustrated by the lack of connection or appreciation from different study teams. Sites are eager to contribute their input into protocol design, readiness assessments and preferences for technology and tools.

Sponsors can implement various measures to facilitate these interactions, such as adopting master confidential and disclosure agreements (MCDAs), establishing rate card budgets, and implementing site communication plans. These initiatives help alleviate the burden on sites and ensure a more collaborative and supportive environment.

BENEFITS OF A FRAMEWORK FOR BUILDING STRONG SITE-SPONSOR RELATIONSHIPS

Building strong site-sponsor relationships and fostering a collaborative ecosystem requires a strategic framework encompassing key pillars. By operating as a single, aligned, and connected organization when interacting with sites, we establish a solid foundation for success. This framework comprises three essential elements: portfolio planning, connected intelligence in data management, and establishing a mutual understanding between sponsors and sites.

First, portfolio planning provides a strategic approach to trial operations, allowing organizations to optimize resource allocation, enhance study planning and design, and respect site resources. By considering the broader picture and aligning trial strategies with strategic goals, sponsors and CROs can maximize internal resources, identify operational synergies, and strategically select sites based on the overall portfolio's needs.

Second, connected intelligence transforms the way data is collected, accessed, and governed throughout the trial process. By integrating feasibility data at the portfolio, study, and site level, organizations can create a centralized and standardized asset that serves as a single source of truth. This connected data approach empowers teams with comprehensive information, facilitates informed decision-making, and enhances collaboration between sponsors, sites, and investigators.

Last, establishing a mutual understanding between sponsors and sites is vital for fostering true partnerships. By moving beyond transactional study-site interactions and actively seeking to under-

stand and appreciate each other's needs, sponsors can prioritize site input in protocol design, readiness assessments, and technology preferences. This mutual understanding leads to multi-study engagement, prioritized patient recruitment and ultimately, more successful clinical trials.

By adopting this framework, organizations can build strong site experiences and cultivate meaningful relationships. This approach not only improves trial outcomes but also accelerates the development of innovative therapies for the benefit of patients worldwide. It requires a shift in mindset, embracing a collaborative and interconnected approach that values the contributions of all stakeholders involved in the clinical trial journey.

Together, let us embrace this framework for building strong site-sponsor relationships, revolutionizing the way we conduct clinical trials, and transforming the landscape of healthcare innovation.◆

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

BIOGRAPHIES

Matthew Jones is the Senior Product Owner for Study Start-Up Technology at GSK. In this role, he is responsible for SSU technology strategy and execution. Previously Matt was Feasibility Lead at IQVIA Technologies, where he oversaw the design and delivery of the company's purpose-built feasibility offerings. He is driven by a passion for optimizing trial operations through fostering true sponsor-site partnerships.

Julia Scanlon is the Feasibility Leader for IQVIA Technologies and serves as Senior Project Manager for implementations of the IQVIA Investigator Site Portal. She is passionate about improving the site and investigator experience through the use of purpose-built technology solutions.

DRY POWDER FORMULATION

Preparing to Deliver the Next Generation of Inhaled Therapeutics

By: Richard Johnson, PhD

INTRODUCTION

The global increase in respiratory diseases, as well as the potential to deliver drugs systemically, has led to increased interest and a shifting landscape within inhaled drug delivery. An alternative to pressurised metered dose inhalers (pMDIs), dry powder inhaler (DPI) formulations have the potential to meet the evolving market trends and deliver the next generation of inhaled therapeutics.

The following outlines the trends and challenges within the inhaled drug delivery market. Specifically, DPI delivery will be explored, including how the challenges with dry powder formulation can be overcome and what the future holds for DPIs.

TRENDS PAVING THE WAY FOR THE EVOLUTION OF THE INHALED DRUG DELIVERY MARKET

Chronic respiratory disorders, including asthma, lung cancer, and chronic obstructive pulmonary diseases (COPDs), have been categorized as a leading cause of global mortality and morbidity by the World Health Organisation (WHO).[1] WHO estimates indicate that approximately 235 million people worldwide suffer from asthma, and more than 3 million people die every year from COPDs.[1]

Due to the rapid and targeted delivery of drugs to the airways and lungs, inhalation remains the most common approach to the prevention and treatment of chronic respiratory disorders.1 Although pMDIs have traditionally been the inhaled therapeutic of choice, a shifting market landscape has opened the door for alternative methods, such as DPIs. Dry powder formulations have the potential to deliver the next generation of inhaled therapeutics due to their distinct set of advantages, including:

Sustainable Inhaled Drug Delivery: Propellants used within pMDIs are usually hydrofluorocarbons (HFCs), which have a high global warming potential (GWP). The high-GWP properties of currently used pMDI propellants mean they have become a target for increased sustainability within the pharmaceutical industry, with legislation aiming to reduce the use of HFCs in key pMDI markets. Despite progress in low-GWP propellants, continued regulatory changes make it unclear which sustainable propellants to invest in. The uncertainty in the propellant market has led to increased interest in DPIs, which do not use propellants and offer a sustainable inhalation solution.

Stable Biologics Delivery: The development of complex and larger biologics has increased interest in DPIs. The large and complex structures of biologics increase their sensitivity and influence their delivery method. Typically, biologics are injected intravenously, bypassing degradation routes (such as the gastrointestinal tract) and ensuring the active product is delivered. Aqueous biologics formulations can show increased sensitivity, which means that factors such as temperature and pressure need to be controlled to avoid degradation and loss of efficacy. In contrast, biologics are inherently more stable in dry powder formulations, providing an innovative solution for product formulation. Adopting dry powder formulations for biologics therefore in-

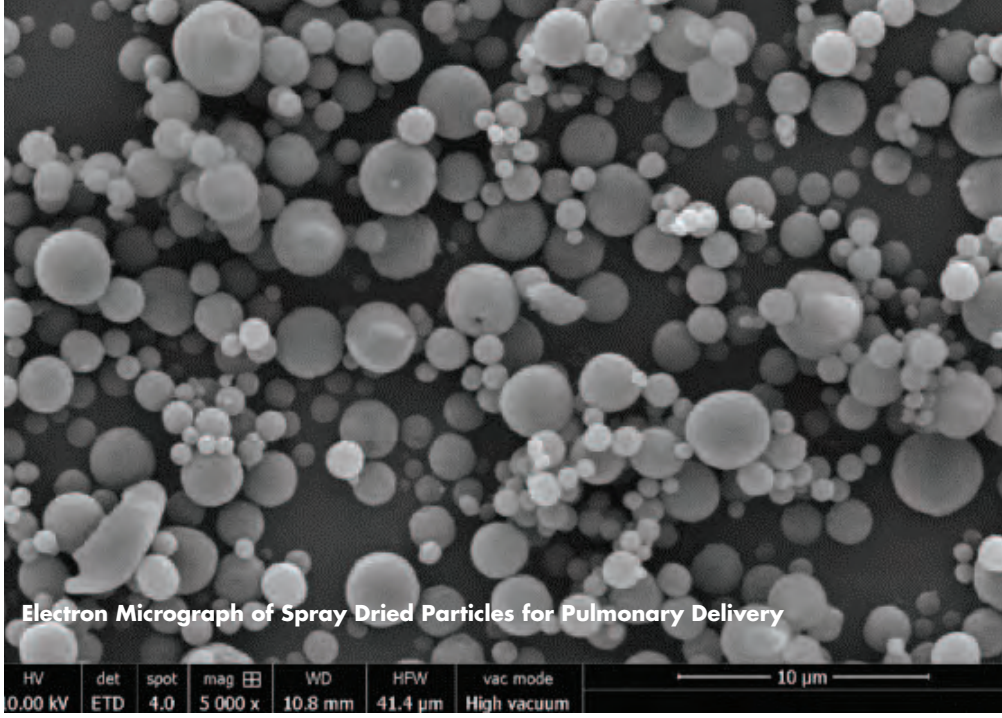
creases shelf life and maintains the efficacy of the product.

Deep Lung & Systemic Delivery: Another important property of dry powder formulations is the area of the lungs to which they deliver the drug. Biologics (in particular, vaccines) need to be delivered into the deep regions of the lung, something DPIs can achieve. If the development of more complex biologics continues, DPIs will therefore be relied upon more for their delivery into the lungs. The ability to deliver drugs deeper into the lungs also opens the door for systemic delivery. Getting drugs into the bloodstream via the lungs is a considerable challenge, but it is entirely possible. Systemic delivery via inhalation could then lead to self-administered pulmonary products, replacing therapies that would traditionally be administered via injection.

The lack of propellants, the compatibility with biologics, and the ability to deliver to the deep lung mean DPIs will be relied upon heavily for the next generation of inhaled therapeutics. However, there are several considerations and challenges drug developers and manufacturers need to navigate to unlock the full potential of DPIs.

MEETING THE GROWING DEMAND FOR DRY POWDER INHALER DELIVERY

Several key milestones need to be hit to successfully bring DPI therapeutics to market and to the patients who would benefit from them. The quickest way to meet these demands is to start with the simplest drug formulation possible (small molecule or biologic) and focus on commercially available DPI devices.



Electron Micrograph of Spray Dried Particles for Pulmonary Delivery

Capsule-based delivery devices are promising for fulfilling the growing demand. Dry powder formulations can be packaged into a capsule and then loaded into a commercially available delivery device. Using standard capsules and commercial devices means the pathway to the clinic is going to be quicker and more cost-effective, compared to developing proprietary devices. Well-established techniques for DPI formulation, such as spray drying, also ensure drug particles are the correct size for delivery, simplifying another development step.

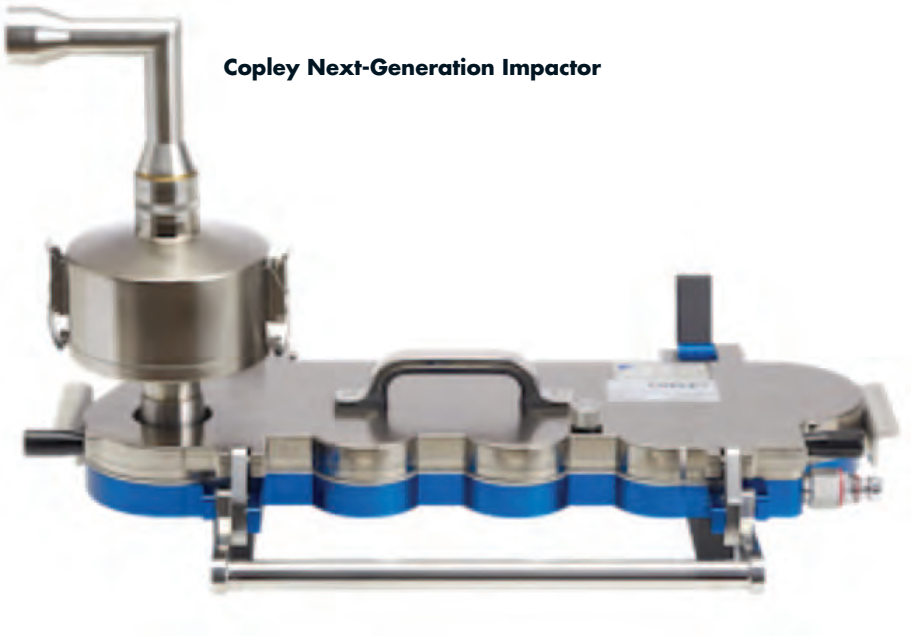
NAVIGATING THE HURDLES FACING DRY POWDER FORMULATION

The full potential of DPIs can be delivered by successfully navigating several hurdles associated with their development.

Selection of excipients is one of the main challenges in the delivery of next-generation inhaled therapeutics. Excipients improve aerodynamic properties and the stability of the product and are therefore essential when working with unstable biologics. However, there are very few excipients that are approved for pulmonary use. The commonly used approved excipients also show incompatibility issues with biologics, further highlighting the need for novel excipients in DPI delivery.

As pre-approved excipients simplify the regulatory pathway, their current lack makes the process more difficult. Precedent excipients can help overcome the challenges with pulmonary excipients. Even if they have not been specifically approved by the FDA, precedent excipients that have been used before during clinical development can help with regulatory approval.

Delivering the correct dose of the drug product is another challenge with DPIs. Dose issues center around the capacity of DPI capsules, which is typically 20-30 mg of powder. The capacity of DPI capsules therefore dictates the formulation of drugs into dry powders, as there is a finite range of how much drug can be delivered. A limited capacity affects some therapeutics more than others, but altering spray drying conditions and excipients



Copley Next-Generation Impactor

helps optimize formulations and particle sizes.

Regulatory compliance must also be carefully considered to provide a safe and efficacious therapy to patients. It is critical to demonstrate the stability of the active ingredient through the packaging and delivery process. Reproducibility must be tightly controlled when filling capsules and when the drug is delivered from the DPI device. Finally, it must also be demonstrated that the active ingredient is reaching the target site within the lungs.

Using a battery of analytical techniques to generate efficacy and safety data at an early stage is a key approach to demonstrating regulatory compliance. Light scattering and laser-based approaches can provide information regarding the geometric size of particles. Geometric particle size affects the aerodynamic properties of DPIs and how the product deposits during inhalation.

The aerodynamic performance of the product needs to be assessed to determine the properties of the product in real-life situations. Analysis with a next-generation impactor is an advanced methodology that can predict how the powder will be delivered and which areas of the lung the product will reach.

The chemical properties of the product are equally as important as the physical properties when determining efficacy and safety. Analytical techniques such as HPLC are used to determine if the drug has been damaged during spray drying or formulation. Dry powder formulations can absorb moisture readily, making thermographic analysis essential to determine moisture content. Microbial testing is also critical to avoid product contamination.

LOOKING TO THE FUTURE OF DRY POWDER INHALERS

Inhaled therapeutics is an area of the pharmaceutical industry that is currently in high demand and is set for continued growth in the future. The global increase in respiratory diseases and uncertainty surrounding pMDIs has increased interest in DPI devices. The compatibility with biologics and the ability to deliver drugs deeper into the lung (which also unlocks the potential for systemic delivery) means DPI devices have great potential within the growing inhaled therapeutics market.

Several challenges remain if DPIs are to reach their full potential and deliver the next generation of inhaled therapeutics. The selection of excipients, the dose and formulation of dry powders, and the physical and chemical properties must all be considered in the development of new DPI therapeutics. Partnering with specialists in DPI devices and dry powder formulations can bring the knowledge, expertise, and technologies required to turn the DPI potential into reality. With partnerships, challenges can be addressed, and the development of DPI products can be accelerated, reaching the patients that will benefit from them. ◆

REFERENCE

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7499344/

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

BIOGRAPHY

Dr. Richard Johnson founded Upperton Pharma Solutions in August 1999, and continues to play a key role in the management and strategic development of the company. With over 30 years of experience in the pharmaceutical, biotechnology, and drug delivery fields, he previously held senior management positions at Andaris Group (Vectura) and Delta Biotechnology (now Albumedix, Nottingham, UK). He earned an honors degree in Biology from the University of York (UK), a PhD from the University of Warwick (UK), and has a proven track record in successfully developing innovative pharmaceutical products from early feasibility studies through to commercial products.

Technology & Services Showcase

Specialty CDMO

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with expertise in complex oral formulations. Adare's specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactures more than 45 products sold by customers worldwide. For more information, visit Adare Pharma Solutions at **www.adarepharmasolutions.com.**

Formulation Development

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

Differentiated Injectable Delivery

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

Medical Manufacturing

Medical Manufacturing is a medical manufacturing partner like no other, with the broadest spectrum of solutions. From precision custom molding capabilities, full-service contract manufacturing and value-added services to a wide range of standard protective parts and medical packaging, Medbio is the one partner you need. Our in-house team of engineers is dedicated to deliver the most effective solutions to meet your needs. Our multiple state-of-the-art facilities include over 80,000 sq ft of cleanroom manufacturing, including custom built automation cells. We are ISO 13485:2016 certified and FDA registered. Together with sister company Caplugs, one of the world's leading plastic molders, we have worked with over 1,500 medical and biotech customers and look forward to putting our vast expertise to work for you. For more information, visit Medbio at **https://medbiollc.com/.**

Technology & Services Showcase

Functional Chemicals

Mitsubishi Gas Chemical (MGC) is a leading company in the field of functional chemicals, such as oxygen barrier and absorbing polymers. MGC established the Advanced Business Development Division in 2015 for tackling a variety of today's problems, and the division created OXYCAPT™ Multilayer Plastic Vial & Syringe to solve some issues of existing primary packaging for injectable drugs. OXYCAPT Vial & Syringe consists of three layers. The inner and outer layers are made of cyclo-olefin polymer (COP), the most reliable polymer in the pharmaceutical industry. The middle layer is made of state-of-the-art polyester developed by MGC. The oxygen-barrier property is almost equivalent to glass and much better than COP. OXYCAPT also provides an ultra violet (UV) barrier. For more information, visit Mitsubishi Gas Chemical at **www.mgc.co.jp/eng/products/abd/oxycapt.html.**

Patient-Focused Delivery Devices

As a world-leading drug delivery device solutions provider, **Nemera's** goal of putting patients first enables it to design and manufacture devices that maximize treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market with its combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil its mission. For more information, visit Nemera at **www.nemera.net.**

Injectable Drug Delivery

Owen Mumford Pharmaceutical Services is a specialist in the design, development, and manufacture of injectable drug delivery systems for the pharmaceutical, biotech, and generics industries. These include single-dose and multi-dose reusable and disposable auto-injectors, pens, and syringes for subcutaneous and intramuscular administration. Our innovative products are designed to meet both the need of our pharmaceutical partners and their patients by facilitating ease of use and improving safety and patient compliance. Our devices are also designed with the aim of reducing complexity and risk for the pharmaceutical and biotech industry in the development of their combination products. Our products are supported by our services, and we work with our partners every step of the way, supporting and guiding from initial concept stage through to taking the solution to market. For more information, visit Owen Mumford Pharmaceutical Services at **www.ompharmaservices.com.**

Global Data & Analytics

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

KEEPING YOU CONNECTED TO YOUR TARGET AUDIENCE.

For more than 20 years, Drug Development & Delivery has successfully connected technology and service providers with R&D scientists, business development professionals and corporate managers working at pharmaceutical and biotechnology companies.

Marketing your technologies, services and products with Drug Development & Delivery keeps you engaged with your key audience.

Call us today or visit us at drug-dev.com and let us show you how.

- Print & Digital Editions
- Website Marketing
- Email Campaigns
- Videos
- Exclusive Whitepaper & Webinar Marketing
- Online Company Profile
- eBooks
- eNewsletters

John Kiesewetter: 541-338-0022
jkiesewetter@drug-dev.com

Amy Nicklaus: 862-274-5872
anicklaus@drug-dev.com

Ralph Vitaro: 973-263-5476
rvitaro@drug-dev.com

drug-dev.com

CAN YOUR CDMO TRANSFORM A DRUG FORMULATION MADE FOR HER

INTO A DOSAGE FORM TAILORED TO THEIR NEEDS?

PEDIATRIC FORMULATION. ADARE DOES IT. FIND OUT HOW.

Adare has over 30 years' experience transforming the challenges of pediatric drug formulation into product solutions that drive compliance. Our scientists combine expertise, integrated services, and specialized technology platforms to develop optimized pediatric formulations that provide ease of application and improved patient outcomes. From NCEs to product lifecycle extensions, we can deliver flexible and convenient medications for your youngest patients.

Connect with our experts today: BusDev@adareps.com

TRANSFORMING DRUG DELIVERY. TRANSFORMING LIVES.

ADARE®
PHARMA SOLUTIONS

ADAREPHARMASOLUTIONS.COM