Drug Development & Delivery

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PFS & Parenteral Delivery

The Science & Business of Pharmaceutical and Biological Drug Development

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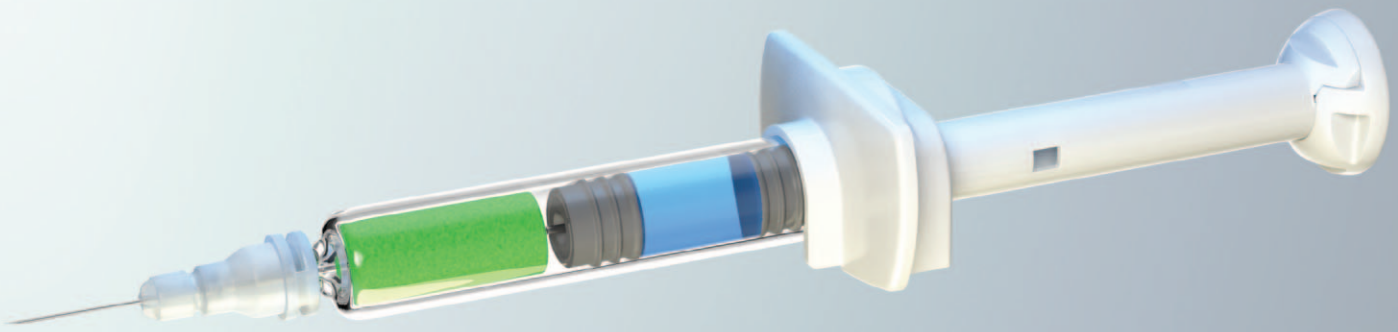

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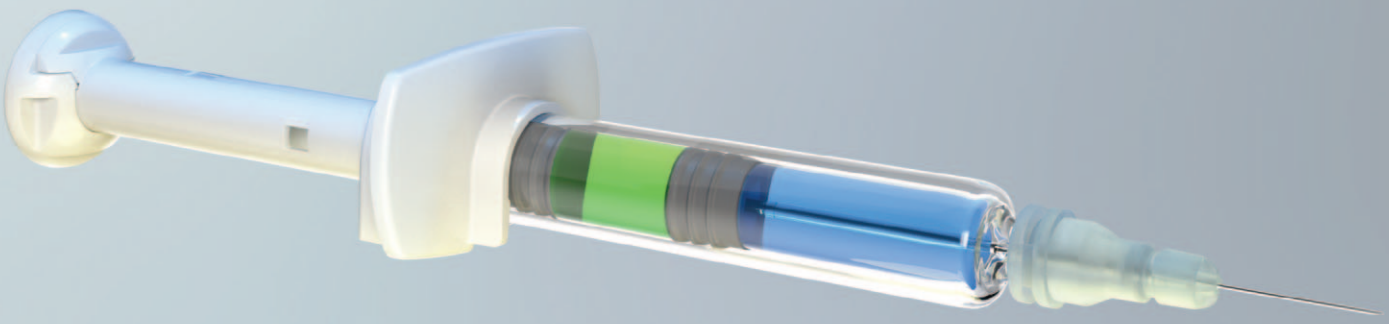

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PFS & Parenteral Delivery

This development and approval activity illustrates the expanding market for prefilled syringes (PFS), expected to reach $28 billion by 2032. The market is driven by the prevalence of chronic disease, greater use of biologics and biosimilars, and the ever-growing trend of self-injection. These trends in PFS as well as advancements in autoinjectors and innovations in parenteral delivery are featured in this exclusive *Drug Development & Delivery* annual report."

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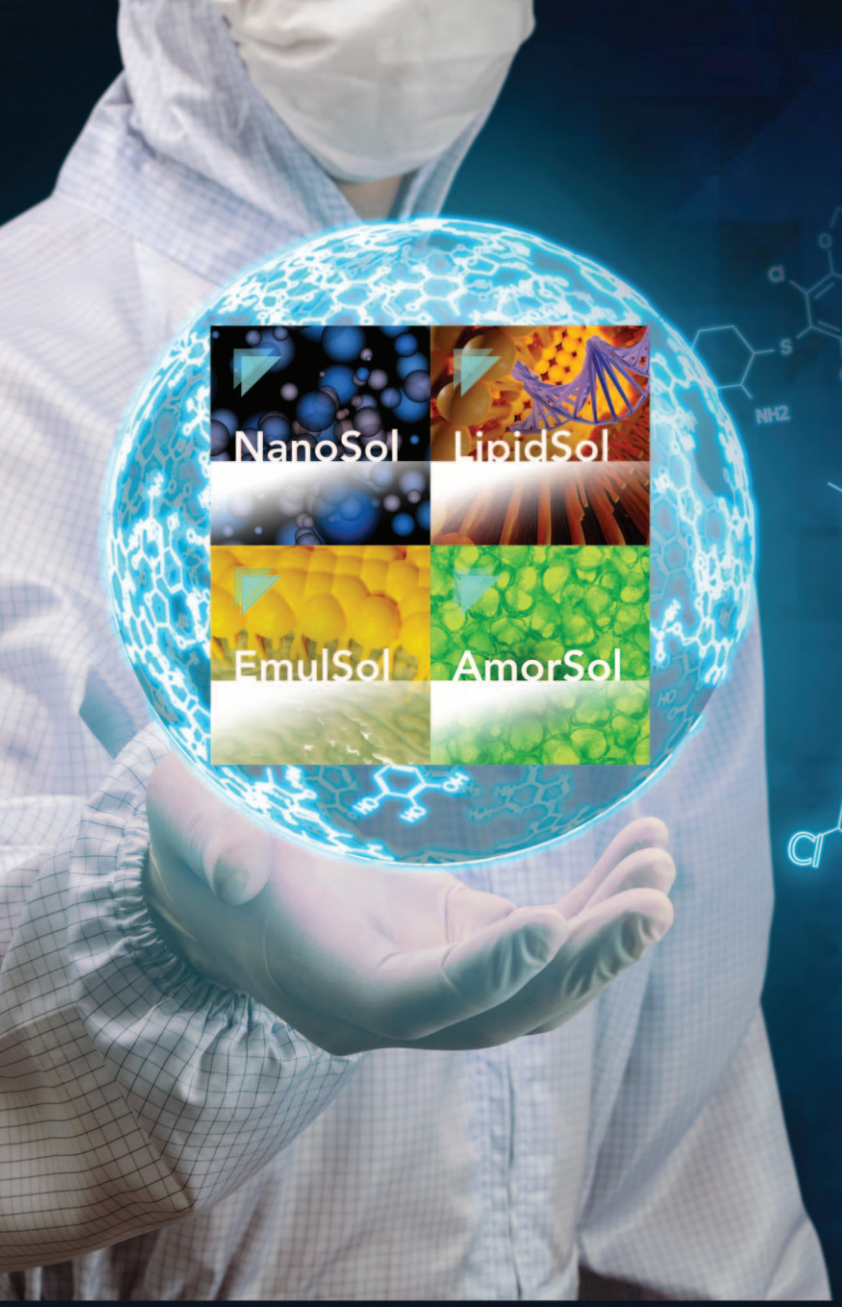

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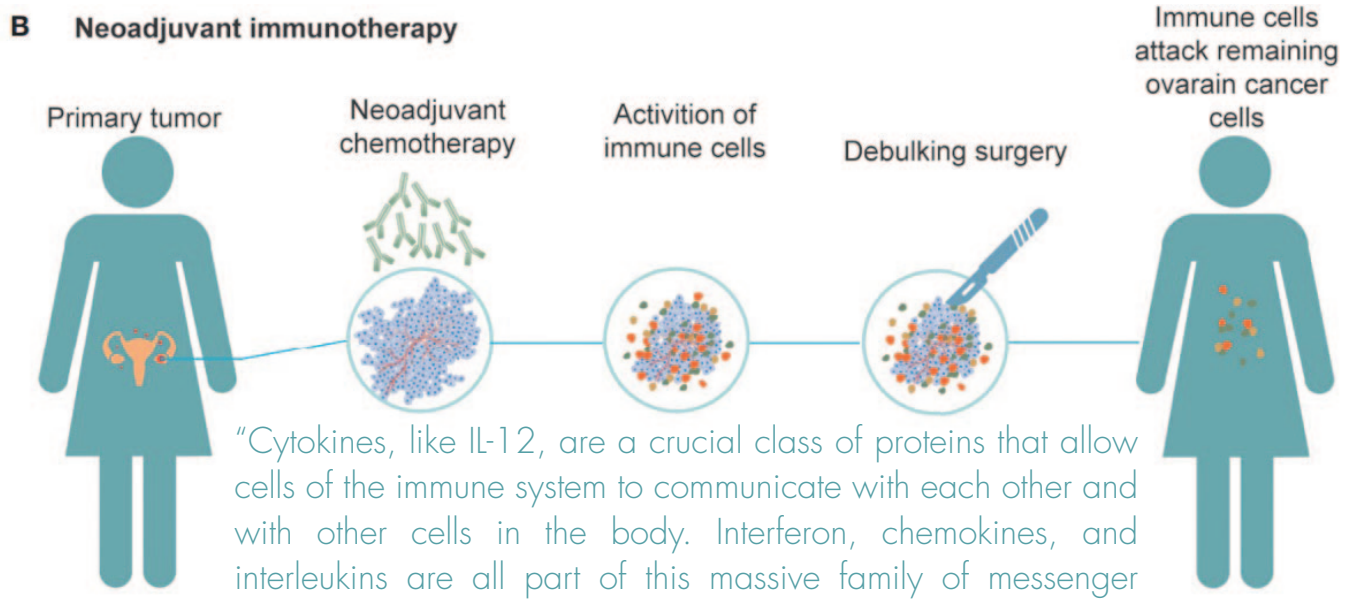

"Cytokines, like IL-12, are a crucial class of proteins that allow cells of the immune system to communicate with each other and with other cells in the body. Interferon, chemokines, and interleukins are all part of this massive family of messenger proteins produced by both immune and non-immune cells. These protein-based signals coordinate cellular processes during day-to-day homeostasis, as well as coordinate immune efforts during various disease states."

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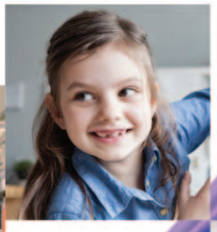

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Aptar CSP Technologies Expands Service Offerings With Launch of cGMP Early Stage Clinical Manufacturing Site for Tablet & Capsule-Based Drug Products

Aptar CSP Technologies, part of AptarGroup, Inc. and a global leader in active material science solutions, announced the expansion of its service offerings with the launch of a cGMP-compliant manufacturing facility in New Jersey. The new site will support clinical packaging for oral solid dose (OSD) and capsule-based DPI drugs utilizing Aptar CSP's proprietary Activ-Polymer platform and Activ-Blister™ solutions.

The expansion addresses growing market demand for enhanced drug stability and nitrosamine risk mitigation. Aptar CSP's Activ-Blister technology integrates a highly-engineered active film material into thermoform and cold-form blister packaging configurations, creating a microclimate that protects individual doses from moisture, oxygen, VOCs, and degradation, including reducing the risk of N-nitrosamine formation. The technology delivers customizable, dose-specific protection tailored to the unique stability needs of each drug formulation.

"Launching this cGMP facility reinforces our commitment to delivering streamlined access to innovative active material science technologies for patients and pharmaceutical partners," said Badre Hammond, Vice President Commercial Operations and General Manager, Aptar CSP Technologies. "By offering early-stage clinical services with custom-designed equipment, we simplify adoption, eliminate implementation barriers, and help avoid lengthy reformulation or repackaging efforts."

The new site, which is the result of a collaboration with MOD3 Pharma, will offer services including R&D support, Phase I and II clinical material manufacturing, full CMC package (Chemistry, Manufacturing, and Controls), stability studies, and clinical supply management.

Aptar CSP's 3-Phase Activ-Polymer platform technology is trusted worldwide to protect high-value products such as drugs, diagnostics, probiotics, medical devices, and implants.

Representatives from Aptar CSP Technologies and its technical partners will be available for meetings at RDD Europe 2025 in Estoril (Lisbon), Portugal, May 6-9. To schedule a meeting at RDD Europe, please contact Dr. Paul Shields, CEO at MOD3 Pharma at pshields@mod3pharma.com. For commercial inquiries, contact Francois Bidet, VP of EMEA Business Development, Aptar CSP Technologies at francois.bidet@aptar.com.

Aptar CSP Technologies is part of AptarGroup, Inc., a global leader in drug and consumer product dosing, dispensing and protection technologies. Aptar CSP Technologies leverages its active material science expertise to transform ideas into market opportunities, accelerate and de-risks the product development process, and provide complete solutions that improve consumers' and patients' lives. The company offers a complete set of services from concept ideation, to design and engineering, to product development, global production, quality control, and regulatory support that results in expedited speed-to-market. For more information, visit www.csptechnologies.com and www.aptar.com.

Can-Fite Has Raised $175 Million for the Development of Namodenoson & Piclidenoson

Can-Fite BioPharma Ltd. recently announced it has raised $175 million in funding to date. These funds have enabled the advancement of its lead drug candidates, Namodenoson and Piclidenoson, into pivotal Phase III studies for liver cancer and psoriasis, respectively.

Can-Fite is a recognized leader in the development of small-molecule therapeutics targeting the A3 adenosine receptor (A3AR), which is highly expressed in both inflammatory and cancer cells. Namodenoson, an orally bioavailable A3AR agonist, is currently enrolling patients in a pivotal Phase III study for advanced liver cancer. It has demonstrated selective targeting of liver and pancreatic tumor cells while sparing healthy tissue. Piclidenoson, also an orally administered A3AR agonist, is in a pivotal Phase III trial for patients with moderate-to-severe psoriasis.

Both candidates have shown favorable safety profiles, anti-cancer and anti-inflammatory properties, and promising efficacy in previous Phase II trials. Cumulative funding has also supported drug manufacturing, regulatory activities with the FDA and EMA, and the development of a broad patent portfolio providing extensive intellectual property protection.

In addition to its lead programs, Can-Fite is conducting a Phase IIa study of Namodenoson in pancreatic cancer, following successful preclinical studies demonstrating its ability to inhibit tumor growth by modulating the Wnt/β-catenin, NF-κB, and RAS signaling pathways. A Phase IIb trial in metabolic dysfunction-associated steatohepatitis (MASH) is also underway under an open IND with the FDA, leveraging Namodenoson's hepatoprotective effects.

To date, Can-Fite has signed seven commercialization agreements with strategic partners for the future marketing of its drug candidates upon regulatory approval. Can-Fite continues to engage with potential partners and seeks to sign additional commercialization agreements in the future.

Motti Farbstein, CEO of Can-Fite, commented: "This funding milestone reflects the strong confidence our investors and partners have in Can-Fite's scientific platform and clinical strategy. Progressing into pivotal Phase III trials marks a significant step toward bringing innovative, oral therapies to patients with serious unmet needs in liver cancer and psoriasis."

Can-Fite BioPharma Ltd. (NYSE American: CANF) (TASE: CANF) is an advanced clinical-stage drug development Company with a platform technology that is designed to address multi-billion dollar markets in the treatment of cancer, liver, and inflammatory disease. The Company's lead drug candidate, Piclidenoson recently reported topline results in a Phase III trial for psoriasis and commenced a pivotal Phase III trial. Can-Fite's liver drug, Namodenoson, is being evaluated in a Phase III trial for hepatocellular carcinoma (HCC), a Phase IIb trial for the treatment of MASH, and in a Phase IIa study in pancreatic cancer. Namodenoson has been granted Orphan Drug Designation in the U.S. and Europe and Fast Track Designation as a second line treatment for HCC by the US FDA. Namodenoson has also shown proof of concept to potentially treat other cancers including colon, prostate, and melanoma. CF602, the Company's third drug candidate, has shown efficacy in the treatment of erectile dysfunction. These drugs have an excellent safety profile with experience in over 1,600 patients in clinical studies to date. For more information, visit www.can-fite.com.

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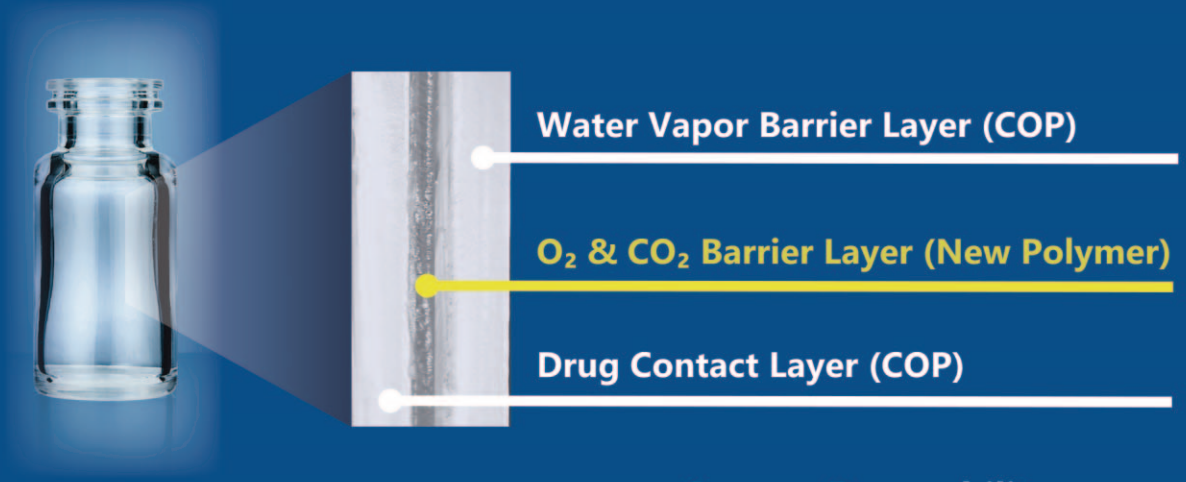

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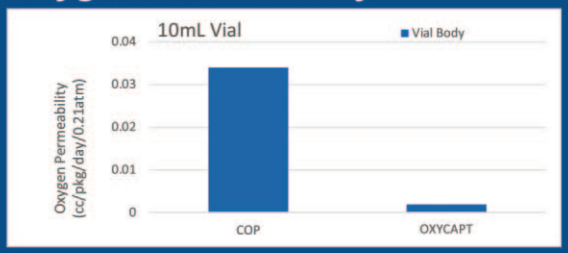
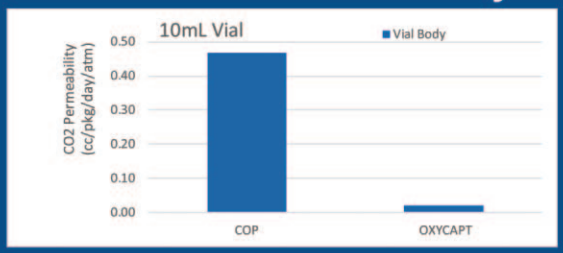


Carbon Dioxide Permeability



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Moleculin Bolsters Annamycin Intellectual Property Portfolio With Granting of Two New U.S. Patents

Moleculin Biotech, Inc. recently announced the US Patent and Trademark Office (USPTO) has granted two additional US patents with claims covering Annamycin. US patent number 12,257,261, titled Preparation of Preliposomal Annamycin Lyophilizate, has claims covering methods of making liposomal Annamycin, and US patent 12,257,262, titled Method of Reconstituting Liposomal Annamycin, has claims covering methods of making liposomal Annamycin suspension. Both patents have a base patent term currently extending until June 2040, subject to adjustment for delays in prosecution and extension to account for time required to fulfill requirements for regulatory approval. Moleculin has additional patent applications related to Annamycin pending in the US, Europe, and in major jurisdictions worldwide.

Annamycin, Moleculin's novel drug candidate, is being positioned to become the first anthracycline demonstrating a lack of cardiotoxicity to be approved and is currently being developed for the treatment of acute myeloid leukemia (AML) and soft tissue sarcoma lung metastases (STS lung mets). Additional preclinical studies performed at a world-renowned cancer center indicate Annamycin may be a potential treatment for many other types of cancers. The new chemical entity uses a unique lipid-based delivery technology and has shown the potential to be used in a wide range of cancers.

Wally Klemp, Chairman and CEO of Moleculin, said "We remain focused on expanding our intellectual property portfolio for Annamycin. Following the issuance of two US patents in 2024, these new patents enhance the exclusivity of Annamycin, bringing to four the total number of US patents related to Annamycin, in addition to the European patents granted. Based on the data seen to date and feedback we continue to receive from clinicians and patients, we are dedicated to advancing this important and much needed treatment option forward. We continue to make solid progress in our ongoing pivotal, adaptive Phase 3 MIRACLE trial and remain on track to report initial data in the second half of 2025."

Annamycin currently has Fast Track Status and Orphan Drug Designation from the FDA for the treatment of relapsed or refractory AML, in addition to Orphan Drug Designation for the treatment of STS lung mets. Furthermore, Annamycin has Orphan Drug Designation for the treatment of relapsed or refractory acute myeloid leukemia from the European Medicines Agency (EMA).

Moleculin Biotech, Inc. is a Phase 3 clinical-stage pharmaceutical company advancing a pipeline of therapeutic candidates addressing hard-to-treat tumors and viruses. The company's lead program, Annamycin, is a next-generation anthracycline designed to avoid multidrug resistance mechanisms and to eliminate the cardiotoxicity common with currently prescribed anthracyclines. Discussions surrounding Annamycin's lack of cardiotoxicity are based on the intent of its design, preclinical studies demonstrating a lack of cardiotoxicity as compared to currently prescribed anthracyclines and reports from clinical trial cardiac data as reviewed by an independent expert showing a lack of cardiotoxicity to date. Annamycin is currently in development for the treatment of relapsed or refractory acute myeloid leukemia (AML) and soft tissue sarcoma (STS) lung metastases.

Bespak Achieves Sustainability Milestone With First Life Cycle Assessment for Pressurized Metered Dose Inhaler Valve

Bespak, a specialist inhalation contract development and manufacturing organization (CDMO), recently announced it has completed its first life cycle assessment (LCA) for its market-leading BK357 pressurized Metered Dose Inhaler (pMDI) valve. This important step comes as a result of Bespak's commitment to looking beyond low Global Warming Potential (GWP) propellants for opportunities to reduce carbon footprint in the pharma industry.

The completion of Bespak's first LCA marks a significant milestone that has been achieved as part of Bespak's overarching sustainability strategy. It follows Bespak's investment in manufacturing capabilities at clinical and commercial scale for low carbon pMDIs incorporating the low GWP propellants, HFA-152a & HFO-1234ze.

The project was undertaken to better understand the carbon impact of Bespak's materials and manufacturing processes, and to increase transparency in the supply chain for pMDIs. The LCA has been independently verified by expert sustainability scientists from Tunley Environmental in line with ISO 14067:2018 standards. A verified LCA certification for industry partners using the BK357 valve will enable them to leverage robust, science-led insights that can support transparency in their sustainability reporting, sustainable procurement frameworks and the transition to net zero carbon emissions. The LCA also provides clear direction for future carbon reduction initiatives at Bespak, including emission-saving opportunities in the material and energy stages of the product life cycle.

Chris Hirst, CEO of Bespak, said: "The completion of the LCA for our widely used and trusted BK357 pMDI valve demonstrates Bespak's active commitment to championing sustainability in the supply chain for the benefit of customers, patients and the planet. We are excited to be actively researching solutions for carbon reduction beyond the propellant switch, and are proud to provide credible, independently verified data to back up our environmental claims."

Benedicta Bakpa, Head of ESG at Bespak, commented: "This important milestone signifies our ongoing commitment to transparency and accountability in driving sustainable operations. As part of our overarching sustainability initiatives, we continue to identify opportunities to reduce our carbon footprint and work towards our near- and long-term net zero targets."

Bespak is a specialist global contract development and manufacturing organization (CDMO) solely focused on the inhaled and nasal drug delivery industry. It develops and manufactures inhaled and nasal drug products, drug delivery devices and components for the global pharmaceutical market. Headquartered in Holmes Chapel, UK, Bespak provides a specialist, fully integrated service to support customers from early-stage feasibility, analytical and formulation, product development and clinical supply, through to full-scale cGMP batch production.

With a long history in the development and commercial supply of pressurized Metered Dose Inhalers (pMDIs), Bespak supplies a major proportion of the world's pMDI dosing valves and actuators. Built on established expertise but ready for the future, Bespak is a long-term innovation partner committed to driving sustainability in the industry. The company has both established capacity and ongoing expansions to enable the manufacture of pMDIs with low Global Warming Potential (GWP) propellants, making it well positioned to lead the green pMDI transition. More information: www.bespak.com.

Crown Bioscience & NEXT Oncology Cement Partnership Extension

Crown Bioscience recently announced the extension of its partnership with NEXT Oncology, one of the world's largest Phase I Oncology Clinical Trial networks. This strategic partnership will continue to leverage Crown Bioscience's extensive experience in developing clinically relevant cancer organoid and patient-derived xenograft (PDX) models, together with NEXT Oncology's global clinical network and Phase I clinical trials expertise.

Through this extended agreement, Crown Bioscience reaffirms its exclusive rights to provide services based on patient samples sourced from NEXT Oncology's industry-leading global clinical trial network. This collaboration underscores Crown Bioscience's commitment to providing the most clinically relevant PDX and organoid models and solutions for translational oncology research.

"We are thrilled to continue our exclusive partnership with NEXT Oncology," said John Gu, CEO of Crown Bioscience. "NEXT Oncology is globally recognized for its pioneering work in Phase I clinical oncology trials. Extending this partnership allows us to broaden our portfolio and strengthen our position as a leader in translational oncology platforms and integrated solutions. Our combined expertise and global reach will ensure rapid and scalable access to groundbreaking cancer models for our biopharma partners."

"NEXT Oncology is excited to continue our strong partnership with Crown Bioscience," said Dr. Anthony Tolcher, CEO of NEXT Oncology. "Together, we will continue to develop new and highly relevant patient models that Crown's biopharma partners can utilize to advance their translational oncology programs. Our combined efforts continue to support both companies' missions to help cancer patients receive the most advanced medicines possible."

Crown Bioscience, a JSR Life Sciences company, is a global contract research organization (CRO) dedicated to accelerating drug discovery and development in oncology and immuno-oncology. We partner with biotech and pharmaceutical companies to provide innovative, tailored solutions spanning preclinical research, translational platforms, and clinical trial support. With the world's largest commercially available patient-derived xenograft (PDX) collection and approximately 1,000 tumor organoid models powered by Hubrecht Organoid Technology, we offer unparalleled insights across 35 cancer indications. Our expertise spans in vivo, in vitro, ex vivo, and in silico methods, complemented by advanced laboratory services that span the entire drug development continuum. Additionally, our extensive biobank of liquid and human biospecimens, complete with clinical histories, enhances oncology research capabilities. Operating from 11 state-of-the-art facilities across the US, Europe, and APAC, our laboratories meet the highest industry standards, including accreditation by the College of American Pathologists (CAP) and the International Organization for Standardization (ISO). To learn more, visit http://www.crownbio.com.

NEXT Oncology is dedicated to the development of new anticancer agents for patients whose current cancer therapy is no longer working to benefit them and are looking for their next option. NEXT Oncology is partnered with Texas Oncology, the largest private oncology practice in the United States with more than 400 referring medical oncologists. Texas Oncology is a practice within The US Oncology Network, a network of independent, community-based oncologists in the U.S. This formidable size and reach provide NEXT Oncology unprecedented opportunities to transform what has come to be expected from clinical trials of new agents.

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

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

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

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

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

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

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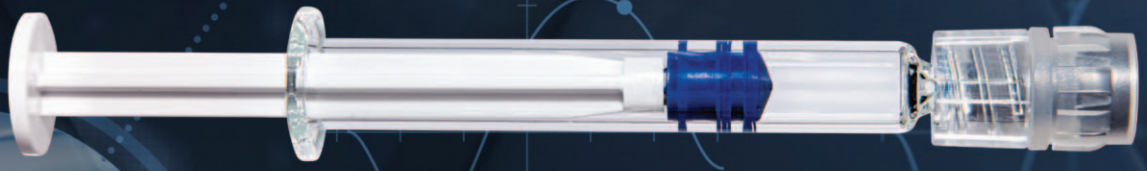

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Formulation Forum

Self Emulsifying Drug Delivery Systems for Improving Oral Bioavailability of Drugs

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

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Jim Huang, PhD
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KEYWORDS: Emulsions, Microemulsions, Nanoemulsions, Self-Emulsifying Systems, Liquid SEDDS/SNEDDS, Solid SEDDS, Absorption, Oral Solubility, Oral Bioavailability, Lipid Classification System, Liquid Capsule

INTRODUCTION

Self-emulsifying/nanoemulsiying drug delivery systems (SEDDS/SNEDDS) have been a subject of continued interest in enhancing solubility and oral bioavailability of drugs as more new chemical entities (NCEs) are being discovered. This enabling technology represents an opportunity for treatment of life-threatening diseases because of lower cost, convenience, and wide acceptance by patient population. Therefore, drug manufacturers are taking a holistic approach for bringing in the innovative molecules to clinics faster. Drug shortages stemming from finding the appropriate excipients and technologies as well efficacies and long-term stability, have also generated opportunities for drug and excipient manufacturers to expedite the development to close the gaps for bringing innovative medicines across all modalities. SEDDS has drawn attention lately because of its simplicity in scale up and manufacturing, cost effectiveness, and its abilities to overcome the absorption via gastrointestinal mucus barrier.[1] It is generally believed that smaller droplet size and surface area, and ability to shape deformation, could help penetrate the mucus layer to enhance the oral bioavailability.[2]

SEDSS/SNEDDS, a homogenized pre-concentrate isotropic mixture composed of drug solubilized and encapsulated in oils, surfactants, and cosurfactant assemblies, are used an alternative to solid oral tablets for immediate release of drugs.[3] Once dispersed in GI fluids, the preconcentrate simultaneously rapidly self-emulsified to smaller particles or oil droplets ranging 10-500 nm o/w emulsions, as shown in Figure 1.[4,5]

FIGURE 1

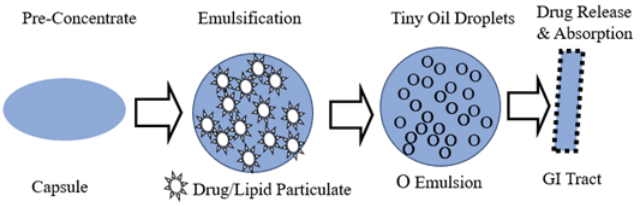

Illustration of self-emulsifying droplet formation from preconcentrate cocktail followed by absorption in the GI tract.

This step is important for SEDDS containing higher percentages of solubilizers and/or surfactants (Type III of lipid formulation classification system (LFCS).[6] Furthermore, faster dispersibility of molecules helps improve their absorption and oral bioavailability.[7] In spite of lower drug solubility and loading challenges compounded with long-term stability for sensitive molecules and those requiring medium to higher doses, with few exceptions, SEDDS/SNEDDS are still used in development of drugs to mitigate or minimize the food effect. This is due, in part, to increase of bile salts, phospholipids, and hydrolysis of digestive triglycerides and their breakdowns in complex lipid aggregates post postprandial in intestine facilitate the solubilization and dissolution of drugs in mixed micelles and uni- and multilamellar vesicles.[8,9] There are, however, challenges due to impediment in release of poorly soluble and lipophilic drugs dissolved in tiny oil droplets, while the soluble and hydrophilic drugs might release more instantaneously.[10] Thus, SEDDS have been applicable for a wide range of molecules with a range of excipients for both lipophilic and hydrophilic molecules. Both solubility and dissolution rate play an important role in improving oral bioavailability by SEDDS administration.

TABLE 1

Lipid Type	Composition	Aqueous Behavior	Characteristics	Application
Type I	Medium and long chain triglycerides (oil)	Requires bile salt for emulsification	Simple, digestion dependent	Nutraceuticals, and lipid soluble vitamins
Type II	Oils and Lipophilic surfactants (HLB < 12)	Spontaneous emulsified	Self-emulsifying, digestion independent	Forms SEDDS, poorly soluble lipophilic drugs
Type IIIa	Oils and high HLB surfactants (<50%)	Forms microemulsions with bile salts	Self-emulsifying, partial digestion dependent	Forms SMEDDS for poorly soluble drugs
Type IIIb	Oils and high HLB surfactants and (>50%)	Forms nanoemulsions with bile salts	Spontaneous self-emulsifying with higher surfactant amount	Forms SNEDDS for poorly soluble and permeable drugs
Type IV	High HLB surfactants and co-surfactants	Forms colloidal micelles	Spontaneous self-emulsifying with higher surfactant and co-surfactant amounts, oil free	Hydrophilic and hydrophobic drugs

Classified SEDDS lipids based on compositions, physical and chemical characteristics, and applications.[7,11]

LIPID FORMULATION CLASSIFICATION SYSTEM (LFCS)

Type I lipid formulation comprised of oils without surfactants inhibits the emulsification of drugs in biological systems, leading to poor drugs absorption due to precipitation in gastrointestinal (GI) tract. However, the presence of pancreatic lipases and slower lipolysis could lead to increase in bioavailability with this formulation. Type 2 lipid formulation comprised of oil and surfactant is the next level wherein the drug is solubilized in surfactants with HLB <12 and self-emulsified as much as possible to facilitate the dispersions in the GI aqueous environment. This could also lead to partial or inadequate solubilization leading to lower oral bioavailability of lipophilic drugs. Type III formulations comprised of high surfactants and co-surfactants with higher HLB values >12, are readily dispersed in aqueous systems by spontaneous self-emulsification process, leading to formation of tiny oil droplets or o/w micro/nanoemulsions and significantly higher oral absorptions than Type I and Type II formulations.[12]

SEDDS FORMULATIONS

Barreiro et al (2024) examined a range of delivery systems for poorly soluble drugs. Of them include the SEDDS/SNEDDS and cited a number of drugs marketed in lipid assemblies. Table 3 lists the approved drugs and their formulation compositions.[13]

To design a better and smarter SEDDS/SNEDDS formulation with smaller particle size and low polydispersity index, a range of solubilizers, surfactants, and oils have been used. Clauss et al (2023) used hydrophobic ion pair with a solubilizer to emulsify insulin glargine complex in a range of excipients composed of Maisine CC as a mixture of mono-, di-, and tri-glycerides of linoleic acid and oleic acid and compared with other solubilizers, including polysorbate 80, Kolliphor® HS15, Labrasol ALF, oleyl alcohol, Plurol oleique CC 497, among others, for immediate emulsification and stability. Long-chain triglycerides help facilitate drug absorption and transport via lymphatic system.[14,15] One formulation was composed of

TABLE 2

Characteristics	SEDDS	SMEDDS	SNEDDS
Appearance	Turbid/cloudy	Translucent	Optically clear
Droplet Size	250 nm to submicron	100-250 nm	<100 nm
Solubilization Capacity	High	High	High
Stability	Thermodynamically unstable	Thermodynamically stable	Kinetically stable
Bioavailability	Moderate increase	Enhanced	Superior
Oil Type	Long chain triglycerides (eg, soybean oil, olive oil)	Medium chain triglycerides (eg, Labrafac, Captex 355)	Medium and short chain triglycerides (eg, Capmul, Miglyol) caprylic and capric triglycerides
HLB of Surfactant	<10	10-12	>12
Co-Surfactant	Not essential	Short chain alcohols (eg, propylene glycol)	Polyethylene glycol (PEG), Transcutol

The comparison of SEDDS, SMEDDS, and SNEDDS.[11]

TABLE 3

Rx Trade name	Drug	Manufacturer	Dosage	Excipient
Sandimmune®	Cyclosporine A	Novartis	Soft gel capsule	Corn oil, linoleoyl macrogolglycerides, sorbitol
Neoral®	Cyclosporine A	Novartis	Soft gel capsule	Corn oil mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, vitamin E
Norvir®	Ritonavir	Abbvie	Soft gel capsule	Oleic acid, Labrafil M-2125CS
Fortovase®	Sanquinavir	Roche	Soft gel capsule	Medium chain mono- and di-glycerides, povidone, vitamin E
Convulex®	Valproic acid	Pfizer	Soft gel capsule	Mono- di glycerides, cellulosic polymers povidone, BHT
Rocaltrol®	Calcitrol	Roche	Soft gel capsule	Triglycerides (coconut oil), sorbitol, parabens
Aptivus®	Tipranavir	Boehringer Ingelheim	Soft gel capsule	Polyoxyl 35 castor oil, propylene glycol, mono- di-caprylic and capric acids, gelatin
Tagretin®	Bexarotene	Ligand Pharma/Eisai	Soft gel capsule	Polyethylene glycol 400, Polysorbate 20, Povidone, and butylated hydroxyanisole
Depakene®	Valproic acid	Abbvie	Soft gel capsule	Corn oil
Vesanoid®	Tretinoin	Roche	Soft gel capsule	Beeswax, hydrogenated soya-bean oil, partially hydrogenated soya-bean oil and refined soya-bean oil
Accutane®	Isotretinoin	Roche	Soft gel capsule	Butylated hydroxyanisole, edetate disodium, hydrogenated vegetable oil (Type-I and Type-II), medium chain triglyceride, refined soybean oil and white wax
Agenerase®	Amprenavir	GSK	Soft gel capsule	Polyethylene glycol 400, Vitamin E-TPGS, propylene glycol

FDA-approved SEDDS drugs

20% Labrasol ALF, 30% Polysorbate 80, 10% Croduret 50, 20% oleic acid, and 20% Maisine CC; whereas, a second formulation, composed of 30% Labrasol ALF, 20% polysorbate, 30% Kolliphor® HS15, and 20% Plurol oleique CC497, were compared for droplet size, polydispersity index, and zeta potential on post self-emulsification in simulated intestinal fluid at pH 6.8. Both formulations were stable over 4 hours, and the PSD, PDI, and zeta potential of both formulations were within the range of each other, though the second formulation showed a slightly higher droplet size compared with the first formulation. In a similar study, Menzel et al (2018) evaluated *in vivo* the self-emulsified formulation of exenatide ion paired with sodium docusate composed of 35% polyoxyl 35 castor oil, 25% Labrafil 1944, 30% Capmul PG 8, and 10% propylene glycol. The release data suggests that blood sugar was controlled in male Sprague Dawley rats.[16]

Gao et al (2021) evaluated the encapsulation of cepharanthine (CEP) in SEDDS composed of 30% oil and emulsifier/co-emulsifier ratio of 5 and achieved the drug loading of >36 mg/ml (3.6%) with droplet size of 38 nm, and the oral bioavailability was >203% compared to free drug. The SEDDS formulations were stable over stable over 6 months as evident from no obvious change on particle size, PDI, and drug loading.[17]

Malkawi et al (2020) evaluated a highly water soluble captopril (CTL), a anionic drug (log P of 0.34) complexed with a cationic polymer in SEDDS composed of 40% Kolliphor® RH40, 20% Kolliphor® EL, and 40% castor oil, and found that droplet size was 100 nm with PDI of <0.5, and showed a sustained release over 3 hours with CTL0: polymer ratios of 1:2 and 1:4. It was also found that only 4%-11% of cationic polymer was incorporated in SEDDS that helped stabilized the drug for sustained release from the oily droplets.[18]

Elnaggar et al (2011) evaluated sildenafil citrate in SNEDDS and nanoemulsions in oral and topical delivery composed of 16% Maisin® 35-1, 32% Kolliphor® RH40, 33% Caproyl 90, and 16% propylene glycol. Sildenafil nanoemulsions with 0.1% drug loading were prepared by adding the drug in placebo SNEDDS diluted in 1:50 mixture with carbonate buffer at pH 10.3.3 The particle size was <200 nm and on dilutions to 50-fold, 100-fold, and 1000-fold, while for nanoemulsions, the droplet size from preconcentrate was about 70 nm (not shown). In vitro release confirmed that SNEDDS formulation showed a similar release as nanoemulsions, upon dialysis of 7.5 mg each sample) with cellulosic membrane (MWCO 12-14K), with faster release in citrate buffer at pH 5 as compared to phosphate buffer at pH 7.4 and carbonate buffer at pH 10.3. In spite of higher *in vitro* drug release by dialysis, transdermal permeability of sildenafil was limited in stratum corneum due to lower water content (20%) by lack of spontaneous self-emulsification in higher concentrations of Kolliphor® RH40 and oils.[3]

Kim et al (2021) evaluated sildenafil in liquid and solid SEDDS for enhancing the oral bioavailability of drugs. Liquid SNEDDS composed of Labrasol:Transcutol HP:Captex

TABLE 4

Solid Carrier	Drug	Method of Preparation	Reference
Soluplus, Neusilin UFL2	Curcumin	Spray drying	21
Silicon Dioxide (Aerosil 200)	Glimepiride	Spray drying	22
Lactose	Docetaxel	Spray drying	23
Manntiol, Fumed Silica	Meloxicam	Lyophilization	24
Microcrystalline cellulose	Furosemide	Compounding as physical blend	25
Silicon Dioxide (Aerosil 200)	Resveratrol	Hot melt extrusion	26
Neusilin US2	Fenofibrate	Hot melt extrusion	27
Neusilin US2, Starch 1500, Avicel PH 102	Ibuprofen	Hot melt extrusion	28

Solid matrices for SEDDS

300 in ratio of 70:15:15 with 1% drug loading, was evaluated against the solid-SNEDDS derived from the same composition as liquid SNEDDS and was adsorbed on a solid porous matrix carrier HDK N20. In comparison with amorphous sildenafil derived from spray dried powder of PVP, Labrasol in ethanol, solid SNEDDS showed significantly higher bioavailability in rats compared to amorphous spray dried powder (AUC 1508 h.ng/ml vs. 1339 h.ng/ml) in spite of similar dissolution behavior.[19]

SOLID SEDDS (S-SEDDS)

Yet, in many of the examples previously cited relate to liquid SEDDS and the approved drugs in liquid soft gel capsules, there have been equal interests to develop an s-SEDDS on solid matrix. Therefore, the research continues to improve the stability of liquid SEDDS as some of the drug may not be stable over their shelf lives.[20] There are several challenges that could unravel; first, identifying the right excipients and solubilizers compatible to drugs, second, should be able to self-emulsify leading to give rise to small droplets, third increase drug loading, and fourth is the stability of drugs in SEDDS. The latter is critical and can be addressed by identifying the appropriate excipients and polymers. The key criteria for matrix are porosity, hydrophilicity, surface area, and good flowability. Table 4 lists a number of solid matrices as carriers for delivery of drugs in s-SEDDS.

CHARACTERIZATION OF SEDDS & S-SEDDS

Several physical techniques are used to characterize the SEDDS formulations in liquids and solids. Though a technique used might be specific for liquid SEDDS, the same technique might be applied to s-SEDDS. For instance, the particle size distribution of SEDDS derived from lipid droplets can be measured by dynamic light scattering and laser diffraction methods. Self-emulsifying efficiency resulting from liquid cocktail and/or solid SEDDS can be measured by rate of droplet formation from each lipid assembly upon contact with aqueous GI fluid that could provide insight into emulsification quality and potential for drug absorption. Other physical characteristics such as cloud point also help determine the stability of formulation at varying temperatures, while the lipolysis and dissolution characteristics provide the *in vitro* release from liquid cocktail and s-SEDDS formulations. These characterizations are important to ensure SEDDS retain the desirable properties to yield faster dispersibility with smaller particles by self-emulsifying process.[29]

s-SEDDS require additional techniques to fully characterize them. For example, powder x-ray diffraction (PXRD) and differential scanning calorimetry (DSC) are used to evaluate the solid state of drug, while infrared (IR) and Raman are typically used to evaluate drug-polymer interactions at molecular levels. SEM and TEM are used to understand the morphology of the drug in the solid matrix. In addition, the powder flowability, compressibility, and Hausner ratio and Carr's index are all contribute to basic understanding of robust s-SEDDS formulations in solid matrices.

FUTURE PERSPECTIVES & SUMMARY

As more NCEs continue to be discovered with less options to find the appropriate excipients and solubilizers for Class II and IV drugs, the pharma industry has begun to evaluate liquid SEDDS for expediting drugs to market. With the understanding of easier to scale up and manufacture than oral solid tablets and capsules, liquid capsules containing SEDDS have gained more traction for early development of NCEs in the recent past. SEDDS is applicable to molecules across all modalities and therapeutic areas, especially those requiring stable formulations and targeted delivery.

With the new paradigm shift in personalized medicines, we also observed that SEDDS can be 3D printed into individual dosages, thus highlighting its broader applicability in producing multi component formulations with customized release kinetics. On the other hand, delivery of oral peptides and proteins with the appropriate permeation enhancers in SEDDS are equally important because it offers a promising platform for enhancing stability and permeability across

epithelial membrane in GI tract. SEDDS encapsulating peptides and proteins, and for biologics for unmet medical needs, can minimize enzymatic degradation and improve permeability across intestinal membrane.[30] Supersaturable SEDDS (Su-SEDDS) created by incorporating hydrophilic polymers/ solubilizers, such as poloxamers, may help precipitate drugs, thus allowing drug to maintain its supersaturated state upon dilution in GI fluids. It is applicable to those drugs having a narrow therapeutic window.[31]

Ascendia's EmulSol® technology can be used for a range of challenging molecules. Designed by selection of appropriate lipids, solubilizers, and surfactants, EmulSol® offers the solutions for enhancing solubility and bioavailability of molecules and biologics across all modalities. Ascendia's GMP manufacturing capabilities equipped with the state of art liquid capsule filling and banding equipment for formulation development and scale up, offer choices for bringing the new therapy modalities from preclinical to the clinic studies at a faster speed. ◆

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TRANSDERMAL DELIVERY

SkinJect's Doxorubicin-Loaded Dissolvable Microneedle Array (D-MNA): A Revolutionary Approach to Transdermal Drug Delivery

By: Raza Bokhari, MD, Edward Brennan, MD, FACS, and Madison Weisz, MS

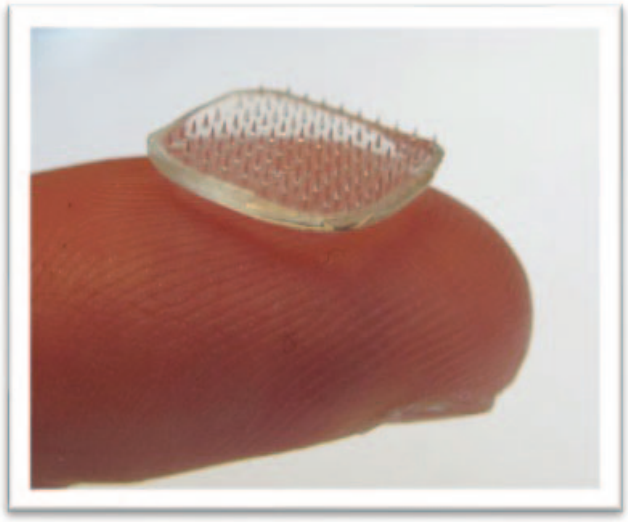
INTRODUCTION

Skin diseases are amongst the most prevalent non-fatal conditions impacting 25% of the world population. These skin diseases are negatively impacting the quality of life, causing loss of productivity and increase in healthcare costs. Amongst skin diseases, non-melanoma skin cancers, particularly Basal Cell Carcinoma of the skin (BCC), result in substantial healthcare expense and loss in productivity. BCC is the most common cancer in the world. In US alone, 5 million new cases of BCC are diagnosed every year.

The holy grail in improving treatment outcomes in skin diseases and substantial reduction in healthcare cost revolves around developing transdermal drug delivery systems (TDDS). TDDS are advantageous due to their high bioavailability, low systemic toxicity, and improved patient compliance. There are different types of transdermal delivery systems currently under development; to deliver large molecules dissolvable microneedle arrays are emerging as a front runner.

Medicus Pharma's wholly owned subsidiary, SkinJect, is focused on advancing the clinical development program of a TDDS to non-invasively treat Basal cell carcinoma of the skin using patented dissolvable doxorubicin containing microneedle arrays (D-MNA). The investigational product represents a significant advancement in precision drug delivery technology. The following explores the D-MNA treatment, highlighting its drug delivery mechanisms, advantages over traditional treatments, and clinical potential.

FIGURE 1



THE EVOLUTION OF MICRONEEDLE ARRAYS

Transdermal drug delivery systems have long been an area of interest due to their potential to bypass the gastrointestinal tract and liver, thereby improving bioavailability and reducing systemic side effects. Microneedle arrays are a subset of transdermal drug delivery systems that utilize tiny needles to penetrate the stratum corneum, the outermost layer of the skin, enabling the direct delivery of drugs into the dermal layer.

Microneedle arrays come in various forms, including solid, coated, hollow, and dissolvable. Dissolvable microneedle arrays, like the one developed by SkinJect, are particularly innovative as they encapsulate the drug within a biodegradable matrix that dis-

solves upon application, ensuring complete drug release and minimal waste.

DOXORUBICIN: A KNOWN ANTI-TUMORAL AGENT

The active drug used in SkinJect's D-MNA, Doxorubicin, is an anthracycline antibiotic widely used in oncology for its potent anti-tumoral properties. Its mechanism of action involves intercalation into DNA, disrupting the replication process and ultimately leading to cell death. However, systemic administration of doxorubicin is associated with significant side effects, including cardiotoxicity, which limits its use.

DESIGN & COMPOSITION OF D-MNA

The SkinJect D-MNA is a tip-loaded dissolvable microneedle array, each array measuring 15 x 15 mm and containing 400 microneedles, each 750 microns deep. The microneedles are designed to dissolve upon insertion into the skin, releasing the embedded drug directly into the peri-epidermal space. Key components include:

- Doxorubicin HCl: A potent cytotoxic agent used in oncology.
- Citric Acid and Sodium Phosphate: Buffering agents ensuring drug stability.
- Trehalose Dihydrate and Carboxymethyl Cellulose (CMC): Structural components that facilitate the dissolution of the microneedles.
- USP Water: The solvent.

MECHANISM OF ACTION

Upon application, the microneedles penetrate the skin's upper layers, dissolving to release doxorubicin directly at the tumor site. This localized delivery enhances drug concentration at the target site while minimizing systemic exposure and associated side effects. The matrix dissolves completely, leaving no residual material, thus enhancing patient safety.

ADVANTAGES OVER TRADITIONAL TREATMENTS

Precision Delivery

D-MNA allows for precise delivery of doxorubicin to Basal Cell Carcinoma sites,

FIGURE 2

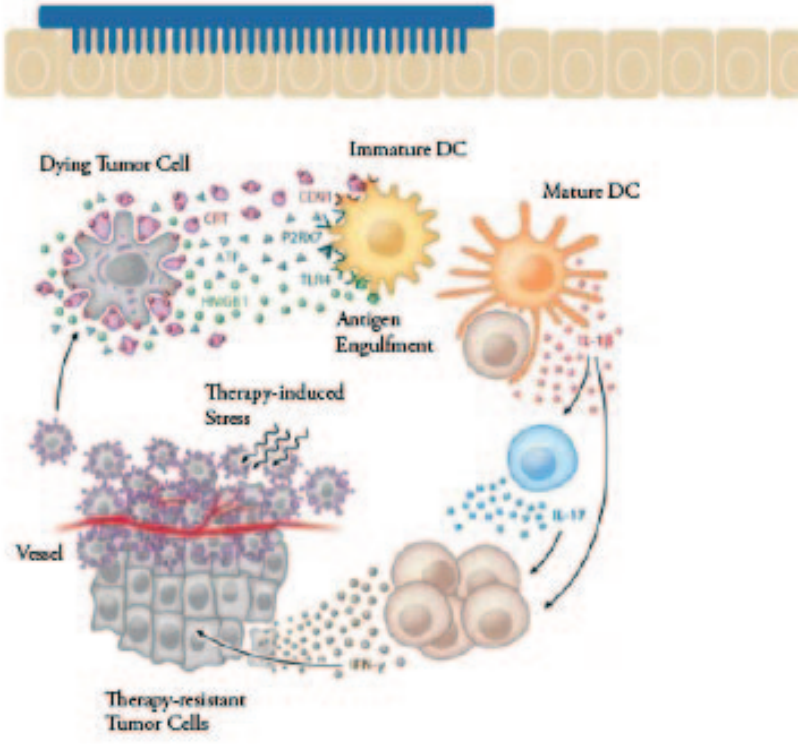
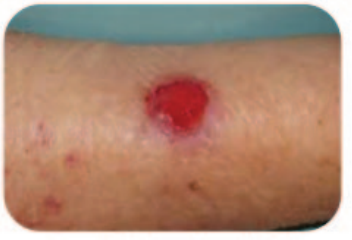
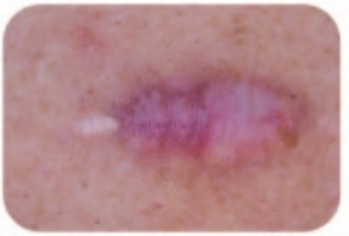


FIGURE 3



Basal Cell Carcinoma (BCC)



BCC treated with Mohs Surgery (lumpy scar)

BCC treated with SkinJect Patch
**requires proof of concept-Phase 2 trial in progress*

improving efficacy compared to topical creams that may not penetrate deeply enough to effectively kill cancer cells. The precision of the microneedles ensures that the drug is delivered directly to the affected area, maximizing therapeutic effects while minimizing systemic effects.

Minimized Side Effects

By localizing drug delivery, the D-MNA eliminates systemic exposure to doxorubicin, thereby minimizing the risk of side effects such as cardiotoxicity. This is particularly important in oncology, where the therapeutic index is often narrow, and systemic side effects can limit the efficacy of treatment.

Non-Invasive

Unlike the current standard of care, painful surgical excision or Mohs micrographic surgery, D-MNA offers a non-invasive alternative with reduced risk of bleeding, scarring, and infection. This offers patients a treatment option with a better quality of life, particularly those who may be averse to painful and aesthetically unpleasant surgical procedures.

Enhanced Stability & Handling

The inclusion of buffering agents like citric acid and sodium phosphate ensures the stability of doxorubicin, while the solid-state storage of the arrays simplifies handling and transportation. This enhances the practicality of the D-MNA, making it easier to store, transport, and use in various clinical settings.

CLINICAL DEVELOPMENT & TRIALS NONCLINICAL STUDIES

Initial nonclinical studies utilized murine and human models of squamous cell carcinoma and melanoma, as there are no Basal Cell Carcinoma animal models. In murine models, D-MNA treatment significantly increased cell death, elevated pro-inflammatory cytokine levels, and improved survival rates compared to controls. In *ex-vivo* human squamous cell carcinoma samples, D-MNA induced significant tumor cell death and modulated the tumor microenvironment toward an anti-tumor phenotype.

Pharmacokinetic studies in mice and minipigs showed that doxorubicin delivered via D-MNA remained localized at the application site, with minimal systemic exposure. Blood level measurements confirmed undetectable doxorubicin in plasma of D-MNA-treated animals, underscoring the efficacy of localized delivery.

PHASE 1 CLINICAL TRIALS

A Phase 1 open-label dose escalation trial completed in 2021 evaluated the safety and tolerability of D-MNA in Basal Cell Carcinoma patients. The study enrolled a total of 13 subjects, used a 3+3 dose escalation design with four dose groups (25 μg, 50 μg, 100 μg, and 200 μg) and a placebo control group.

RESULTS

- **Safety:** No serious adverse events (SAEs) or dose-limiting toxicities (DLTs).
- **Tolerability:** The D-MNA was well-tolerated across all dose levels, with minimal local reactions.
- **Efficacy:** Preliminary assessments indicated positive responses in Basal Cell Carcinoma lesions, with 6 patients showing complete lesion response at each dose level.

The Phase I trial also monitored various biomarkers to better understand the biological response to D-MNA treatment. Biomarkers such as inflammatory cytokines and immune cell infiltration were assessed, providing insights into the mechanism of action and potential immune-modulating effects of the treatment.

FUTURE DIRECTIONS

Building on the success of the Phase 1 trial, notably the pristine safety outcome and complete clinical response on histological examination of 6 Basal Cell Carcinoma patients, SkinJect plans to initiate a Phase 2 trial to further evaluate D-MNA's safety and efficacy among a larger Basal Cell Carcinoma patient cohort in Q3 of 2024. In addition to evaluating safety, tolerability, and efficacy, the trial will aim to optimize the dosage and administration schedule to maximize therapeutic outcomes. Particularly, the study is designed as a double blinded, randomized trial set to enroll up to 60 subjects among 5-6 clinical study sites. The study will further evaluate the 100 and 200 μg dose levels against a placebo control group.

One of the clinical sites participating in the Phase 2 trial will also be incorporating both artificial intelligence (AI) and confocal microscopy as supplemental endpoints. The company aim is to minimize invasive intervention at all levels.

CONCLUSION

SkinJect's D-MNA represents a groundbreaking advancement in transdermal drug delivery, offering a precise, non-invasive, and effective alternative to traditional BCC treatments primarily relying on Mohs surgery. According to 360iResearch's Global Forecast 2024-2030, Medicus Pharma Ltd. is ranked # 7 as a leading player in BCC, ahead of leading Pharma companies in the space.

By leveraging dissolvable microneedle technology, SkinJect enhances drug delivery efficacy, and patient safety, and

FIGURE 4

Company	Quadrant	Ranking	Score	Business Strategy	Product Satisfaction
Bausch Health Companies Inc.	Forefront	#1	8.26	7.66	8.86
Regeneron Pharmaceuticals, Inc.	Forefront	#2	8.06	8.16	7.95
F. Hoffmann-La Roche AG	Forefront	#3	7.12	8.74	5.51
Bristol-Myers Squibb Company	Forefront	#4	7.08	6.99	7.16
Sanofi S.A.	Vital	#5	6.52	8.97	4.07
Sun Pharmaceutical Industries Ltd.	Forefront	#6	6.38	6.47	6.30
Medicus Pharma Ltd.	Pathfinder	#7	6.07	3.36	8.79
LEO Pharma A/S	Pathfinder	#8	5.66	3.08	8.25
Perrigo Company PLC	Vital	#9	5.48	6.45	4.50
Amgen Inc.	Pathfinder	#10	4.93	2.66	7.20
AbbVie Inc.	Vital	#11	4.83	7.80	1.87
Teva Pharmaceutical Industries Ltd.	Vital	#12	4.82	6.61	3.03
Biofrontera AG	Pathfinder	#13	4.80	1.78	7.82
Almirall, LLC	Vital	#14	4.79	5.89	3.68
Glenmark Pharmaceuticals Limited	Pathfinder	#15	4.24	1.60	6.87
Eli Lilly and Company	Niche	#16	4.15	4.00	4.30
Galderma S.A.	Vital	#17	3.96	6.57	1.34
Sol-Gel Technologies Ltd.	Pathfinder	#18	3.58	1.15	6.01
Redx Pharma PLC	Niche	#19	2.89	2.92	2.87
Medivir AB	Niche	#20	2.43	1.28	3.59
Elekta AB	Niche	#21	1.98	2.93	1.03
OncoBeta GmbH	Niche	#22	1.84	1.93	1.75
SkinCure Oncology	Niche	#23	1.17	1.77	0.57

ease of use. As clinical development progresses, D-MNA has the potential to revolutionize treatment landscapes for Basal Cell Carcinoma and other non-melanoma skin cancers. ◆

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BIOGRAPHIES

Raza Bokhari, MD, Executive Chairman & CEO, is a recipient of Philadelphia Business Journal's 40 under 40 award. He isa physician turned serial entrepreneur and has a demonstrated successful track record in aggregating and accelerating life sciences, healthcare services and Pharmaceutical R&D companies. He is the managing partner of RBx Capital, LP and also serves as the Chairman of the Board of Parkway clinical Laboratories (PCL) a fifty-year-old College of American Pathologist (CAP) accredited, CLIA certified *in-vitro* diagnostic laboratory. He previously served as Executive Chairman and CEO of FSD Pharma (Nasdaq: HUGE), where his strategies successfully pivoted the company out of medicinal cannabis and into a clinical stage pharmaceutical R&D, a transition marked by a NASDAQ listing in January 2020, and raising nearly $100M institutional capital to fuel growth and expansion. He earned a Doctor of Medicine degree from the University of Punjab, Rawalpindi Medical College, and an Executive MBA from Temple University, Fox School of Business & Management. In addition to his corporate roles, he serves as the Vice Chairman of the World Affairs Council of Philadelphia. He formerly served on the Board of Temple University's Fox School of Business and Management as Chairman of the Executive Advisory Committee and was a Trustee of the esteemed Franklin Institute and Foreign Policy Research Institute. He, through his family foundation, believes in giving back and investing in the community. In recognition of a $1 million gift, he made to his alma mater, Temple University, its Fox Business School named the Innovation & Entrepreneurship Institute Suite in his honor. The school acknowledged Dr. Bokhari in 2018 by naming him a Centennial Honoree, a special collection of entrepreneurs, visionaries, and disruptors who helped shape the Fox School and the business world since 1918. More information on Dr. Bokhari, is available at www.Razabokhari.com.

Edward J. Brennan, MD, FACS, Chief Medical Officer, is a veteran pharmaceutical and clinical research executive with over 25 years of drug development experience. He has held senior medical leadership roles at major companies, including Wyeth, GlaxoSmithKline, and IndiPharm. As Medical Director at Wyeth and GSK, Dr. Brennan led clinical development programs that resulted in 10 FDA drug approvals. He oversaw teams responsible for all phases of clinical research as well as interactions with regulatory authorities. His therapeutic expertise includes Immunology, Oncology, Women's Health, and Genetic Diseases. Before industry roles, Dr. Brennan practiced medicine as an internist. He received his MD from Temple University School of Medicine after completing a Bachelor of Science in Pharmacy.

Madison Weisz, MS, is currently serving as Vice President at Medicus Pharma, where she excels in asset valuation, clinical study design, medical and regulatory writing, programming, and statistical analysis. She has a background in clinical development and data analytics, with her most significant prior roles at Ocugen Inc and the US Chamber of Commerce Foundation. Through her educational background in Applied Economics from George Washington University and her career experience in entrepreneurship and biotechnology, she offers a unique approach to biostatistics, positively impacting clinical study outcomes.

Drug Development
EXECUTIVE

Anshul Gupte, PhD, RAC Drugs

VP, Pharmaceutical Development

PCI Pharma Services

pci PHARMA SERVICES

PCI Pharma Services: Driving Precision, Agility & Partnership in Complex Drug Development

With the rise of targeted therapies, complex biologics, and ultra-potent small molecules, the role of pharmaceutical development has evolved far beyond its traditional scope. Today, it demands greater integration into the drug development pathway, condensed timelines, and technical agility across drug delivery formats and therapeutic modalities.

Drug Development & Delivery recently spoke with Anshul Gupte PhD, RAC Drugs, Vice President of Pharmaceutical Development at PCI Pharma Services, about phase-appropriate development, technical hurdles in pharmaceutical sciences, building agile teams, and what sponsors should prioritize when planning their strategy for novel therapies.

Q: How would you define the role of pharmaceutical development in today's drug development landscape?

A: Pharmaceutical development is not a one-time event. It's a continuous, evolving function that plays a critical role across the full lifecycle of a drug product, from selecting the appropriate molecule post-discovery through "druggability" studies to extending the life cycle of the drug product through reformulation. The scope of pharmaceutical development begins with defining Target Product Profile (TPP) and ensuring that the Critical Quality Attributes (CQA), such as, identity, strength, purity, and potency are built into the final drug product.

Pharmaceutical development in today's drug development landscape involves evaluating and establishing a drug product that is stable and manufacturable across

multiple drug product presentations throughout the clinical to commercialization life cycle. It's an iterative process, interacting upstream with drug substance development and downstream with packaging development.

As the product progresses through clinical stages, the formulation evolves. A powder-in-capsule or a liquid in a vial drug product may ultimately become a modified-release tablet or a prefilled syringe product. At each phase (early, mid, and late-stage), our work supports different goals: speed and flexibility in early development, robustness and scalability late stage, and long-term stability and reproducibility by the time we reach commercial.

Today's development landscape is dominated by targeted therapies, which create a unique set of challenges. These include low bioavailability challenges due to the drug discovery paradigm, content uniformity challenges due the low doses required to achieve the desired pharmacological activity (as these are targeted modalities), and safe handling challenges for highly potent compounds.

Moreover, pharmaceutical development also encompasses packaging — understanding how the drug product interacts with its final container closure system, whether it's a blister pack, bottle, vial, syringe, or cartridge. So it's not just about formulation and process — it's also about ensuring compatibility and stability through to the final packaging configuration.

Q: What is your personal philosophy on how pharmaceutical development should be approached scientifically, strategically, and operationally?

A: Scientifically, pharmaceutical development should be conducted following Quality by Design (QbD) principles as it provides a systematic approach to development. QbD works through predefined objectives, emphasizing product and process understanding and control based on sound science and quality risk management.

We always begin with the end in sight, which translates to what's required in terms of desired final product quality, safety, purity and effectiveness. Defining these through the TPP should always be the first step. But TPP isn't static; it becomes more focused as the development journey progresses. Initially, it's broad and flexible, but by the time you're entering mid to late-phase trials, you're working within defined specification limits that reflect real-world use, regulatory expectations, and patient needs.

Strategically, I believe in building a flexible, stepwise, phase-appropriate development plan, thinking several stages ahead, but always focusing on the immediate goals of the current phase, such as starting with a simple neat API in capsule formulation that has sufficient stability for the duration of a first-in-human study, followed by development of a robust formulation for later phase clinical studies.

A phase-appropriate plan should emphasize defining clear inputs and outputs for every stage. What data do we need to generate at this point? What knowledge must we carry forward to the next phase? That operational discipline ensures each phase builds intelligently on the previous.

Operationally, communication is a cornerstone. We work closely with our clients' clinical and CMC teams to align what they want with what is scientifically and operationally feasible. Our job as a CDMO is to interpret the information provided by the client into a viable formulation that's scalable and patient-friendly, without locking ourselves into a rigid path that won't adapt well as requirements evolve.

Q: How does PCI apply phase-appropriate development in practice?

A: We think of phase-appropriate development simply in terms of translating the pre-clinical and clinical journey of the drug product (such as tox batches, Phases 1/2/3) to stage gates for our pharmaceutical development process. Phase-appropriate development is about defining your goals and technical rigor based on where you are in the drug development lifecycle.

In early development, the goal is to get to the clinic fast. It's crucial to remain flexible during development to cover a wide dose range and adapt the formulation and process with non-clinical or clinical data. As we move through the clinical phases, we begin identifying Critical Material Attributes (CMA), CQAs, Critical Process Parameters (CPP) and understanding the interplay between CMAs, CPPs, and CQAs. Evaluation of the aforementioned elements leads to optimal control strategy and specifications for the DS, ingredients, and the process steps.

Drug substance is often being scaled from lab to pilot to commercial scale concurrently as the drug product is being developed. That means communication between drug product and drug substance teams (or CDMOs) is critical. You can't develop a robust formulation without understanding how the API might change in morphology, particle size, or impurity profile as it scales. For targeted therapies in particular, the margin for error is minimal.

Q: What are PCI's current pharmaceutical development capabilities across oral and sterile formats?

A: Our facility in Tredegar, Wales, offers the full range of Oral Solid Dose (OSD) and Liquid formulation and analytical development, supported by on-site clinical and commercial manufacturing and packaging. The site specializes in handling High Potent APIs (HPAPIs). We support toxicological batches, First in Human (FIH), early-phase and late-phase clinical development.

The typical OSD processes supported include direct compression, roller compaction, wet granulation, milling, compression, encapsulation, and film coating. We support a variety of dosage forms, such as, tablets, capsules, powders, solutions, and suspensions for Immediate Release (IR), Paediatric dosing, Orally Disintegrating Tablets (ODTs), modified-release (MR) products, and others.

Our facilities in Bedford, NH, and León, Spain, offer sterile formulation and analytical development, supported by on-site clinical and commercial Sterile Fill Finish (SFF). Bedford is a recognized leader in lyophilization development, with over 700 lyophilization cycles successfully developed, optimized, and transferred in manufacturing. Our León site also has unique capabilities in microparticles, nano-emulsions, and ophthalmic development.

PCI is investing approximately $10M to further expand our development offering. The investment will ensure that, in addition to non-potent compounds, we will be able to handle HPAPIs, small molecules, biologics, and a range of conjugates, such as ADCs, PROTACs, and others. Our investment is focused on three fundamental pillars: the right facility, appropriate equipment, and technically competent talent. Through these, we will establish Pharmaceutical Development Centres of Excellence (CoE) at our Bedford and León facilities, which are expected to be operational in early 2026.

Through our development CoEs, we will be able to support a wide range of formulations, including liquids, emulsions, lyophilized products, ophthalmics, and diagnostic reagents, as well as an extensive variety of drug product presentations – vials, syringes, cartridges, bottles, and IV bags. We will also provide technical partnership and solutions for complex modalities and formulations, such as long acting injectables (LAIs) and high viscosity injectables for subcutaneous or intramuscular routes.

Q: How does PCI deliver an integrated development and supply solution?

A: PCI's three segments – Development and Manufacturing (D&M), Clinical Trial Supply and Commercial Technology Services – provide integrated services to our clients throughout their supply chain.

Each of our three development sites (Tredegar, Wales; Bedford, NH; and Léon, Spain) have co-located formulation and analytical teams to ensure speed, coordination, and agility. We have identified areas that we need to supplement our knowledge and capabilities with agile and competent partners. These partnerships allow us to offer specialized bioavailability/solubility enhancement solutions or specialized analytical testing, ensuring that every element of development – from development to commercial packaging – is aligned. We work closely with our clinical manufacturing and packaging teams on site and throughout our global network, resulting in industry-leading packaging integration. With high-potency and sterile packaging facilities in the UK (Hay, Bridgend) and the US (Philadelphia, Rockford), PCI brings packaging into development discussions early to prevent formulation-packaging incompatibilities.

This is supported by global clinical and commercial distribution capabilities, enabling us to truly offer a "molecule-to-market" solution under one network.

Q: What are the biggest technical hurdles in formulation development today?

A: The absence of HPAPI handling capabilities in both oral and sterile development has been a key barrier to offering comprehensive development solutions for targeted modalities, such as ADCs, PROTACs, and others.

Today, some of the most significant technical challenges in formulation development include poor solubility and bioavailability, as well as stability concerns for oral solid dose (OSD) formulations. In sterile development, challenges include poor solubility, the need for high-concentration formulations, and stability issues.

Q: How does your team approach complex problem-solving and communication?

A: We train our scientists to be accountable stewards of the drug product. When a problem arises – say, a formulation or analytical issue or unexpected issue during batch manufacture or release – we expect our teams to study the data and propose suitable hypotheses. We bring those to the client immediately, rather than working in a silo to find the "perfect" answer.

We work collaboratively, engaging clients in the troubleshooting process from the beginning. That's how we save time and resources — by solving problems as one team, rather than wasting cycles chasing the wrong hypothesis.

We also emphasize managing API with care. Especially during early phase of development, the material is precious. So, we train our teams to plan experiments meticulously, use only what's necessary, and always get client buy-in for optional studies.

Q: Finally, what advice would you give companies planning their development strategy for novel drug products?

A: Start early. Engage a drug development partner who offers integrated services, not just formulation and analytical development but also manufacturing and packaging. Nobody can do everything, but the simpler your supply chain, the fewer risks you face. Vertically integrated drug substance and drug product CDMOs present a great solution, but understanding their capabilities is crucial as they might be fully integrated, but they have expertise only in certain aspects of the drug development process.

Make sure your partner is flexible, scientifically robust, and honest about what they can and cannot do. And find someone who's willing to find the best solution to your molecule rather than pushing their solution to fit your molecule. This could mean engaging with external expertise where needed. We've done this ourselves, partnering with best-in-class solubility and specialized testing vendors to supplement our core strengths.

Above all, treat your CDMO as a strategic collaborator. Bring them in early and share your plans. Let them help you build a roadmap for your product. That's how you accelerate development and avoid costly missteps. ◆

NASAL DRUG DELIVERY

Overcoming the Challenges of Formulation Development

By: Eric Kaneps

INTRODUCTION

Nasal administration has emerged as a promising drug delivery route in many different indications. Nasal drug delivery offers the potential for fast action, increased bioavailability, and an improved patient administration experience. The nasal drug delivery market was worth US$19 billion in 2022 and is expected to grow to US$30 billion by 2030 as demand for intranasal drug products increases.[1] As well as offering an administration route for formulations containing new chemical entities (NCEs), nasal drug delivery can also be utilized in the repositioning of approved therapies through the 505(b)(2) regulatory pathway.

While nasal drug delivery offers many advantages, challenges remain associated with formulation development in intranasal products. The pharmaceutical industry must successfully navigate these challenges to unlock the full potential of nasal drug delivery and deliver innovative therapies to the patients who need them.

The following will explore the nasal drug delivery landscape, including the benefits of nasal administration compared with other routes and the unique formulation challenges associated with this delivery method. The consequences of failing to address nasal product formulation challenges and approaches for overcoming challenges will also be discussed, along with product scaling and commercialization.

EXPLORING THE BENEFITS OF NASAL DRUG DELIVERY

With the progression of nasal drug delivery, the administration route has gone from being used predominantly in local treatments for rhinitis and decongestion to more complex indications that benefit from the blood-to-brain delivery method that nasal sprays can exploit. More research studies and clinical data have emerged, increasing the understanding of nasal delivery and leading to its exploration in many other applications. Intranasal delivery is now an attractive administration route for many different indications, including Parkinson's rigidity, migraine, panic attacks, Alzheimer's disease, multiple sclerosis attacks, and cardiovascular events.[2]

One aspect of nasal administration that makes it an attractive option for these, and other indications, is the rapid onset of action that can be achieved for both local and systemic delivery. The nasal mucosa is highly vascularized and rich in immune cell populations, which can result in rapid delivery and high systemic availability of administered drug products.[3] By bypassing the liver, nasal drug delivery avoids first-pass metabolism, allowing drug products to be absorbed directly into the systemic circulation and increasing bioavailability.[3] For inhaled vaccines, increased immune cells result in a rapid immune response and onset of action. Additionally, nasal administration offers local delivery by directly targeting drugs to the brain from the nasal cavity.[3,4]

Aside from bioavailability benefits, nasal drug delivery also has the potential to improve the patient administration experience. Nasal products are often relatively easy for patients to use compared with injectable drugs, leading to the potential for self-

administration. This patient-centric delivery is also non-invasive, a distinct advantage when compared with other methods that need to be administered via injection.

Many pharmaceutical companies are interested in nasal drug delivery for the development of NCEs. However, nasal administration is also being explored as a method to create new, more competitive versions of drugs already on the market through reformulation. Repositioning of already approved medications with reformulation can be achieved through the 505(b)(2) regulatory pathway. By repositioning existing products, developers can deliver the benefits of non-invasive nasal administration to patients who need these therapies. Examples of therapies that could benefit from reformulation into nasal products include emergency injectable drugs and vaccines.

Taking all the advantages of nasal drug delivery into consideration, it is clear why many drug developers in the pharmaceutical industry are increasingly choosing nasal administration for their products over oral or parenteral routes. However, to deliver on the potential of nasal drug delivery, drug developers need to overcome the challenges associated with this administration route, including the unique aspects of formulation development and manufacturing.

THE UNIQUE FORMULATION CHALLENGES OF NASAL DRUG DELIVERY PRODUCTS

Nasal drug products are drug/device combinations, requiring a device to spray the formulation into the nasal cavity and onto the site of action. Nasal products therefore face challenges relating to the

interaction between the drug formulation and the spray device as well as the development of the active pharmaceutical ingredient (API) formulations themselves. Both the drug and the device need to work together in combination to ensure a safe and effective product.

The nature of drug/device combinations means that nasal products require an interconnected approach to development. Pre-formulation and formulation development, nasal spray device selection and spray method development activities should be undertaken in unison. These studies are required to gain an understanding of the physicochemical properties of the API and the parameters that could affect how readily the formulation atomizes when it is released from the device (such as viscosity, surface tension, and density). Both the design of the spray device and the interaction between the device and the formulation can affect how the final drug product performs. Performing activities, such as formulation development and nasal spray device selection at the same time, also helps to ensure that the final product is functional and safe.

Specific factors that need to be considered throughout nasal drug/device preformulation, formulation, spray device selection and spray method development include:

- The choice of aqueous suspension, hydroalcoholic, or co-solvent formulations, or non-aqueous systems if the drug substance is relatively insoluble in water.
- If the final drug product needs to be preservative-free and how aseptic manufacturing will be achieved.
- If any excipients or preservatives need to be added to produce stable and effective formulations.
- The number of doses that will be delivered per device.
- Any spray characteristics that could af-

fect device selection, such as priming, pump delivery, droplet size distribution and spray pattern, as these could affect the performance of the final product.

CONSIDERATIONS FOR API FORMULATIONS & EXCIPIENTS

Other challenges in formulation development relate to the API being explored and its chemical properties. Although nasal administration as a delivery method avoids first-pass metabolism, poor solubility of a growing number of APIs can still negatively impact bioavailability and must be overcome. It is predicted that as many as 90% of APIs in the development pipeline face difficulties with solubility and bioavailability.5

The addition of excipients should be considered to help during formulation development. Excipients can improve bioavailability and achieve the desired stability and shelf-life of the final product. However, choosing which excipients to add to a formulation can be challenging.

Some excipients can act as penetration enhancers or mucoadhesives in the formulation of liquid nasal sprays by increasing contact/residence times in the nasal cavity or increasing absorption by enhancing permeability.

As APIs become more complex, selecting appropriate excipients becomes more challenging. Novel excipients are increasingly being used to address these problems, which bring their own challenges. Developers need to ensure that excipients are safe, of high quality, and comply with regulations, which requires more work with novel excipients that have not been used previously.

Finally, nasal drug delivery is also being explored for the treatment of mental health disorders, such as depression, anxiety, and schizophrenia. For these applications, nasal delivery provides the benefit of local administration and directly targeting the brain through the nasal cavity. Many of these applications include the use of controlled substances, which require further compliance with the Drug Enforcement Agency (DEA).

Overcoming the challenges associated with formulation development and device selection is critical for the safety and performance of the final nasal product. In turn, ensuring the safety and efficacy of the final product helps to meet the demand for nasal administration, which means that these innovative therapies can be delivered to the patients who need them.

The formulation development challenges in nasal drug delivery are not straightforward, and delivering on the potential of nasal administration is a complicated undertaking. A proactive approach is required to solve issues, prevent possible delays, and deliver nasal drug products to patients. Pharmaceutical companies are therefore increasingly partnering with contract development and manufacturing organizations (CDMOs) that have expertise and experience in nasal drug delivery. By leveraging CDMO partnerships, nasal drug developers can successfully navigate the challenges of formulation development and build a solid foundation for scaling their products to commercial levels.

OVERCOMING FORMULATION CHALLENGES IN NASAL DRUG DELIVERY

Partnerships with CDMOs can help to overcome the unique formulation challenges associated with nasal product drug/device combinations. The main challenge involves performing all of the preformulation, formulation, nasal spray selectio,n and spray method development studies all at the same time. This requires teams to work closely together, with good communication and collaboration to achieve this and successfully develop a new nasal spray product. Partnering with a CDMO can bring together all the required processes under one roof to streamline this aspect of formulation development and avoid any potential delays.

Comprehensive services that can be performed in parallel, all at the same time, with the help of CDMOs include:

- Pre-formulation and formulation studies
- Analytical development and validation
- Spray device selection studies
- Spray characterization method development and validation
- Process development and validation
- Quality-by-design services
- On-site stability programs
- Validation and regulatory support

Nasal drug developers can also rely on support from CDMOs to overcome the challenges associated with API chemical properties and excipient selection. The lessons learned from years of experience in nasal drug development and working with similar products can be leveraged to quickly troubleshoot issues and help to develop a safe, stable, and efficacious drug product. Products that contain controlled substances can also benefit from CDMOs that offer DEA-specific services and have experience working toward compliance.

In addition to helping overcome the challenges associated with nasal product formulation development, pharmaceutical companies can benefit from CDMO partnerships in other ways. Nasal specialist CDMOs can provide access to cutting-edge technologies and carefully designed facilities that can help support successful nasal drug development. These include multiple manufacturing lines supporting unit-dose, bi-dose, and multi-dose nasal spray formulation, filling, and assembly. Facilities are also continuously updated so that CDMOs can continue to support the unique needs of nasal product development in the future.

Working with a CDMO from the early stages of nasal product formulation development also helps define a clear pathway of progression for the developer. With-

years of experience in the nasal drug delivery space, CDMOs can provide valuable insights to help ensure success. These include advising on areas where timelines could be expedited, identifying potential risks that could cause delays, and navigating regulatory requirements.

ENSURING SEAMLESS SCALABILITY & COMMERCIAL SUCCESS

In nasal drug delivery, successful formulation development sets the foundation for product scalability and commercialization in the future. Pharmaceutical companies must carefully consider how the challenges with formulation development can impact the later stages of the project and product scalability. Ultimately, this enables the successful development of innovative nasal drug products and delivery to the patients who need them.

Taking a proactive approach to nasal drug delivery from early in formulation development sets a solid foundation when it comes to product scaling and commercialization. By bringing services together all under one roof, communication and collaboration between different teams are improved, helping to overcome the challenges of formulation development and enabling product scaling and commercialization in the future. ◆

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BIOGRAPHY

Eric Kaneps, VP of Sales & Marketing, has over 25 years of experience in Sales, Business Development, and Account Management in the pharmaceutical industry. He worked at DPT Laboratories as the Director of Business Development from 2001- 2016. In this role, he transitioned the OTC/Consumer Health based business toward Pharmaceutical-based Nasal and Injectable Products, which became the foundation for the new re-named entity-Renaissance Lakewood, LLC. In between his roles at the Lakewood site, He was Sr. VP of Business Development for Pharma-Tech Industries, a contract manufacturing organization that specializes in prescription and OTC ingestible and topical products. He earned his BS BA in International Business & Economics from The Ohio State University.

Drug Development
EXECUTIVE

Gastón Salinas

CEO

Botanical Solution Inc.

Botanical Solution

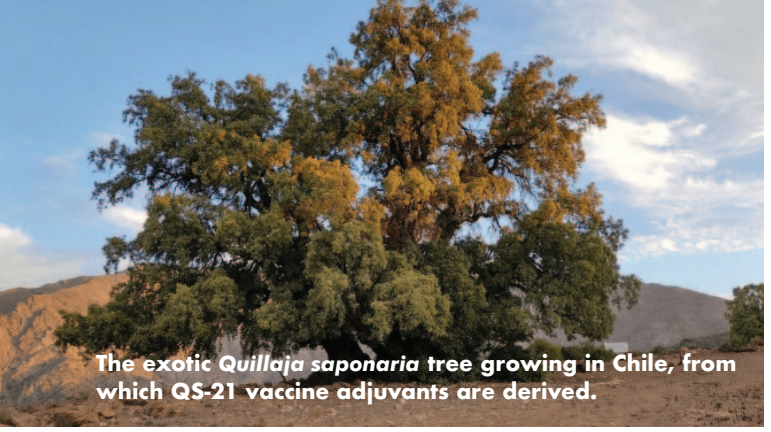
Botanical Solution Inc.: Launching a Revolution in Economical & Environmentally Sustainable QS-21 Vaccine Adjuvant Production

Gastón Salinas is a visionary leader in the field of sustainable biotechnology, renowned for his transformative contributions to pharmaceutical and agricultural innovations. As the Chief Executive Officer of Botanical Solution Inc. (BSI), a company he co-founded in 2013 and has led as CEO of the US-based entity since 2019, Mr. Salinas has played a pivotal role in the company's emergence as a global leader in Advanced Botanical Materials (ABM). Under his strategic direction, BSI has pioneered groundbreaking plant-based biofungicides, such as Quillibrium®, and sustainable manufacturing of the critical vaccine adjuvant QS-21, traditionally obtained from tree bark, which is used in immunizations for shingles, malaria, RSV, and COVID-19.

Chile, is where Mr. Salinas and BSI cofounder Gustavo Zúñiga, PhD, called home. Chile is also where a beautiful, adjuvant-producing tree grows, called the *Quillaja saponaria*. Dr. Zúñiga proved that the *Quillaja Saponaria* could be grown through plant tissue culture and achieve a scalable manufacturing system. The pair recognized they could produce their own plants, and the first application was to use the plant extract as a biofungicide. They soon discovered its usage for vaccine adjuvants – the gold standard vaccine adjuvant of which there is a shortage. Mr. Salinas and Dr. Zúñiga set out to address this shortage by cultivating a virtually unlimited supply to meet the world's needs.

While Chile was a good pilot market for the technology, Mr. Salinas wanted to bring the value proposition to a global scale. He moved to Davis, California in 2019, right before the COVID pandemic. He quickly learned that there was a huge interest in the QS-21 molecule, which he says turned out to be quite the "box of surprises."

Fast forward to 2024 when BSI secured $23.3 million in Series A funding, facilitating key partnerships, including a significant collaboration with Croda Pharma, and driving BSI's expansion into new markets. Last year, BSI won two Pharmaceutical Technology Excellence



The exotic *Quillaja saponaria* tree growing in Chile, from which QS-21 vaccine adjuvants are derived.

Awards: the Innovation award for its innovative manufacturing process that sustainably produces QS-21, reducing costs and environmental impact; the Business Expansion award for strategic scaling of production capabilities, R&D advancements, and successful market partnerships, which have positioned BSI as a leader in the rapidly growing botanical ingredients market and a key player in global vaccine development.

Mr. Salinas recently spoke with *Drug Development & Delivery* about the company's transition from agriculture to pharmaceuticals, addressing the global shortage of QS-21, and developing the QS-21 gold standard vaccine.

Q: Describe BSI's transition from serving the agriculture market to the pharmaceutical sector?

A: We had the opportunity to look at a much larger business opportunity for the compound. We were selling the agriculture product to farmers through our exclusive distributor Syngenta for about $30 to $50 per liter whereas a single gram of the pure QS-21 compound in pharmaceutical grade was worth up to $400,000. This is night and day economic impact. We proved on the agriculture side that we were able to successfully de-risk the technology for growing the plant at commercial scale and rolling out the technology to as many countries as possible. This gave us a solid foundation to translate the agriculture value proposition and repurpose to the pharmaceutical space.

Q: Can you please explain how QS-21 was traditionally obtained and how BSI has revolutionized the process?

A: These are very old *Quillaja saponaria* trees that mostly grow in Chile. The plant naturally expresses the QS-21 compound as a response to an environmental condition, such as a pest attack or stress. No other trees produce the compound. Traditionally, you needed to chop down the tree to get the compound from the inner bark. It's a real challenge. The older the tree, the higher likelihood of having higher yield of QS-21 to make it economically feasible.

In contrast, BSI grows QS biomass year round indoors using a proprietary plant tissue culture platform. The process is a combination of proprietary handling and environmental protocols, know-how, and plant lines that, when combined, allow growth of green QS tissue (biomass) while eliciting production and accumulation of QS-21, among other compounds. We have learned how to stress the plant tissue to accumulate the compound in sufficient quantities to make it economically feasible. We harvest the biomass on a weekly basis to extract and get down to the pure compound. Traditionally, the industry has relied on reverse-phase HPLC methods for QS-21 purification, which is highly demanding on the use of organic solvents like acetonitrile, creating another even greater sustainability issue. BSI has already solved this problem, too.

Q: What is meant by "gold standard" solutions and what is the QS-21 gold standard vaccine?

A: Vaccines elicit so-called Th1 and/or Th2 responses. Th2 responses are mediated by antibodies whereas Th1 responses are mediated by cells, particularly antigen-specific killer cells.

Alum only induces Th2 responses while QS-21 induces both Th1 and Th2 responses. Alum was commercially introduced in the 1930s and has worked in many vaccines (S. pneumonia, HPV, and polio). Thus, if the invading organism can be eliminated, then the vaccine usually can use Alum as an adjuvant. But, if the offending organism establishes a persistent commensal infection, the vaccine needs to elicit a Th2 response. AS01b with QS-21 was commercially introduced in 2017 and gives both a Th1 (cell mediated immunity) and a Th2 (antibody response). This is important and has enabled new vaccines such as the Shingrix® (herpes zoster), Mosquirix® (malaria), and Arexvy® (RSV) vaccines from GSK. All three of these GSK vaccines are caused by infectious agents that develop persistent commensal infections that our immune systems cannot fully clear.

Q: Why is the QS-21 supply chain so fragile?

A: Some have tried to fully synthesize QS-21 in the past, but no prior effort has succeeded in making it cost effectively, likely because there are too many steps involved. Hence, the industry has continued to need very old QS trees as the unique source of raw materials for obtaining QS saponins. There are deforestation laws in Chile intended to prevent the over

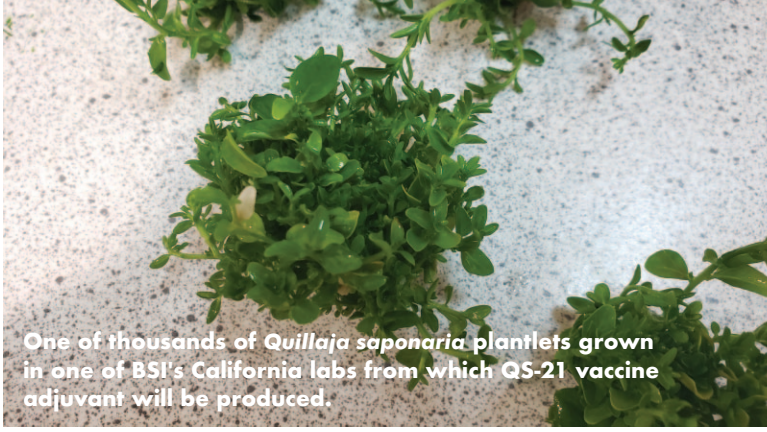
exploitation of these ancestral trees. QS saponins are used in multiple industries that include food and beverages, cosmetics, industrial, agricultural, and pharmaceutical applications. As demand for these products continues to grow, more pressure will be put on the supply chain, increasing the sustainability burden. In addition to the importance of producing and manufacturing of QS-21 is the need for a robust supply chain to make sure there will be enough for current and future highly efficacious vaccines that may require this distinct component. If we were to face another global pandemic, the need for securing or stockpiling these materials is one of those lessons learned from the last pandemic. The technology would allow the US and other countries to have a local source of this distinct compound, if needed.

Q: What is so distinctive about QS-21?

A: The compound is not new. It's been in the literature for more than 30 years. It wasn't until 2017 that it made it into a commercial product, in this case Shingrix. What's so distinctive about this molecule is its ability to trigger specific immune responses (Th1 and Th2) and let the immune system recognize the antigens to deliver the expected result. It has been proven, at least for shingles, that when you combine QS-21 with an antigen, you can get almost lifetime durability. After COVID, durability of immunity to vaccination or protection has become a hot topic. For many, receiving a booster shot every six months is a no-go. The holy grail would be to have a lifelong protection against diseases with fewer vaccine doses. Efficacy and durability are associated with QS-21.

Q: Beyond Shingrix, how close is industry to producing other longer-lasting vaccines with QS-21 and for what indications?

A: There is one FDA-approved vaccine against COVID-19, which is adjuvanted with QS-21 and other *Quillaja Saponaria* saponins. This adjuvant system is called Matrix M. The vaccine was originally developed and marketed by Novavax and soon will be distributed by Sanofi. There are also COVID and flu vaccine candidates adjuvanted with Matrix undergoing clinical testing. My dream is to make QS-21 available for malaria, tuberculosis, respiratory syncytial virus, and other vaccines. That dream will come true not too far from now for high-impact countries and those less privileged.



One of thousands of *Quillaja saponaria* plantlets grown in one of BSI's California labs from which QS-21 vaccine adjuvant will be produced.

Q: Please describe the partnership between BSI and Croda.

A: In the last five years, Croda has done a fantastic job trying to secure access to key pharmaceutical ingredients for commercial and clinically relevant vaccines. QS-21 and QS supplements fall into that category. BSI will supply QS-21 to Croda, and Croda will supply QS-21 to pharma companies as an excipient or in formulations. Croda has developed internally and in-licensed the most clinically relevant vaccine adjuvant systems portfolio that need QS-21 to work. We believe Croda is a company best positioned to help us grow the QS-21 market not only for FDA-approved vaccines, but also for future new vaccines.

Q: What is BSI doing with the $23.3 million in Series A funding and how are you attracting other investors?

A: This year, we plan to roll out QS-21 under GMP standards in connection with the Croda partnership. We have a thorough business plan to keep investing in key manufacturing capabilities required to make QS-21 at greater scale. There is also growing interest in other compounds that come from the QS plant, such as QS-7. That is the next low hanging fruit. Both QS-21 and QS-7 compounds are present in FDA-approved vaccines. QS-7 has been studied to be less reactogenic than QS-21 in a preclinical setting, which may translate into less pain and side effects. Both compounds follow similar purification systems.

There are at least three or four other molecules that have kept pharma companies interested in us and we are in the best position to make them available. So, we could be moving from supplying one molecule to up to four. As a company, we have learned we need to create and invest in capabilities internally to make the compounds and formulate in different presentations. In connection with the expansion plan, we will pursue series B funding later this year. ◆

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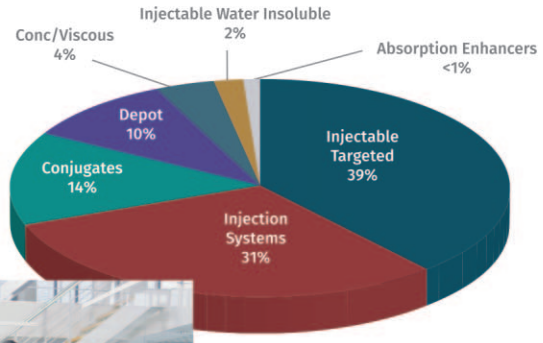
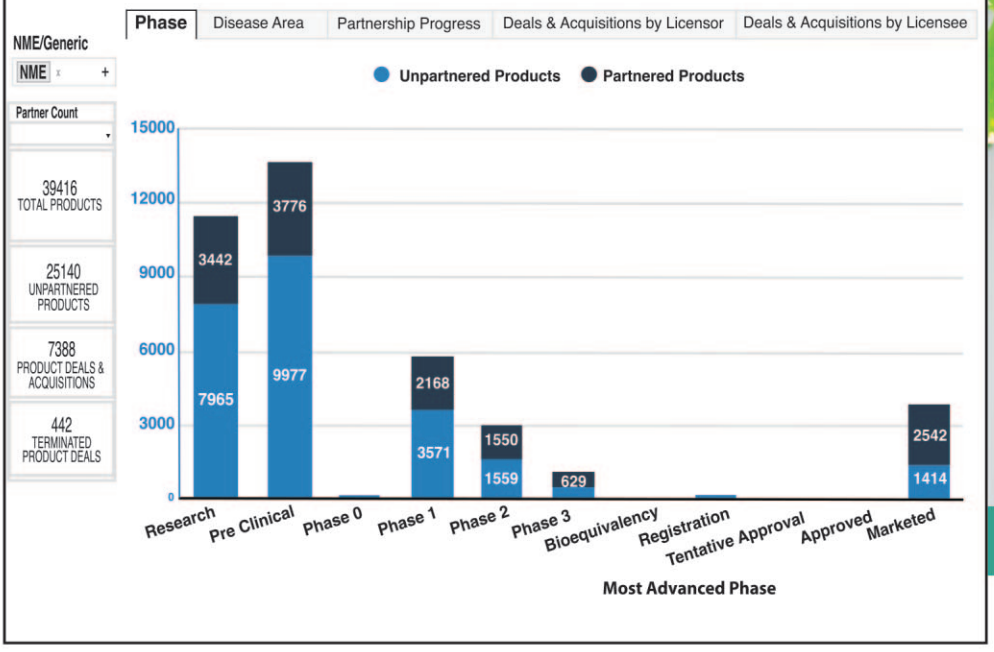
Excipient vs Strength	375 mg telaprevir
HYPROMELLOSE ACETATE SUCCINATE 12070923 (3 MM2/S) **(Core/Content)**	375 mg
SODIUM LAURYL SULPHATE (Core/Content)	7.58 mg
DIBASIC CALCIUM PHOSPHATE ANHYDROUS **(Core/Content)**	75.76 mg
CROSCARMELLOSE SODIUM **(Core/Content)**	30.3 mg
MICROCRYSTALLINE CELLULOSE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

Evaluate New and Promising Technologies



Injectable Drug Delivery Technologies

Screen Potential Partnering and Investment Opportunities



Assess Development Pipeline and The Competitive Landscape

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Special Feature

PFS and Parenteral Delivery: Innovation Is Focused on Patient-Centric, Smart & Sustainable Solutions

By: Cindy H. Dubin, Contributor

Aenova offers huge capacities for fill and finish of biologics and small molecules (Photo: Aenova).

At the October PDA Universe of Pre-Filled Syringes and Injection Devices conference, two injection devices took center stage. The Innovation Award was presented to Crux Product Design and Pfizer for a 3D imaging and analysis of large-volume viscous injections with fast delivery rates in a porcine model. Their study takes steps toward providing high-resolution micro-CT visualizations with quantitative analysis of spatial injectate distributions and tissue responses (backpressure, bleb/wheal formation, leakage, intramuscular, and intradermal penetration) for different volume, viscosity, and rate combinations. For the first time, the interactions between injected formulation and tissue layers (including blood/lymph vessels) are shown in detail with 3D reconstructions and X-ray video for real-time visualization of fluid transport through SC tissues. The Partnership Innovation Award was presented to AstraZeneca and Team Consulting for a mechanical solution for reusable autoinjectors designed to realize cost and sustainability benefits.

Just this month, Halozyme Therapeutics, Inc. announced that argenx received FDA approval of VYVGART® Hytrulo prefilled syringe for self-injection to treat generalized myasthenia gravis and chronic inflammatory demyelinating polyneuropathy. The 20- to 30-second single-dose subcutaneous injection was developed as part of argenx's partnership with Halozyme's ENHANZE® technology, which enables high-volume biologics delivery.

VYVGART followed ANI Pharmaceuticals, Inc. FDA approval of Purified Cortrophin® Gel in a prefilled syringe. This new presentation will be available in 40 USP units/0.5mL and 80 USP units/mL single-dose options through Cortrophin Gel's established specialty pharmacy network. The prefilled syringe reduces administration steps for patients using Cortrophin Gel, which remains available in 5mL and 1mL vials.

This development and approval activity illustrates the expanding market for prefilled syringes (PFS), expected to reach $28 billion by 2032.[1] The market is driven by the prevalence of chronic disease, greater use of biologics and biosimilars, and the ever-growing trend of self-injection. These trends in PFS as well as advancements in autoinjectors and innovations in parenteral delivery are featured in this exclusive *Drug Development & Delivery* annual report.

Aenova: Additional Fill-Finish Capacity of 40 Million PFS/Vials Goes Live in 2026

As a leading global CDMO for the human and animal health pharmaceutical industry, Aenova has strong expertise in sterile manufacturing at its Latina site (Italy). Over the last two years, more than 30 million euros have been invested to offer customers modern, Annex 1-compliant, aseptic filling technology for sterile dosage forms, in particular vials and PFS. This new production is fully operational and a further fill-finish line with a capacity of 30 to 40 million PFS and vials will go live in 2026. Aenova is also currently investing along the entire process of manufacturing infrastructure, analytical capabilities, and cold chain warehouse, providing customers a comprehensive portfolio in the fill-finish area. The Latina technical team provides functional solutions and assures process reproducibility and reliability for accurate filling dosing and plunger position systems (with +/-1% accuracy), considered cutting edge for biologics autoinjector assembly, says Annalisa Barile, Vice President Operations, Aenova.

"As a result, Aenova will be able to offer its customers additional production capacity for PFS and vials using the isolator technology, enabling them to respond quickly to market demand, for example for diabetes medication," she says. "Customers also benefit from differentiated technologies with development and large-scale manufacturing capabilities for small molecules and biologics. Additionally, Aenova has regulatory approval for many countries."

Aenova offers a full range of technologies to contain human intervention to provide proper Class A continuity and to ensure that product is protected from contamination. The current line, under oRABS, is suited for hydrogen peroxide sensitive products. The Ready-to-Use (RTU) technology also ensures the highest standards in terms of sterile assurance and foreign particles reduction, she says. The line has 100% IPC for weight checks, ensuring a robust and reliable filling process and can run various formats, filling from 0.5mL to 10mL syringes or vials. "Thus, Aenova offers its customers the necessary flexibility in formats," says Ms. Barile.

Cold chain capabilities with ultra-freezers for drug substance and extensive 2-8°C storage space complete the offering for a risk-free transportation process. An automatic visual inspection machine and manual or semiautomatic machines are qualified and run commercial products.

Aktiv: Patented Autoinjector Technology Accommodates Various Containers

Aktiv offers the PenPal autoinjector platform, which enables delivery of complex injections. PenPal is a gas-driven autoinjector platform with ultra-high performance reliability and capabilities to accommodate any standard glass syringe or cartridge up to 5.5mL. The device can deliver high concentration drugs at a controlled injection rate. "This technology platform allows pharmaceutical partners to use different sized primary containers, and any needle gauge and length, without making any significant changes to the actual autoinjector device," says Amir Genosar, CEO of Aktiv.

Aktiv has demonstrated injections of over 100,000cP using PenPal's high-pressure injection configuration. The patented technology applies pressure in equilibrium to both the primary container plunger and the external container walls simultane-

Aktiv's PenPal platform is reimagining autoinjectors by redefining simplicity, performance, and the user experience.

ously, thereby preventing high stress during the injection delivery. PenPal architecture consists of six molded components and four off-the-shelf components, presented in two subassemblies for integration with the filled primary drug container.

Aktiv CTO Greg Langley says that patients benefit from the device performance reliability and unique human factors of the PenPal platform. "Audible, visual, and tactile feedback are presented to the user, and automatic needle retraction eliminates the current problematic practice that requires the user to count before manually removing the needle. The device also features an easy-to-inspect 360-degree inspection window. Dose ranging becomes extremely simple with PenPal because the primary drug container can be filled to any desired level without making any changes to the device."

Artcraft Health: Answering a Need with a No-Fail Training Device

"When it comes to patient-initiated injection delivery, you could do a lot worse than not training patients – you could train them ineffectively," says Marty Mason, Senior Director of Demonstration and Training Devices at Artcraft Health. According to Mason, this is a growing problem. Pharmaceutical companies and clinicians are becoming increasingly frustrated with autoinjector training devices that do not last as long as expected or whose sounds and motions are inconsistent. As a result, patients do not receive training that mirrors the use of a real commercial device, clinicians lose faith with the brand, and complaint calls stack up.

The situation grows more complicated when you consider that patients are being trained on injecting themselves with a needle – not an easy task even in the best of training circumstances. Artcraft Health Chief Creative Officer Stephanie Murrin says: "Many patients struggle with needle anxiety and self-injection, particularly those who are injection naïve. This can be a real barrier to treatment initiation and adherence. The right education that helps build skills, knowledge, and confidence is critical to get patients over that hurdle, so they have a positive experience and outcome."

The demoX™ electronic autoinjector training device from Artcraft Health.

Artcraft Health, a full-service health education agency that partners with pharmaceutical, biotech, healthcare service, and medical device companies, recognized the need for a reliable training device that could help ensure successful patient onboarding. The result was demoX™an electronic autoinjector training device. DemoX is designed to replicate any commercial autoinjector, and it delivers five times as many demo cycles (at least 1,000) as traditional training devices, so clinicians can be better equipped to provide the training their patients need. Mason says: "With demoX, patients can be set on a path for more successful outcomes from the start."

During the development of demoX, Artcraft Health focused on including features that would help make the device foolproof for training. They also strove to match the commercial experience as closely as possible for a seamless transition from training to real use. Some of the features include a reset button, audible click sound, and plunger drop motion – all of which are identical to the commercial device. DemoX also has a built-in demonstration counter that provides an audio readout of the number of uses to date so clinicians can monitor how long the device lasts. It also includes an early lift-off notification that alerts the user when demoX has been lifted from the skin too early.

"In addition to developing a training device that serves an unmet need, it feels good to know that we can offer a sustainable and cost-effective choice," Mason says. "DemoX can reduce the number of trainers needed, contributing to reduced cost, waste, and carbon footprint."

Bora Pharmaceuticals: Mitigating "Unknown Unknowns"

Bora Pharmaceuticals is a full-service global CDMO with a network of facilities specializing in the development and manufacturing of complex oral solid, liquid, and semi-solid dose forms, ophthalmics, biologics, and sterile injectable pharmaceutical products for both clinical and commercial supply. At its Baltimore, Mary-

Bora's state-of-the-art Groninger FlexPro 50 isolator filling line at its facility in Baltimore, MD, which helps Bora stay ahead with patient-centric solutions.

land, sterile fill-finish facility, Bora manufactures and packages a portfolio of clinical and commercial sterile injectable products, including both small molecules and biologics. The site's capabilities for vials, syringes, and cartridges are designed for flexible and scalable manufacturing, supporting a variety of batch sizes, with approximately half of current products having a rare disease indication.

From PFS to autoinjectors to other formats, patient-centric drug delivery is continuously evolving to better serve patients. "Bora stays at the forefront of patient-centric solutions with its state-of-the-art Groninger FlexPro 50 isolator filling line, which features an integrated lyophilizer and capabilities for filling PFS, cartridges, and vials," explains Tara Lorenz, Senior Director of Commercial Operations at Bora Pharmaceuticals. "Whether a client's autoinjector uses a syringe or a cartridge as the primary container, Bora provides technology solutions that will ultimately benefit patients."

For PFS, advances in plunger and needle design have resulted in enhanced product delivery, particularly for viscous products, while also reducing the risk of devices clogging. Key design elements that have improved the patient experience include ergonomic features to reduce the force needed to inject with a device, safety features such as retractable needles and shielding mechanisms, and customization and flexibility options for delivery such as multi-dose variants or designs to support delivery – from microdoses to larger volumes.

The next generation of PFS innovation will continue to improve the patient experience with a focus on personalized medicine. "These designs may include the integration of smart technologies and AI, which will demand careful consideration of factors such as ensuring safety and regulatory compliance, securing patient data, and designing user-friendly interfaces," says Ms. Lorenz. "Real-time monitoring and predictive maintenance may well enhance reliability, while seamless integration with healthcare systems could improve data management. Balancing cost-effectiveness with benefits is crucial to the adoption of these features, however consideration of these elements would ensure smart injectable devices are safe, effective, and beneficial for healthcare providers and patients."

Bora has extensive experience in tech transfer. Ms. Lorenz says a Bora client markets its PFS product in several configurations, including as a prefilled autoinjector and an on-body injector. Bora successfully supported the tech transfer and commercial launch of this product, building a trusted partnership along the way. She says this collaboration was driven by Bora's technical expertise, transparency, responsiveness, and agility in mitigating "unknown unknowns."

"The partnership with Bora was transformative for this client as with Bora's support it was able to meet an important milestone that ultimately enabled them to provide chemotherapy patients with immune support and enhance their quality of life," she says.

Catalent Biologics: At the Intersection of Science, Engineering, & Digital Integration

Catalent Biologics provides comprehensive CDMO services for injectable and parenteral products, leveraging more than 30 years of expertise in process development, formulation, and manufacturing. A state-of-the-art facility supports biologics, biosimilars, vaccines, and sterile injectables from pre-clinical development through commercialization.

"We address critical market needs through our integrated approach to prefilled syringe development and manufacturing, with specialized capabilities in high-viscosity formulations, combination products, and device assembly," explains Andrea Como, Vice President, General Manager, Core Biologics, Catalent. "Our

Catalent Limoges, a European center of excellence for clinical and small-scale commercial manufacturing.

isolator technology and flexible filling lines accommodate various container formats for vials, syringes, and cartridges while ensuring product integrity and sterility. By offering end-to-end capabilities from early development through small-scale commercial manufacturing, we help pharmaceutical companies overcome the complex technical challenges of combination products while accelerating time-to-market for life-changing therapies."

Patient-centricity has fundamentally transformed PFS development. User testing across diverse populations, including patients, caregivers, and healthcare providers, has become essential to identify critical design requirements. This feedback drives innovations in ergonomics, intuitive operation, and safety features. Catalent begins every design process by addressing patients' needs. Mr. Como says this approach considers factors such as age demographics, dexterity limitations, cognitive abilities, and prior device experience.

"For instance, we've implemented larger pull tabs for patients with limited hand mobility and optimized packaging text for those with visual impairments," he says. "Our recent investment in autoinjector device assembly machines enables us to provide customers and their patients with solutions that not only ensure accurate medication administration but also enhance the overall treatment experience. Additionally, considering the entire patient journey has expanded our focus beyond the device itself to include packaging accessibility, storage requirements, and disposal considerations."

The future of PFS innovation lies at the intersection of formulation science, device engineering, and digital integration. "Catalent is positioned at this intersection, working to deliver the next generation of injectable solutions that prioritize patient needs while addressing the technical challenges of increasingly complex biologic therapies," says Mr. Como.

In fact, he is witnessing significant advancements in addressing high-viscosity and high-concentration biologics, which have traditionally posed delivery challenges. Novel syringe materials, optimized spring mechanisms, and advanced flow-rate controls are enabling comfortable delivery of complex formulations.

Secondary packaging is also evolving beyond mere protection to become an integral part of the user experience. Smart packaging with temperature monitoring, authentication features, and patient instructions is enhancing safety and compliance. Additionally, environmentally sustainable materials are becoming increasingly important as the industry addresses its ecological footprint.

Looking ahead, connected devices represent the next frontier, he says. Autoinjectors with digital capabilities will provide real-time injection data, medication reminders, and integration with healthcare systems. "This connectivity will enable more personalized treatment regimens and improved adherence monitoring," he says. "The most transformative innovations will likely come from collaborative development approaches that bring together expertise in formulation, device design, human factors, and manufacturing processes."

Congruence Medical Solutions, LLC: Accurate & Precise Microliter Dosing with PFS

Congruence Medical Solutions, LLC is engaged in the design, development, and supply of drug delivery device solutions addressing unmet, emerging and hard-to-solve problems in microliter dosing, injection of viscous/high-dose drugs, and minimizing drug waste at the point of injection. Recently, the US FDA cleared the company's Microliter Dosing Syringe as an Ophthalmic Syringe with an indication for use in microliter volume injections into the eye (intravitreal).

According to Glenn Thorpe, Head –

510(k) Cleared, User-filled Microliter Dosing Syringe from Congruence Medical Solutions, LLC.

Sales, Business Strategy, Congruence Medical Solutions, LLC, this device was developed to improve patient safety by enabling accurate, precise microliter dosing, and by providing high quality drug contact materials. "The latter is addressed by using a prefillable syringe in a user-filled configuration, enabling access to advantages of prefillable syringes for applications where prefilling is not feasible," he says. "In the case of sensitive applications, such as injections into the eye, there is benefit from high quality materials of construction of prefillable syringes, including silicone-free."

The Microliter Dosing Syringe is available as a 510(k) cleared device in various models from 9 microliters to 100 microliters and has been shown to be accurate within 3 microliters with 95% confidence levels, Mr. Thorpe says. A number of human factors studies have shown high acceptance and preference (>80%).

He adds that because the device employs a prefillable syringe, transition to a prefilled embodiment is seamless and can leverage the experience of non-prefilled embodiment. The device enables a standard ISO-11040-compliant PFS to administer precise microliter volumes.

"Given the significant overall risk in drug product development, we anticipate that more drug development programs in sensitive applications could employ prefillable syringe to minimize the risk from unknown and unpredictable leachables from hypodermic syringes," says Mr. Thorpe. "The device also preempts the need for dose markings on the syringe barrier because dose metering is controlled by the device."

Credence MedSystems: Advancing Intravitreal Drug Delivery

Intravitreal injections are a common treatment for retinal diseases such as age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion. As these conditions rise in prevalence and innovator molecules come off patent, the pharmaceutical landscape is expanding to include not only innovative biologics and gene therapies, but also a growing number of biosimilars that require intravitreal administration.

John Merhige, Chief Commercial Officer, Credence MedSystems, Inc., says the Credence MedSystems Micro-Dose™ Syringe System provides a critical solution to support the precise, safe, and sterile delivery of these therapies – offering microliter-level accuracy, a clinician-centric design that supports proper use in clinical settings, and compatibility with terminal sterilization as well as secondary packaging to enable sterile-field use.

"Intravitreal dosing demands exceptional precision," he says. "Many ophthalmic therapies, including biosimilars of anti-VEGF agents such as ranibizumab and aflibercept, are administered in small volumes where dose variability can impact efficacy or cause complications like elevated intraocular pressure. The Micro-Dose Syringe System is engineered to deliver consistently accurate microliter doses, ensuring that the drug products are administered within their narrow therapeutic window. This is particularly important as biosimilars enter the market and clinicians must maintain confidence in their consistent performance."

Sterility is another critical factor in intravitreal therapy. Infections such as endophthalmitis, though rare, can be devastating and are more likely when aseptic techniques or sterile integrity are compromised, says Mr. Merhige. The Micro-Dose Syringe System is compatible with terminal sterilization methods, ensuring that the drug-device combination arrives sterile and ready-to-use. Effective terminal sterilization, however, also depends on secondary packaging design. The Micro-Dose packaging must be specifically engineered to support sterilant penetration while preserving barrier integrity and device performance.

"This design ensures reliable sterilization without compromising ease of use or functionality – helping pharmaceutical

The Credence Micro-Dose™ Syringe System to facilitate intravitreal dosing.

companies meet regulatory requirements for combination products while streamlining logistics and handling for healthcare providers," he says. "This capability is vital, especially in outpatient and ambulatory surgical settings where these procedures are typically performed."

Equally important is the clinician-centric design of the Micro-Dose System, which promotes proper administration by enhancing clinician control and confidence. Its ergonomic form factor reduces user fatigue and time of injection while enabling the precision required for ocular injections, explains Mr. Merhige. The system's design facilitates the use of silicone-free and crosslinked silicone syringes that would otherwise present challenges associated with higher break loose and glide forces.

"If higher forces do present challenges, Credence can employ its Force-Assist™ technology to further improve control and comfort for clinicians during administration," he explains. "Combined with its prefilled, ready-to-use format, the device minimizes preparation steps, reduces contamination risk, and improves workflow efficiency in high-throughput retinal practices."

The Credence Micro-Dose Syringe System meets the evolving needs of intravitreal drug delivery. As evidence, Credence is collaborating with a leading pharmaceutical manufacturer for the deployment of Micro-Dose in an intravitreal dosing application. "With the global intravitreal injection market projected to exceed $10 billion by 2028 (according to Grand View Research), driven by the increasing burden of retinal diseases and the rise of biosimilars and advanced therapies, this system offers a reliable, precise, and user-friendly solution that prioritizes safety, compliance, and patient care in retinal disease management," he says.

LATITUDE Pharmaceuticals: Integrated Approach Accelerates Timelines

LATITUDE Pharmaceuticals specializes in advanced drug delivery solutions, with a significant focus on injectables and parenteral formulations. LATITUDE offers comprehensive services for the development of sterile products, including preclinical and clinical-stage parenteral formulations such as solutions, nanosuspensions, nanoemulsions, liposomal formulations, and lipid nanoparticles. LATITUDE's services span formulation development and analytical testing to clinical trial material (CTM) manufacturing under cGMP.

By offering flexible cGMP manufacturing capabilities with a focus on Phase 1 and Phase 2 CTM, LATITUDE is especially suited to meet the needs of emerging biotech companies and early-phase clinical programs. Matthew A. Singer, PhD, Vice President, Head of Business Development, LATITUDE Pharmaceuticals, says: "Our integrated approach accelerates development timelines and reduces technical risk, providing a seamless transition from formulation to first-in-human studies."

LATITUDE addresses critical needs in the pharmaceutical industry by enabling the development of challenging injectable products, particularly those with poor solubility and/or bioavailability, stability issues, or requiring targeted delivery. "LATITUDE's expertise in solubilization, advanced formulation, and their application to injectables helps our clients overcome even the most difficult formulation barriers. LATITUDE supports a wide range of actives, including small molecules and biologics," says Singer.

When providing secondary packaging for LATITUDE's pharmaceutical drug product manufacturing, key considerations focus on tamper-evidence and preserving product integrity throughout the chain of custody. Tamper-proofing is critical to deter and detect unauthorized access. Features such as tamper-evident seals, shrink bands, breakable caps, and tamper-indicating adhesives are typically incorporated into LATITUDE's secondary packaging. These components comply with regulatory guidelines (e.g., FDA 21 CFR, EU FMD) to ensure legal and safety standards are met.

To safeguard medicine integrity, packaging must provide protection against, and monitoring of, environmental factors such as temperature fluctuations, moisture, light, and oxygen. "The materials that LATITUDE uses are durable and provide a robust barrier to prevent contamination or degradation of the container," he says. Serialization and track-and-trace technologies like 2D barcodes or RFID tags can also be considered to ensure traceability and accuracy.

Packaging plays an important role in protecting the safety and integrity of the injectables produced at Lifecore Biomedical.

Lifecore Biomedical: An Injectables CDMO Ensuring Serialization & Safety

As an injectables CDMO, Lifecore Biomedical enables partners to comply with regulatory requirements for packaging, such as those set forth in the US Drug Supply Chain Security Act. "Our engineering team has helped our partners implement a variety of secondary packaging techniques such as tamper-evident seals on carton flaps that tear away the carton's artwork when opened," says Tony Bassette, manufacturing engineering supervisor, Lifecore Biomedical. "For quality control, we use sensors that measure and verify correct placement of the seals. Also, we heat-seal Tyvek pouches, creating a robust seal that is tamper evident."

Another aspect of packaging protection relates to serialization of products. For instance, one of Lifecore Biomedical's partners had the CDMO serialize individual cartons of commercial product. Those cartons are then packed into a six-pack that form a saleable unit, and those units are serialized as well, he explains. Next, four of the units are put into a case that is also serialized. All of the serial data is then aggregated for logistical tracing. This allows tracking of each individual carton to its placement on a specific pallet during shipping. Camera systems are utilized throughout the process to ensure that the printed serialization data is accurate and legible, he adds.

Lubrizol: Polymer Can Be Integral to Parenteral Development

Approximately 60% of potential active pharmaceutical ingredients (APIs) under development – and more than 40% of those in reformulation – are poorly water soluble, says Matt Finkelhor, Lubrizol Commercial Manager, Global Novel Polymers, Lubrizol. To address this challenge, Lubrizol's Apisolex™ polymer, a GMP-validated, injectable-grade excipient, enhances the solubility of BSC Class II and IV APIs by up to 50,000-fold. This polyamino acid-based polymer offers a non-toxic, non-immunogenic, biocompatible, and biodegradable alternative to other solubilizers while allowing for higher drug loading, he says.

"Low solubility drugs present significant challenges in pharmaceutical development, often leading to limited bioavailability and efficacy," says Mr. Finkelhor. "This can restrict treatment options and hinder the development of potentially valuable therapeutics. Apisolex polymer enables formulation of low solubility drugs, for intravenous or subcutaneous administration, expanding the range of viable drug candidates."

Apisolex polymer technology can be

Lubrizol's Apisolex™ polymer improves solubility for intravenous or subcutaneous administration.

an integral solution for parenteral drug development projects where traditional excipients or other formulation techniques have failed or where a patent-protected technology is desired, he explains. Apisolex allows for the development of APIs that were previously unable to progress, while avoiding the adverse effects associated with other solubilizers. In addition, Apisolex polymer offers the potential to deliver some APIs by the subcutaneous route due to higher solubilization properties.

"The polymer is a versatile, efficient, and safe excipient technology employing a poly (amino acid) chemistry to overcome the challenges of existing solubilizers," says Mr. Finkelhor.

Apisolex technology holds robust patent protection in the US and internationally, which allows for applications with new chemical entities via IND/NDA and drug products entering the market via the FDA's 505(b)(2) regulatory pathway.

Noxilizer: NO_2 Proves to be a Viable Alternative to EO

Noxilizer offers nitrogen dioxide (NO_2) sterilization for single-use products like prefilled syringes, autoinjectors, and other medical devices. NO_2 provides many benefits over other sterilization methods, including an ultra-low temperature process (10°C-30°C) that maintains drug integrity; minimal vacuum option to prevent stopper movement and contamination of the drug product; surface sterilization with low to no residuals to enable use of polymer syringes/cartridges/vials; and simple and safe to bring in house to reduce manufacturing time and supply chain risk, explains Maura O. Kahn, Senior Vice President, Commercial, Noxilizer.

Companies may access NO_2 sterilization by purchasing and installing sterilizers in their own facility or their CMO or utilize contract sterilization services. "NO_2 is a leading alternative to ethylene oxide (EO)," she says.

Noxilizer has successfully participated in a three-way partnership with a global biotech company and a CMO. The drug product is filled by the biotech company and shipped to the CMO where assembly and packaging take place. The biotech company installed a Noxilizer sterilizer in the CMO.

"Now, the manufacturing time has decreased from six months to two months because assembly, packaging, sterilization, and final packaging happen in one location," Ms. Kahn describes. Additionally, the drug product is only shipped once during the manufacturing process versus three times when using contract sterilization.

"While all partnerships take effort, we have set up standard weekly and monthly calls/meetings," she adds. "Each quarter, we meet in person. The result is that we are keeping communications flowing among the three companies. The product is now on the market and patients and physicians have access to another choice in their treatment."

Noxilizer has several other customers awaiting regulatory approvals at the FDA and EMA.

PCI: Scalable PFS Solutions Speed Clinical to Commercial Transition

PCI is a CDMO that provides integrated end-to-end sterile injectable drug development, manufacturing, combination product assembly, and advanced packaging solutions to increase product speed to market. The company has launched more than 90 products each year over five decades of service. Spanning the cycle from development to commercialization, PCI offers injectable drug delivery solutions for large- and small-molecule therapies. Integrated sterile drug manufacturing, injectable assembly, testing, and packaging solutions optimize dosing for patients.

"Patient-centric solutions are profoundly reshaping the design and use of prefilled syringes in the pharmaceutical industry," says Bill Welch, Executive Director Market Development at PCI. "As therapies become more specialized and the focus shifts toward enhancing the patient experience, prefilled syringes are increasingly prioritizing usability, safety, and convenience."

For patients managing chronic conditions who require frequent injections, patient-centricity is critical and emphasizes ease of use, particularly for self-administration. He says that modern PFS designs now feature ergonomic grips, clearer labeling, and intuitive handling features, enabling patients and caregivers to administer treatments safely and confidently, outside clinical settings.

When it comes to sterile fill-finish, final assembly, testing, and packaging require rigorous attention to quality, precision, and regulatory compliance. CDMOs like PCI Pharma Services are investing in scalable final assembly and packaging technologies to ensure consistent, high-quality PFS production, including advanced aseptic prefilled syringe fill-finish capabilities and device testing systems.

PCI takes a collaborative approach when partnering with biopharma companies to ensure the success of their prefilled syringe programs. From engaging early during the sterile drug product development/manufacturing stage, facilitating proactive clinical discussions and guid-

ance on device strategy, qualification and selection through to actual PFS introduction during clinical trials packaging design, scale-up, regulatory readiness, and commercial launch.

"Every stage of development is driven by a shared commitment to the patient," says Mr. Welch. "We work closely with our partners to align drug delivery, aseptic filling, container closure selection, device functionality, human factors, labeling, testing, and packaging into a cohesive ecosystem – one designed to optimize usability, safety, and ultimately, therapeutic success. Device agnostic scalable technologies, complemented with an established range of PCI-owned tooling, allows our client partners to progress through clinical trials to commercialization with reduced investment and within an accelerated timeframe."

SCHOTT Pharma: Advances in Large-Volume Subcutaneous Drug Delivery

SCHOTT Pharma is a drug containment and delivery system provider with a portfolio of prefillable polymer and glass syringes, cartridges, vials, and ampoules. SCHOTT Pharma has addressed the growing need for large-volume prefillable syringes and devices for subcutaneous (SC) drug delivery with its new syriQ BioPure® 5.5mL glass PFS that can be used in an autoinjector, and the SCHOTT TOPPAC® infuse polymer syringes with a filling volume of up to 50mL for use with the KORU™ Near Body Device infusion system.

"Patient-centricity continues to be crucial," says Dr. Sven Pohle, Global Product Manager Glass Syringes at SCHOTT Pharma. "Both patient and user experience are improved through a shift from in-

SCHOTT Pharma's solution for large-volume prefillable glass and polymer syringes.

hospital, intravenous administration to SC administration in a homecare setting and by new SC drug formulations that allow reduced injection frequency. The developments of large-volume, high-dose SC medications and of large-volume containers and devices, such as autoinjectors and pumps, support this patient-centric trend. For this purpose, the syriQ BioPure 5.5mL glass PFS has been developed as a co-design with the YpsoMate® (Ypsomed) 5.5 autoinjector, with careful consideration of how to optimize patient comfort and ease of use of the system."

For SC formulations larger than 5.5mL, polymeric PFS and infusion pumps can be used for at-home administration. "SCHOTT TOPPAC infuse 10, 20, and 50mL PFS are designed for use in the KORU infusion system, which is a reusable pump with a broad volume range and a patient-centric design," says Christoph Zauner, Head of Product Management Polymer Solutions at SCHOTT Pharma.

Tamper-evidence is an important factor for protecting patient safety in PFS packaging. SCHOTT Pharma's latest PFS innovation is the next-generation of SCHOTT TOPPAC infuse PFS that utilizes a tamper-evident cap-and-label system developed in collaboration with SCHOTT Pharma's Alliance to Zero partners. The Alliance aims to reduce carbon footprint with sustainable packaging solutions that ensure product and patient safety.

Several features of the new system improve safety and reduce medicine and packaging waste. The Cyclic Olefin Copolymer (COC) material used in SCHOTT TOPPAC syringe barrels is break-resistant and offers longer shelf life through increased stability compared to PP, says Mr. Zauner. A new, functional label can provide oxygen and light protection, and it covers the syringe shoulder completely to provide a first-opening indication for each syringe, which reduces the possibility that usable medicine will be discarded. An RFID chip can be integrated into the label to enable automated inventory and digital first-opening indication. The new system uses an optional cardboard box as a secondary package in place of the traditional plastic blister package. The box protects the PFS against mechanical impact and dust, yet it is easier for users to open and to recycle. It also saves space during transport, which can reduce carbon footprint.

"Through collaboration, SCHOTT Pharma has created a packaging system that meets the needs of their customers, healthcare providers, and patients, while also improving sustainability," says Mr. Zauner.

Simtra BioPharma Solutions: Patient-Centric Innovation

Prefilled syringes are becoming the preferred method of delivery for patients and providers alike due to the expansion of injectable therapies, especially biologics and specialty pharmaceuticals. Their convenience, safety, and dose accuracy make them ideal for at-home administration. This shift comes with a heightened focus on patient-centric design that demands new levels of collaboration between pharmaceutical companies and contract development and manufacturing organizations (CDMOs).

"PFS are often used directly by patients, many of whom may have limited dexterity or impaired vision – such as elderly populations," says Greg Sacha, PhD, Global Senior Scientist, Simtra BioPharma Solutions. "Features like large print gradations and ergonomic plungers are no longer optional; they are critical for ensuring adherence and confidence during administration. Usability studies and human factors engineering must be integrated early in the development process to reduce the potential for error and discomfort."

In addition, performance must be validated through rigorous testing. During development, PFS undergo extensive stability studies to ensure integrity over the product's shelf life. Among these, break force and glide force testing are crucial. These tests evaluate the force required to initiate and maintain plunger movement within the syringe. "If the force is too high, patients may hesitate or be unable to complete administration," he says. "In some cases, "chattering" – when the plunger moves unevenly – can disrupt dose delivery and cause patient anxiety. Addressing these challenges early on reduces the risk of compliance issues later."

Secondary packaging also plays a pivotal role in both user experience and safety. Individually sealed blister packs help guard against tampering and make it easy to identify compromised doses. This approach also aligns with healthcare provider needs, facilitating automated medication dispensing in hospitals and nursing units. Dr. Sacha says: "As packaging technology advances, incorporating smart features – such as time-temperature indicators or tamper-evidence tech — will likely become more prevalent, supporting better monitoring and traceability throughout the supply chain."

Looking ahead, innovation is focused on minimizing residual volumes within the syringe after injection. Especially in high-cost biologics, even small losses can lead to significant waste. Future designs may optimize plunger mechanics or barrel coatings to ensure a more complete dose is delivered, maximizing efficiency and reducing overall drug fill volumes.

Partnerships between pharma innovators and CDMOs are central to bringing these complex products to market. Successful collaborations integrate packaging and device development from day one, he says. For example, many innovator companies have specialized teams dedicated to both primary and secondary packaging. Their insights into patient use cases and protection requirements ensure the final product meets regulatory and manufacturing standards and improves the patient experience.

"CDMOs with expertise in human-centered design, robust testing protocols and flexible manufacturing platforms will be best positioned to meet the needs of both drug developers and the patients they serve as the demand for self-administered injectables grows," he says.

Stevanato Group: Cutting Injection Time in Half

Ready-to-Use (RTU) containers, including syringes, vials, and cartridges are the DNA of Stevanato Group. Focusing on the parenteral market, the company supplies containers, drug delivery systems, and assembly and testing equipment – all supported by analytical and device testing services. Biologics, especially highly concentrated formulations enabling dose frequency reduction, require optimal container/device compatibility and minimal interaction between drug and materials used, potentially leading to protein aggregation, inorganic extractables, underdosing, and delamination.

In response, Stevanato Group developed the Alba® prefillable syringe platform, which features a new cross-linked coating and involves a plasma treatment designed to minimize interaction between the drug and its container. "One standout feature of Alba syringes is their ultra-low sub-visible particle content, enhancing compatibility with biologic drugs and ensuring patient safety," says Daniel Martinez, Head of Product Management DCS & Analytical Services, Stevanato Group. Alba syringes can be supplied with a special Thin Wall (sTW) needle with an increased internal diameter. This innovation lowers the extrusion force and reduces injection time by nearly 50%, he says.

Cutting injection time was the goal of one customer. This leading pharmaceutical company reported out-of-specification injection times with a PFS intended to be used in an autoinjector for its high-concentration monoclonal antibody (mAb) product. A study conducted by the Technology Excellence Center (TEC) team revealed an issue with the silicone coating. The sprayed-on silicone leached out when in

contact with the drug. As an alternative, the cross-linked silicone coating used in Alba syringes was proposed, significantly reducing the migration of silicone and providing a more stable and predictable gliding force. The customer's main concern of injection time was successfully met, says Mr. Martinez. In addition, the interactions between the drug and container components were assessed using both, drug product and a placebo. "This underlines the importance of early collaboration between pharmaceutical companies and the container supplier, able to provide strong, data-driven analytical capabilities and support," he says.

Prefillable syringes offered by Stevanato Group are engineered with several key features to ensure they work seamlessly with autoinjectors, enhancing the overall injection experience for patients. Tighter tolerances and a controlled distance between the needle tip and the syringe shoulder ensure a consistent injection depth, he explains.

"The designed-in high mechanical resistance, including features such as small round flanges and the avoidance of glass-to-glass or metal-to-glass contact, doubles the glass's resistance, resulting in less breakage during handling and administration," says Mr. Martinez. "Another critical factor is a consistent break-loose and extrusion force profile throughout the entire product's shelf life. These features ensure a reliable patient experience, support timely launches, and minimize total cost of ownership."

In addition to technological advances, one of Stevanato Group's next innovations has introduced new sustainability practices focusing on alternative materials and processes enabling more sustainable sterilization techniques while maintaining the overall performance. For example, Stevanato Group communicates regularly with customers on a sustainable version of secondary packaging focused on biopolymers and recycled plastic. A bio-circular version of polystyrene and polypropylene that is used to produce secondary packaging of syringes has been identified, he says.

West Pharmaceutical Services: Innovations in Safety, Usability & Technology

West Pharmaceutical Services provides primary containment systems and services, enabling pharmaceutical and biopharma companies with a wide range of choices to take their drug through the clinical phases and into the market in vial containment, or in a drug delivery or wearable device that encapsulates a prefilled syringe or cartridge. From a services standpoint, West works with customers that have a platform or custom device, supporting them through design, industrialization, manufacturing, assembly, labeling, and packaging across a network of global facilities. Typically, West works with customers to procure, qualify, and validate equipment for commercial volumes, but West also has the ability for small-batch clinical volumes to enable expeditious turnaround times for the purposes of design verification testing, human factor studies, and other device services.

"By providing these types of integrated services, we can share our expertise, knowledge and capabilities – especially in the case of emerging pharma/biopharma companies – and therefore derisk the drug delivery device pathway to patient," says Madhu Raghunathan, Senior Director, Technical Services Business Development and Market Strategy, West Pharmaceutical Services.

He says that several innovations may advance the current state of drug containment and delivery. First, there is a greater demand for reusability (multiple use) and sustainability, as well the removal of preservatives such as Benzoates, Sorbates, and Propionates that are added to the drug during the formulation phase. "Removal of preservatives while ensuring sterility across multiple administration seems at odds with each other, but novel technological solutions can help address this dichotomy," says Mr. Raghunathan.

Second, technological solutions such

West works by the side of customers from concept to patient to develop products that promote the efficiency, reliability and safety of the world's pharmaceutical drug supply.

as pneumatically powered injection mechanism that support the self-administration of highly viscous biological drugs could become mainstream, as could adoption of smart tags/labels for improved tracking and traceability and safety. He explains that tamper-proofing and safeguarding drug product integrity comes in different varieties. For example, seals – considered to be secondary closure components – perform critical functions such as maintaining primary packaging integrity by firmly holding the stopper in place, protecting the injection site on the stopper, and providing evidence of tampering.

"Specialized folding box designs, novel closures such as West's manufactured Daikyo PLASCAP® RUV closure, use of integrated near-field-communication tags, are also increasingly used to ensure tamper-proofing of injectable drugs," he says.

Innovations in autoinjectors and safety devices are supporting the acceleration of drug delivery from a hospital and clinic setting to home environment wherein the drug is delivered in a PFS format. Mr. Raghunathan says: "Technological advancements such as enhanced digital monitoring, improved usability and safety features for easier drug administration paired with comprehensive testing and human factors studies, are making it simpler for patients to self-administer drugs." ◆

Reference

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SALIPRO BIOTECH

BIO-RAD

Salipro Biotech & Bio-Rad Laboratories: A Powerful Solution for Antibody Discovery Against Challenging Transmembrane Targets

Salipro Biotech and Bio-Rad have been working in partnership for a little over a year to provide a straightforward solution for the discovery of novel antibody therapeutics for transmembrane proteins. This collaboration has already been successful in yielding multiple novel human antibodies targeting the wildtype chemokine receptor CXCR4, with affinities exceeding those of ulocuplumab (Bristol-Myers Squibb's monoclonal antibody designed to treat hematologic malignancies). The new CXCR4-targeting antibodies have been shown to inhibit CXCL12 mediated cell migration better than ulocuplumab, offering the potential for enhanced efficacy and novel immuno-oncology therapeutic avenues.

Drug Development & Delivery recently interviewed Dr. Jens Frauenfeld, CEO, Salipro Biotech, and Dr. Francisco Ylera, R&D Team Lead at Bio-Rad Laboratories, to understand how the collaboration is leveraging the Salipro® platform alongside Bio-Rad's Pioneer™ Antibody Discovery Platform to target transmembrane proteins.

Q: How does the Salipro® platform enhance the drug discovery capabilities of your pharmaceutical and biotech partners?

Salipro: Our mission is to mine the vast untapped potential of membrane proteins and turn challenging drug targets into opportunities for therapeutic innovation. We have built a team with extensive expertise that, alongside our Salipro platform –

which stabilizes membrane proteins in their native forms - is enabling entirely new routes to drug discovery, opening up new treatment possibilities.

By maintaining the protein's natural environment with surrounding lipids, our Salipro platform ensures the structural and functional integrity of membrane proteins, allowing for accurate drug discovery assays and reliable structure-based drug design. The production of Salipro particles is scalable and tailored for high-throughput screening platforms, including DNA-encoded and phage display libraries, such as Bio-Rad's Pioneer Platform. This facilitates the rapid evolution of large libraries of potential drug candidates.

The Salipro platform is applicable to a wide range of membrane proteins, including G-protein coupled receptors (GPCRs), ion channels, SLC transporters, complexes, and more. This versatility allows for a broad range of applications across various therapeutic areas with significant unmet medical needs. In addition, the technology enables a one-step reconstitution process, eliminating the need for complex and time-consuming protein engineering or the use of whole cells or virus-like particles. This facilitates the rapid evaluation of large libraries of potential drug candidates, significantly increasing the efficiency of the drug discovery process

Q: What is Bio-Rad's Pioneer™ Platform and how is it advancing the discovery of antibody therapeutics?

Bio-Rad: The Pioneer™ Platform is our custom therapeutic antibody service that accelerates the discovery of clinical-quality candidates in industry-leading timelines. The key advantages Pioneer offers include its large library size, ability to select antibodies with subnanomolar affinities directly from the library, and the rapid delivery of highly developable lead candidates.

Pioneer features an extensive Fab library with 225 billion unique human antibody sequences, significantly increasing the chances of identifying superior therapeutic antibodies with subnanomolar affinities. A larger library not only boosts competition for target binding but also provides broader antigen epitope coverage, resulting in more diverse, high-affinity candidates.

Additionally, the platform focuses on germlines with favorable properties often found in therapeutic antibodies, ensuring the developability of lead candidates. The library is also optimized through meticulous cloning strategies, eliminating sequences with frameshifts or stop codons. This results in an impressive 92% functional light chain (LC) and heavy chain (HC), with the library's quality confirmed via next-generation sequencing (NGS).

The proprietary SpyDisplay selection system is at the heart of Pioneer, which uses SpyTag technology to covalently display Fabs on filamentous phage, enhancing efficiency. By utilizing a single vector for both selection and expression of clones, SpyDisplay streamlines the entire workflow. In conjunction with the TrailBlazer™ modular antibody assembly platform, Pioneer enables rapid identification and characterization of diverse lead candidates. Another advantage is its capability for bispecific generation and high-throughput screening through SpyLock Technology, setting it apart from other platforms.

Q: What are the synergies between the two platforms, and how do they integrate?

Salipro: The combined approach uses purified proteins rather than just target overexpressing cells to optimize the antibody generation and characterization process. This approach allows for rapid initial in vitro antibody characterization, for example measuring antibody affinity or demonstrating target specificity, speeding up the overall workflow compared to running corresponding cell assays.

The synergies between these two technologies extend beyond antibody discovery however. The Salipro-stabilized membrane proteins also serve as tools for characterizing newly discovered antibodies. Techniques such as surface plasmon resonance (SPR) and bio-layer interferometry (BLI) are often hindered by the instability of membrane proteins, making it difficult to accurately assess antibody binding kinetics and affinities. Salipro's technology overcomes this, providing a stable platform for detailed antibody characterization.

Bio-Rad: Salipro and Bio-Rad have developed a powerful solution which simultaneously tackles two critical bottlenecks in the antibody discovery process. By stabilizing membrane proteins and facilitating efficient antibody screening and characterization, the combined workflow will work to accelerate antibody drug discovery and development.

Q: What are the most significant challenges associated with the study of membrane proteins?

Salipro: Membrane proteins play a critical role in fundamental cellular processes, representing about 30% of the human proteome. They are therefore attractive targets for therapeutic intervention across a wide range of diseases, including cancer,

cardiovascular disease, and neurological disorders, and are the targets of more than 60% of drugs on the market.

Despite their significance, the majority of membrane proteins currently remain undruggable, mainly because they are notoriously challenging to work with due to their inherent instability outside of their natural lipid bilayer environment.

Current standard methods for studying membrane proteins suffer from limitations that significantly impair drug discovery efforts. These include difficulties in preserving the correct folding and functionality of the proteins, as well as time consuming protein engineering efforts that often result in non-native membrane proteins. As a result, these standard methods often fail to support efficient screenings for new drug candidates or fail to provide reliable structural data for rational drug design.

The Salipro platform technology addresses these critical bottlenecks by stabilizing membrane proteins in their native forms, via the direct reconstitution of membrane proteins with their native lipids from crude cell membranes into Salipro particles, enabling the development of next-generation therapeutics targeting previously inaccessible membrane proteins.

Q: What are the outcomes of the collaboration, and how will these results accelerate the development of antibody therapeutics?

Bio-Rad: The collaboration has achieved very exciting results in a short timeframe, demonstrating the potential of the combination of the Salipro and Pioneer platforms to accelerate the development of antibody therapeutics.

Following Salipro's first hit generation campaign, a number of CXCR4-specific antibody clones demonstrated superior affinity and improved performance in a functional cell assay in comparison to the benchmark CXCR4 therapeutic antibody, potentially offering a promising alternative.

Salipro: We see three main outcomes from this collaboration:

1) The identified antibody clones, which have stronger binding to CXCR4, and improved functionality compared to ulocuplumab, could therefore lead to better therapeutic outcomes. They may be more effective in stopping cancer growth and spread, and could potentially be effective at lower doses, resulting in fewer side effects.
2) We also observe that several of the antibodies may bind to a different epitope as compared to ulocuplumab or may have a different way of binding to CXCR4. This could become a key differentiator to develop novel approaches in cancer therapy. Depending on further characterization, these binders have the potential to provide a new mechanism of action, which can enhance the therapeutic efficacy of the antibodies.
3) The Salipro technology works efficiently with all classes of membrane proteins, suggesting that it could rapidly enable the development of novel antibodies against a wide range of prominent drug targets previously considered undruggable.

Q: What are the next steps for this collaboration?

Salipro: We have received several requests from pharma companies expressing interest in the new anti-CXCR4 binders, based on their exciting characteristics. This is work in progress and may lead to additional collaboration opportunities to fully develop the antibodies as novel therapies.

Bio-Rad: We are very excited by the results of the pilot project and look forward to supporting our customers in combining the Pioneer Antibody Platform with Salipro's technology to provide a powerful solution for their challenging transmembrane targets.◆

THERAPEUTIC FOCUS

Targeting Chronic Inflammation in Obesity

By: Johnny Peppers, PhD, and Christopher Mojcik, MD, PhD

INTRODUCTION

According to the World Health Organization, 16% of adults aged 18 and over were living with obesity in 2022, a number that has more than doubled since 1990.[1] As obesity rates continue to climb, the health community has reacted with great concern – a fact that is evident in the surge of obesity drugs now flooding the market.

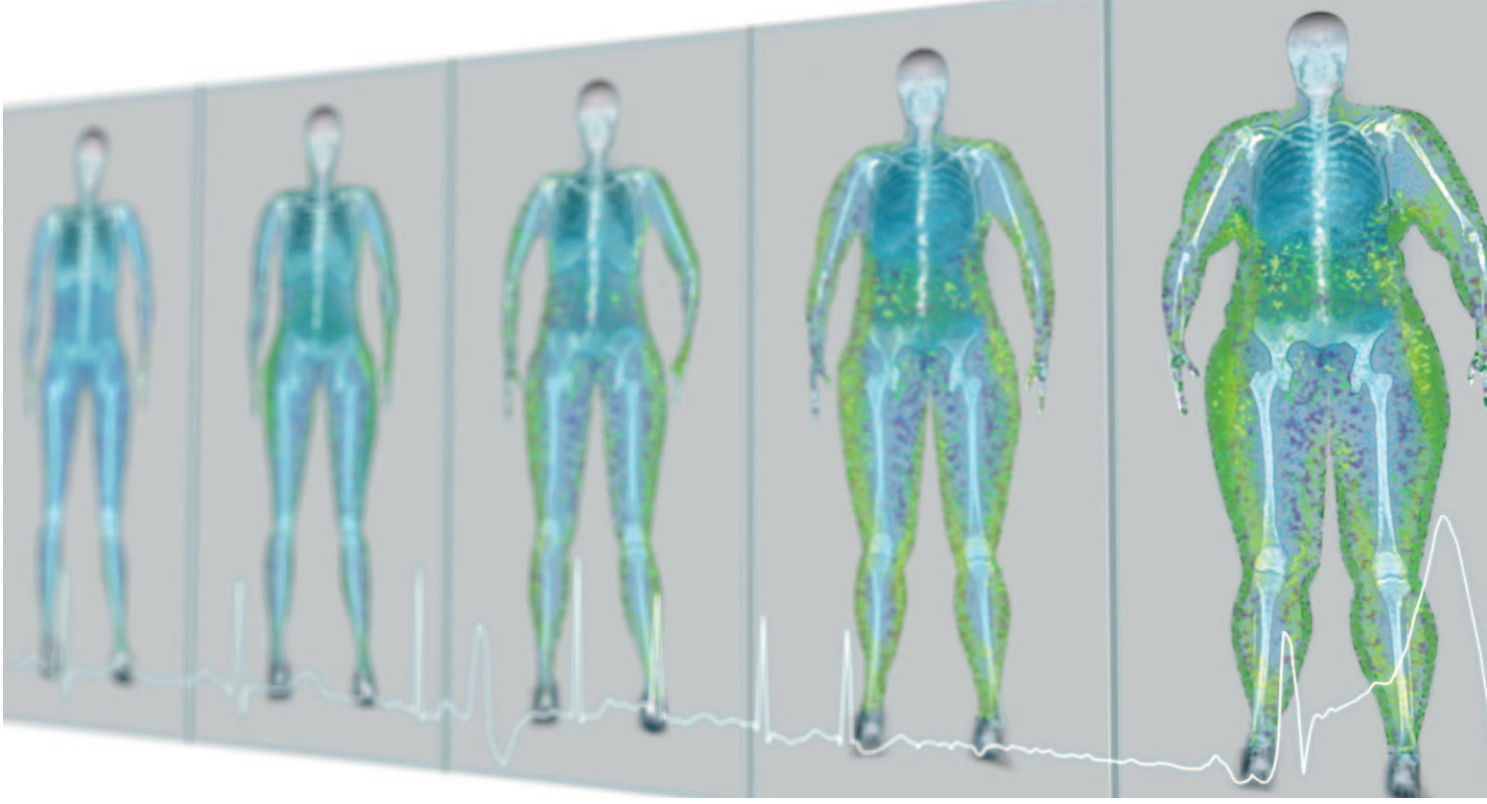
Broadly defined as an excess of weight that puts an individual at higher risk for adverse health outcomes, obesity is commonly associated with negative implications for cardiovascular and metabolic health. Increasingly, however, obesity is becoming understood as an inflammatory disease, with impacts across a wide variety of systems. As we progress in treating obesity and its associated comorbidities, understanding and addressing the inflammatory impact of obesity is going to be an important element of developing effective, beneficial therapies. Here, we'll explore the connection of obesity and inflammation, the current treatment landscape, and directions for future treatment.

THE IMPACT OF OBESITY & INFLAMMATION

Adipose tissue plays an important role in the body as a metabolic and endocrine organ, which secretes necessary hormones, such as leptin, adiponectin, and omentin. As fat tissue progresses into obesity, an increased number of macrophages and other immune cells are recruited into the tissue, where they stimulate the production of pro-inflammatory cytokines, such as: tumour necrosis factor (TNF)-alpha, which can signal necrosis or apoptosis; interleukin (IL)-6, which stimulates acute immune response and fever; and leptin, which impacts food intake and energy expenditure. In addition to creating local inflammation, these lead to toxic lipid accumulation and oxidative stress, which can damage cellular structures and increase susceptibility to numerous obesity-related complications. Meanwhile, the production of anti-inflammatory factors, such as IL-10, adiponectin and omentin, decreases.

Together, these heightened levels of pro-inflammatory cytokines have been associated with a variety of health conditions and outcomes. For example, inflammation contributes to the narrowing of blood vessels in atherosclerosis. It can also lead to other cardiovascular and pulmonary conditions – not to mention diabetes, chronic kidney disease, cancer, metabolic syndrome, and gastrointestinal and liver diseases.

The inflammation associated with obesity also increases the risk of autoimmune diseases and impacts their severity. Evidence suggests that obesity contributes to worse outcomes in inflammatory autoimmune conditions such as gout, rheumatoid arthritis, osteoarthritis, psoriasis, psoriatic arthritis, and multisystem inflammatory syndrome in children. Indeed, the relative risk of gout in men increases stepwise with increasing body mass index. And obesity can also play a role in response to treatment for autoim-



mune diseases. For example, the response to some forms of rheumatoid or psoriatic arthritis treatment is blunted in obese patients, with a much lower likelihood of achieving low disease activity compared to non-obese counterparts.[2,3]

TODAY'S TREATMENT LANDSCAPE

In many cases, addressing obesity through weight-loss treatments can also help to improve inflammation-linked comorbidities. Weight loss has been shown to have a positive impact on many such conditions. For instance, a loss of at least 10% of body weight has been linked to a reduction in cardiovascular disease.[4] And for every pound of weight lost, there is a decrease of four pounds of pressure on the knee joint, a reduction highly meaningful to patients with knee osteoarthritis.[5] Nevertheless, improvements in glucose, insulin and blood pressure, which come with weight loss, have been shown to revert to the baseline with even mild weight regain.

Current weight loss options primarily consist of lifestyle changes, pharmacotherapy and bariatric surgery. Of these, only bariatric surgery has been shown to have lasting effects on weight, with an average regain of under 5% of total weight lost after seven years.[6] But, it is only recommended for a specific subset of patients.

The long-term benefits are not so promising for other treatments. Within five years, patients are likely to regain up to 80% of weight lost through lifestyle changes.[7] Anti-diabetes and anti-obesity medication semaglutide – a gluten-like peptide1 (GLP-1) receptor agonist (RA) – can help maintain a total weight loss of 10% for more than four years; however such drugs may be a lifetime commitment.[8] Patients discontinuing semaglutide can expect to regain two thirds of weight initially lost through the drug within two years.[9]

However, in addition to their effect in weight loss, GLP-1 RAs have also shown notable success in reducing inflammation. These drugs suppress the secretion of inflammatory cytokines, such as IL-6 and TNF-alpha, by interacting with receptors in immune cells and modulating immune signals. This is thought to be a major contributing factor in the ability of GLP-1 RAs to improve outcomes in inflammation-linked comorbidities such as major adverse cardiovascular events and chronic kidney disease.

While weight loss, alone, may improve some inflammation-linked comorbidities, in most cases, its focus is on reducing obesity rather than targeting inflammation. And for patients who struggle to achieve or maintain weight loss, or who do not wish to take GLP-1 RAs in perpetuity, treating the cause of their conditions may seem out of reach.

WHAT'S NEXT FOR TREATING INFLAMMATION IN OBESITY

As highly effective weight loss drugs have successfully entered the market, we can now focus on improving treatment for obesity-driven inflammation. One potential route for future drug development is to specifically evaluate a potential therapy's impact on inflammatory markers such as circulating concentrations of IL-6, TNF-alpha and other such cytokines. These bio-

markers can be used as an additional dimension through which the efficacy of an obesity therapeutic can be evaluated for its ability to address inflammation-linked comorbidities.

Additionally, there is a great deal of promise in using immunotherapies that specifically target the white adipose tissue microenvironment to improve inflammation-linked comorbidities. There are two ways that immunotherapies can accomplish this: (1) direct treatment that influences cells or signalling pathways; or (2) indirect treatment that targets cytokines after they have been secreted.

While research in this area is still in early stages, some clinical trials in humans have shown potential in moderating inflammatory responses and improving outcomes for comorbid disease. For example, empagliflozin, a sodium-glucose transport protein 2 inhibitor, has had encouraging results in type 2 diabetes and atherosclerotic cardiovascular disease, by interfering with the secretion of inflammatory cytokines from obese white adipose tissue.[10] As well as seeing health benefits due to the reduction of inflammation, patients receiving this treatment experienced greater weight loss than those on placebo.

More study is necessary to gather information on the safety, efficacy and long-term benefits of such immunotherapies. This approach to mitigating inflammation may involve some toxicities and adverse events in patients. Further, the immune landscape of adipose tissue is very complex. So, developers must be careful that any such therapies only impact the desired immune responses, or risk interfering with beneficial immune system function.

THE OBESITY TREATMENT OF TOMORROW

Current treatments, particularly incretin hormones, such as GLP-1 RAs, have provided a powerful tool in addressing obesity and its comorbidities. Yet there is still quite a long way to go. Many developers are working toward obesity therapeutics that enable long-term maintenance of weight, do not reduce lean weight alongside fat, and that can be taken orally rather than as an injection. Among all of these avenues of research and development, the ability to treat the inflammation, which is driven by obesity, is central to the improvement of health outcomes.◆

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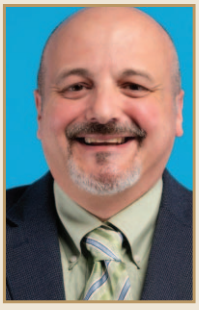


Dr. Johnny Peppers is Executive Director, Global Drug Development, Therapeutic Expertise, at ICON, and has been involved in clinical drug development and medical affairs for over two decades. This experience includes designing and implementing phase 1-3 clinical trials, medical affairs, post-marketing clinical research, KOL interactions and regulatory agency (FDA/EMA/PMDA) interactions. His therapeutic expertise includes immunology and autoimmunity, dermatology, allergic conditions and infectious diseases. He holds a PhD in immunology, a Master's Degree in biology and statistics and a mini MBA in pharmaceutical development. He is also an adjunct member of the CPCD and has a decade of paediatric clinical development experience, leading several clinical programs involving paediatric patients.

Dr. Christopher Mojcik is Senior Director, Therapeutic Area, Drug Development Solutions at ICON. He has over 25 years of experience in clinical research, including 14 years working with large and small pharma. He has worked with ICON for over six years. He is an MD with 12 years of experience in clinical and academic rheumatology, including seven years in private practice. His therapeutic expertise includes rheumatology, immunology, and autoimmunity. He also has experience with small molecules and biologics, Phases I-IV clinical trials, and in small (including orphan) to large indications. Christopher holds a PhD in immunology and was an instructor for seven years in Biology Sacred Heart University, Fairfield, CT.

DRUG DEVELOPMENT

The Next Frontier in Immunotherapy for Ovarian Cancer

By: Khursheed Anwer, PhD, MBA, and Douglas V. Faller, MD, PhD

INTRODUCTION

Ovarian cancer is the deadliest form of gynecological cancers, with nearly 20,000 new cases reported annually in the US alone.[1,2] While many other cancers have seen significant advances over the past decade, ovarian cancer treatment has remained relatively unchanged. This, compounded by the frequency of late-stage detection, has created a pressing need for a powerful and safe ovarian cancer therapy. Interleukin-12 (IL-12) has long held interest for cancer researchers as a cytokine with multiple mechanisms of action. Although recombinant human IL-12 (rhIL-12) injections have produced favorable immunological and clinical responses in patients with various malignancies, treatment-related hematological and liver toxicities have limited clinical utility due to rapid increase in blood IL-12 levels causing serious systemic toxicity. To overcome the shortcomings of rhIL-12 administration, IL-12-based therapy should produce IL-12 protein levels locally at the tumor site in a durable manner while maintaining a favorable safety profile.

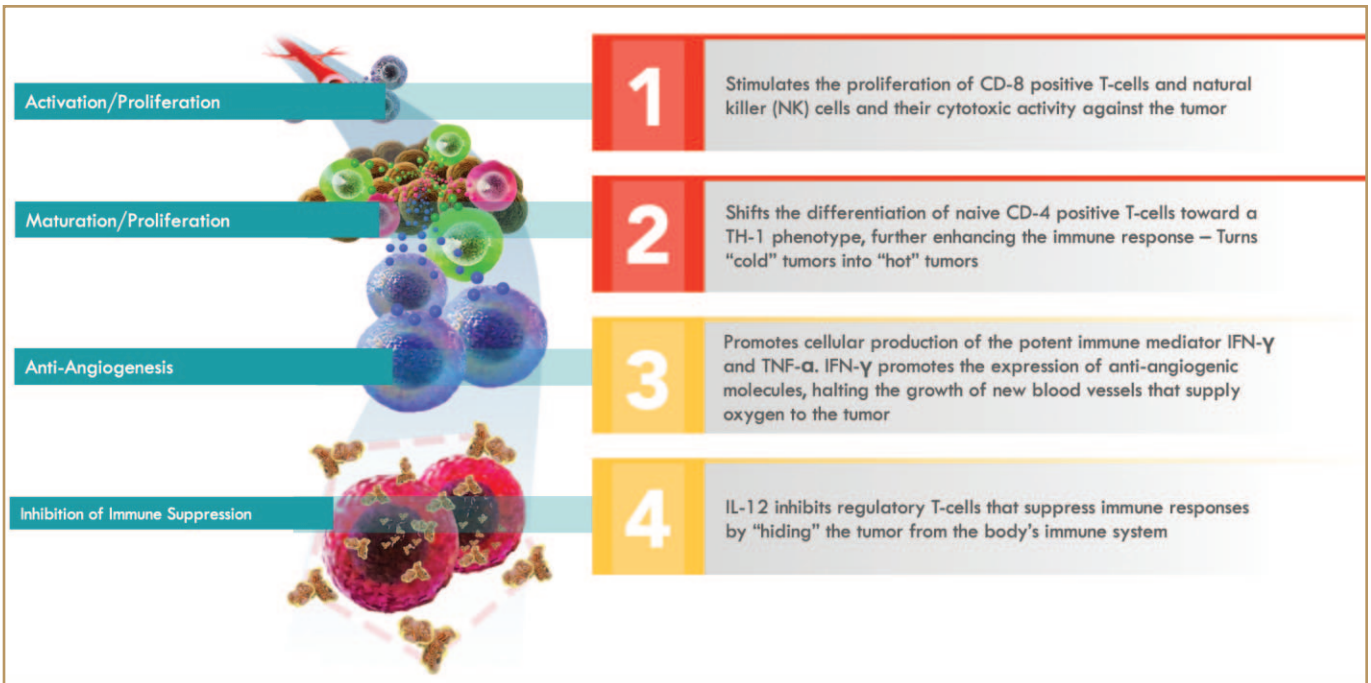
The following will highlight a new delivery system (TheraPlas®) being used to develop a more localized IL-12 immunotherapy for ovarian cancer and review its promising Phase 2 results.

THE UNHARNESSED POTENTIAL OF INTERLEUKIN-12

Cytokines, like IL-12, are a crucial class of proteins that allow cells of the immune system to communicate with each other and with other cells in the body. Interferon, chemokines, and interleukins are all part of this massive family of messenger proteins produced by both immune and non-immune cells. These protein-based signals coordinate cellular processes during day-to-day homeostasis, as well as coordinate immune efforts during various disease states.

Due to their central role in important signaling pathways, cytokines have long been studied and harnessed for their therapeutic potential. Many cytokine-based immunotherapies exist, and they are a particularly prevalent form of cancer treatment. These immunotherapies aim to boost or redirect the immune response and kickstart the body's defense system into removing cancerous cells.

IL-12 has been heavily explored as an immunotherapy option based on its proven anti-cancer activity. IL-12 is a signaling powerhouse, bridging the gap between our innate and adaptive immune responses by recruiting important cancer-fighting cells and boosting anti-tumor activities. For example, IL-12 has been shown to enhance the growth and cytotoxicity of natural killer cells and T-cells, two cell types capable of destroying tumor cells. IL-12 directly boosts production of IFN-γ, another cancer-fighting cytokine and master immune stimulator. IL-12 also has anti-angiogenesis properties that can inhibit blood vessel formation in new tumors, enhances antigen presentation, and plays a role in increasing antibody production.



Interleukin-12 (IL-12) is a powerful immune-modulating agent. IL-12 can induce anti-cancer immunity through multiple mechanisms.

Given this impressive resume, IL-12 is a prime candidate for cancer immunotherapy treatments, and animal models further support the anti-cancer abilities of IL-12. For treatment of both solid tumors and blood cancers, administering IL-12 in mice was a highly effective anti-cancer therapy.[3] Notably, IL-12 treatment was even beneficial when given in combination with chemotherapy, a particularly interesting finding given that chemotherapy can prevent an effective immune response in some cases.[3]

However, these promising preclinical results have not yet been successfully transferred to the clinic. In the 1990s and 2000s, many IL-12 trials were piloted, using a variety of therapeutic approaches and targeting a diverse set of cancers that included breast cancer, melanoma, lymphomas and others.[3] IL-12 was injected subcutaneously, intravenously, in combination with other therapies, and across a broad range of dosages. Unfortunately, although supported by the best efforts of many experienced research teams and clinicians, treatment with IL-12 was not the rousing success that preclinical trials suggested it could be.

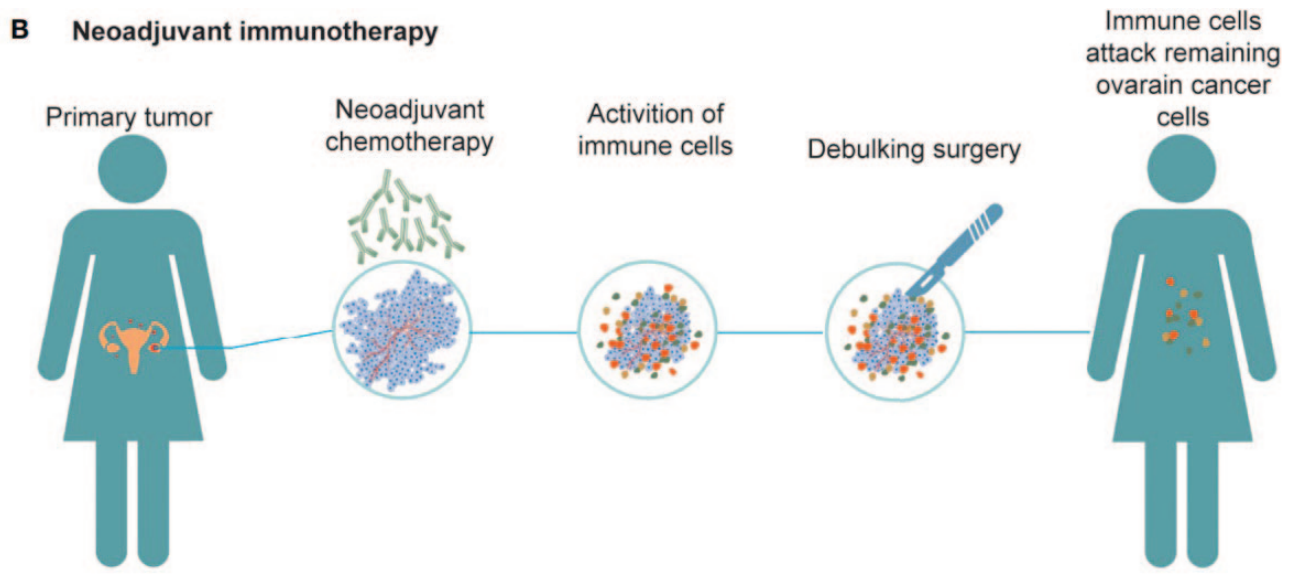
It was found that IL-12 treatments were less potent than predicted as the tumor microenvironment was preventing IL-12 therapies from being highly efficacious.[3] Human tumors are more heterogeneous than mouse tumors, which makes it harder for the immune system to effectively recognize the entirety of the cancer. This also contributes to a more robust tumor microenvironment that acts as a sort of shield for the invasive cancer. This microenvironment can effectively dampen the body's immune response at a local level and is a major contributor to the persistence and progression of many cancers.

Another concern was that systemic distribution of IL-12 produced unpleasant and occasionally dangerous side effects. The most common side effects were flu-like symptoms (headache, chills, fatigue), but there were also cases of cytokine release syndrome, otherwise known as a "cytokine storm," that occurs when the body releases too many cytokines too quickly. This can result in dangerously high fevers, generalized inflammation, and life-threatening organ failure in more extreme cases.

Fortunately, the tumor microenvironment is not impenetrable. More recent studies of IL-12 as an anti-cancer agent have explored strategies to overwhelm the local tumor microenvironment with a more targeted application of IL-12. More focused approaches to IL-12 immunotherapy would presumably reduce unwanted side effects as well. Early results are highly encouraging, providing hope that the promise of IL-12 may soon be realized.

NEW HOPE FOR OVARIAN CANCER PATIENTS

Treatment of ovarian cancer is one field that could particularly benefit from a safer and more efficacious IL-12 therapy. Ovarian cancer is the second most common gynecologic cancer in the US and the



Ovarian cancer in newly diagnosed patients is the optimal setting for immunotherapy and IMNN-001. Before debulking surgery, IMNN-001 can harness the still intact local immune system to display an anti-tumorigenic microenvironment. By directly accessing the intra-peritoneal tumor microenvironment and local immune system, intraperitoneally administered IMNN-001 is well positioned to offer clinical value to ovarian cancer patients at an early stage of their disease in combination with neoadjuvant and adjuvant chemotherapy.

deadliest cancer of the female reproductive system.[2] This is due in part to the difficulty of early detection. Early symptoms are often subtle, and 80% of diagnoses occur as late-stage cancers (stage III/IV).[4] Within the US, approximately 13,000 people lose the fight to ovarian cancer each year, making it the fifth leading cause of death in women and highlighting the need for improved treatment regimens.[1,2]

The current standard of care is platinum-based chemotherapy and surgical intervention, depending on the state of disease progression. Platinum-based chemotherapy drugs rely on platinum ions to cause DNA damage within rapidly dividing cancer cells. This systemic therapy can be combined with a procedure known as tumor debulking surgery, in which tumors are removed from the patient to minimize the number of cancerous cells. Ovarian cancer has not seen the same therapeutic advancements as other cancers; however, and this standard treatment approach has not evolved much since the 1960s. This has unfortunately left overall survival rates quite low, with 49% of ovarian cancer patients, including all disease stages dying within 5 years of diagnosis.[1,2]

Fortunately, we may be entering a new era in the treatment of ovarian cancer. For instance, a new class of drugs called PARP inhibitors represents a promising step forward. PARP inhibitors work by halting single-strand DNA repair, forcing cells to rely on a form of DNA repair known as homologous recombination. A common mutation found in both breast and ovarian cancer cells (BRCA mutations) often results in inefficient homologous recombination, preventing cancer cells from repairing their DNA and eventually killing the cell.

Three PARP inhibitors were approved for use against ovarian cancer between 2014 and 2017: olaparib, rucaparib, and niraparib. Given that both platinum-based chemotherapy and PARP inhibitors rely on interfering with cancer cell DNA, one of the primary use cases for these new drugs is patients who have responded positively to platinum-based chemotherapies. This approach, called maintenance treatment, focuses on preventing ovarian cancer from growing or recurring. The results have been promising, with progression-free survival rates improving by around 6 months (or longer in selected subgroups) in people being treated with PARP inhibitors and may also produce a survival benefit.

Based on this success, some PARP inhibitors are now approved for maintenance in patients whose tumors have responded to initial chemotherapy/surgery; that is, using PARP inhibitors after the initial therapy for newly diagnosed patients. However, the effectiveness of PARP inhibitors relies on cancer cells being deficient in homologous repair, which is not always the case. There are also concerns that PARP inhibitors may increase a patient's risk for blood cancers, similar to the risks associated with chemotherapy treatment. Thus, while PARP inhibitors are a much-needed advancement in the treatment of ovarian cancers, the majority of

patients with advanced ovarian cancer will still suffer recurrence after a few years. Additional treatment options are sorely needed.

IMNN-001: ENCOURAGING PROGRESS FOR A NOVEL IL-12 IMMUNOTHERAPY

Recently, a new IL-12 immunotherapy, IMNN-001, has shown promising potential for ovarian cancer treatment. Initial forays into IL-12 immunotherapies emphasized the need for local delivery of IL-12 at the tumor site to avoid cytokine release syndrome and to achieve higher tumor distribution in the immunosuppressive tumor microenvironment. IMNN-001 was designed based on a novel technology platform known as TheraPlas that has provided the technological tools to do just that.

TheraPlas is a non-viral nanoparticle delivery system that can be used to engineer cells with anti-cancer nucleic acid-based therapies. In early clinical research for IMNN-001, TheraPlas was used to deliver a DNA plasmid vector encoding IL-12. The TheraPlas delivery system protects the IL-12 plasmid from degradation following injection and enhances cellular uptake of the plasmid for a more efficient gene transfer. This results in the robust and durable production of IL-12 at the site of the tumor. As cells secrete IL-12 into their environment, a more localized concentration of IL-12 is achieved. This focused delivery of IL-12 reduces the risk of serious systemic toxicity, including cytokine storms, and helps overwhelm the tumor microenvironment with these powerful cytokine proteins.

This investigational immunotherapy recently completed a randomized and controlled Phase 2 clinical trial (OVATION 2) in which it demonstrated a favorable safety profile and quantifiable improvements in patient outcomes, when compared head-to-head with chemotherapy/surgery.[5,6] In this trial, the treatment group received IMNN-001 alongside the standard of care platinum-based chemotherapy, while the control group received standard of care alone. The treatment group achieved a 13-month increase in median overall survival compared to the standard of care. This study also saw a 27% increase in progression-free survival rates, an improvement of approximately 3 months.

This is the first immunotherapy treatment to achieve clinically meaningful improvements in both progression-free and overall survival rates, when used as a first-line treatment (in conjunction with chemotherapy) for newly diagnosed advanced ovarian cancer patients. A closer look at the data is even more encouraging. Women who received more treatment cycles of IMNN-001 showed an even more significant improvement in overall survival (close to 16 months). The addition of PARP inhibitors to IMNN-001 further enhanced patient outcomes, indicating a positive outlook for combinational treatments involving these two new therapies. Throughout the entirety of the study, including an extended monitoring period, there have been no reports of serious immune-related adverse events and the safety profile for this IL-12-based immunotherapy remains encouraging.

The TheraPlas delivery system, which is independent of a viral vector and a device, may finally allow researchers and clinicians to harness the cancer-fighting power of IL-12. While further investigation is needed, such exciting results are a welcome reprieve to those fighting ovarian cancers or concerned about their genetic risk of developing it. A Phase 3 clinical trial of IMNN-001 is scheduled to begin this year and will continue to explore the safety and efficacy of the first immunotherapy shown to improve survival rates for ovarian cancer.

These early clinical results demonstrate that TheraPlas is well-tolerated and effective at delivering IL-12 to the peritoneal cavity, inviting exploration of this delivery system for use in other cancers, including colorectal, uterine, and pancreatic. Researchers have demonstrated anti-cancer application of TheraPlas technology in animal models of pancreatic and colorectal cancer metastasized into abdominal cavities.

SUMMARY

Ovarian cancer is a daunting disease that has long stumped researchers' best efforts to control and cure it, especially in late stages. The therapeutic application of IL-12 has been similarly difficult due to serious systemic toxicity and low bioavailability at the tumor site, resisting our best efforts to wrestle it into a functional immunotherapy, despite the enormous potential it displays in early clinical trials and animal studies. The TheraPlas delivery system, due to its ability to produce IL-12 locally at the tumor site in a durable manner without causing serious systemic toxicity typically associated with the delivery of recombinant IL-12, has found a way to kill two birds with one stone, advancing IL-12 immunotherapies and extending the lives of ovarian cancer patients and survivors. While the full safety and efficacy profile of IMNN-001 must still be established in

Phase 3, the first two phases of this clinical trial encourage cautious optimism that a better standard of care for ovarian cancer is possible, and that we may be able to apply these lessons to other cancers as well. ◆

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BIOGRAPHIES

Khursheed Anwer, PhD, MBA, is Executive Vice President and Chief Science Officer of IMUNON, Inc. He was previously President and Chief Science Officer of EGEN, Inc., a position he held since 2009, before the company was acquired by IMUNON in June 2014. Dr. Anwer joined EGEN, Inc. in July 2002 as Vice President of Research and Development and directed the company's clinical and research and development functions throughout his tenure at the company. He was previously Director of Pre-Clinical Development at Valentis, Inc. From 1993 to 1999, he served in several positions at GeneMedicine, Inc., where he led several research projects in the area of non-viral gene therapy. Dr. Anwer has a PhD in physiology/pharmacology from Ohio University and received postdoctoral training from the University of Texas Health Science Center at Houston. He has authored more than 40 publications in the area of non-viral gene therapy, resulting from his active career in research and development. Dr. Anwer has served as an adjunct faculty member in the Biology Department at the University of Alabama in Huntsville and a board member of the University of Alabama Business School, STEP.

Douglas V. Faller, MD, PhD, is Chief Medical Officer of IMUNON, Inc. Dr. Faller has more than 30 years of experience at biotechnology and pharmaceutical companies leading strategies across discovery, preclinical, clinical and regulatory stages of small molecule development in several therapeutic areas including oncology, immunology and hematology. He also brings more than 25 years of experience in academic clinical and laboratory research settings with a focus on drug discovery and development, oncology and hematology, and cell and molecular biology. Dr. Faller most recently served as Chief Medical Officer at Skyhawk Therapeutics, where he was responsible for global clinical and regulatory development of novel small molecule RNA-splicing modifiers for the treatment of hematological and solid tumors and rare neurological diseases. Before that, he served as Chief Medical Officer at Oryzon Genomics, Inc. Previously, he worked at Takeda for more than five years, most recently serving as Executive Medical Director where he led the development of multiple early and late-stage therapies including small molecule and CAR-T programs for leukemias and lymphomas, and solid tumor programs including in gynecologic oncology. Dr. Faller received an MD from Harvard Medical School and a PhD and BS from the Massachusetts Institute of Technology. He was professor of medicine at Harvard Medical School, and subsequently he founded and served as first director of Boston University Comprehensive Cancer Center where he was also Grunebaum Professor for Cancer Research and professor of medicine, biochemistry, pediatrics, microbiology, pathology and laboratory medicine. Dr. Faller is the scientific founder of multiple biotechnology and pharmaceutical companies.

Drug Development
EXECUTIVE

Nathan Givoni
Co-Founder & CEO
Gelteq

GELTEQ

Gelteq: A Breakthrough Ingestible Gel Drug & Nutrient Delivery System

The evolution of drug delivery methods has been slow over many centuries and has stalled with the invention of edible gels, introduced in 1986. While technology has rapidly advanced in many other areas over the past few decades, we have seen minimal advancements in drug delivery and crucial issues such as dosage increases, targeted delivery, and control of viscosity have remained unsolved. Additionally, millions of adults and children have dysphagia, or difficulty swallowing pills, causing challenges and stress when medications are needed. Gelteq is aiming to fill a crucial void with its unique formulation that directly addresses this issue along with numerous others that traditional drug delivery has, including the taste unpalatable ingredients and issues with dosage control. The company is focused on advancing and commercializing its delivery solutions within five core verticals: pharmaceuticals, over-the-counter medications, nutraceuticals, veterinary pharmaceuticals, and sports nutrition.

Drug Development & Delivery recently interviewed Nathan Givoni, Co-Founder and CEO of Gelteq, to discuss challenges with traditional drug delivery and the company's innovative ingestible gel platform designed for drug and nutrient delivery.

Q: How did the business idea start?

A: Gelteq was formed through the shared determination between myself and my co-founder Simon Szewach, who is also Executive Chairman of the Board, to find alternatives for medication and nutrient delivery that do not require patients or consumers to take large pills or measure out specific powders to get the care they need.

We each watched patients and members of our families struggle with issues like dysphagia, diabetes, hypertension, and other indications that require exact

medication, and knew that there had to be a better way. From our initial meeting and discussion, we've worked on and refined Gelteq's core technology to create a gel-based oral delivery platform that is much more accessible and easier to swallow than traditional pills or powders.

Gelteq's story is far from linear, heading down a few directions and false starts before ultimately focusing on our current trajectory. The perseverance of our team has been inspirational, and we are all committed to this platform as a better alternative for drug and nutrient delivery.

Q: Is the gel technology a new delivery method developed by Gelteq? What are the advantages and challenges of formulation development?

A: Yes, Gelteq's gel platform is a new drug and nutrient delivery method created through a patented process, and we have several other patents pending as well. There are many advantages to the platform beyond just being more accessible for those who can't take pills, such as being both chemically and physically stable while being capable of including active pharmaceutical ingredients (APIs). The platform is also fully customizable, targeted, and flexible to the client's needs and wants, as we can tailor our gels to solve specific problems or achieve a specific outcome. It is also a much more pleasant experience that destigmatizes medication consumption with a more food-based presentation versus traditional medication delivery methods.

There are a few areas that we are still focused on advancing. We are working through determining solutions for ingredients that are more difficult to contain in the gel matrix. We have many different patented and patent-pending methods/formulations/solutions that we can apply to solve the problem of difficult ingredients and achieve a stable end product, but each new API can present a new challenge. Ingredient solubility is also a challenge and lastly, flavoring.

We like to work directly with clients on each of these challenges so we can tailor solutions to their needs and desires. Overall, the benefits to their customers and the increased accessibility are worth the challenges we overcome through our process.

Q: What is Dysphagia? What are the causes and symptoms? What are the possible treatments?

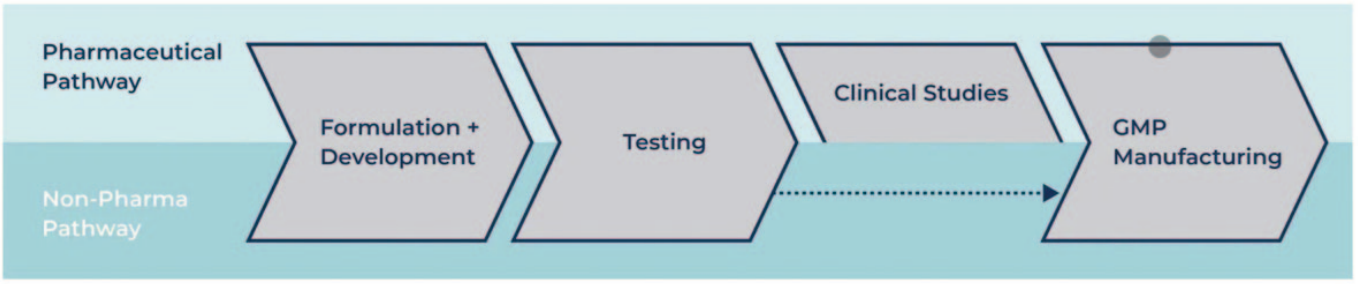
A: Dysphagia is the medical term for someone who has difficulty swallowing. It can range from mild discomfort to an inability to swallow at all, with other symptoms including chest pain, coughing or choking, pain while swallowing, pressure in the chest or neck, and more. There are many different causes including nervous system or brain disorders, muscle disorders, or physical throat blockages. This is an indication that can affect anyone, and impacts millions around the world, according to the National Foundation of Swallowing Disorders. Treatments include medications, changes in eating habits, surgical procedures, and texture modifications, among others. Gelteq's solutions provide a customizable drug delivery platform with dysphagia-friendly textures that are convenient and easy-to-consume while avoiding the risk of choking, making it easier for those with dysphagia to take medication – which can include lifesaving pharmaceuticals.

Q: What are the capabilities of the gel? How does the technology work for different compounds and their solubility and digestion?

A: Gelteq's proprietary gel platform has the capability to hold and deliver large doses without losing any taste profile or accessibility, issues that have traditionally been the case with pill or liquid medications. This ensures a better dosing experience for the patient and ultimately promotes better ongoing therapeutic adherence for patients who may otherwise struggle with their medication. The gel is also capable of combining water-soluble, solid components, and lipid-soluble excipients into one formulation that can be tailored for rapid digestion or delayed release profiles using different gel matrices through the platform.

Q: What medical conditions are you currently working on, and what are your plans for these products?

A: Our team has already worked on medications with a wide array of capabilities, such as diabetes, pain management, allergy, hypertension, and acid reflux. We have plans to take products through the regulatory pathways in the US with the FDA and with the requisite European bodies. Our initial preclinical work is already done with several APIs, and we expect clinical trials to begin shortly.



As a company, Gelteq is open to working with partners at any stage of the development cycle who are interested in turning their products into a more accessible and pleasant gel-based medication.

Q: What is the process when a customer comes to Gelteq wanting to develop their product into a gel?

A: Our team employs a detailed process when it comes to developing products with our partners. First, we listen to their product concept and the problems they are hoping to solve with our platform. Then, we go through a rigorous R&D testing program of the ingredients involved to ensure capability and provide the partner with an outline of the costs and feasibility. The next step is prototype development and testing with things like flavoring, batch capabilities, stability of the formulations, and more. For pharmaceutical products, there will then be the preclinical/clinical programs for approval. Next will be the required regulatory documentation and then Good Manufacturing Practice (GMP) for mass production.

Q: What are the types of partnerships and collaborations Gelteq seeks?

A: Gelteq is focused on product development and incorporating our technology into more markets across the globe. We are always open to partnerships, whether it be as a licensee partnership or collaborations to make new products. These can either be new drug applications or via bioequivalent pathways. An ideal partner for our company would be one with an API in a sector which they believe would be well-suited for our gel technology, such as oncology or geriatric medications, or a partner with a well-established sales pipeline looking for a new product to integrate into its pipeline.

Q: Can you please discuss your development status to date? What are the next critical steps for Gelteq? Are there any plans for clinical trials?

A: As a company, we continue to focus on the pharmaceutical development of several APIs with our gel platform, which includes achieving regulatory approvals post-clinical trials. We have also begun working with veterinarian medications and are excited by the preclinical results we've seen so far that our technology can open doors for animals in the same way it can for humans.

We have also developed an extensive library of vitamin and health related supplements for licensing. We have several APIs in our current development pipeline, which are in the preclinical stage, and several more that we expect to begin clinical trials in the next few months. Our team has already submitted or is currently in the process of submitting multiple 505(b)(2) applications to the FDA or similar pathways in other regions.

Our goal is to continue to expand with partners worldwide, and to positively impact people and animals who are taking products using the Gelteq platform. ◆

CONTRACT SERVICES

When Choosing Stent, Catheter & Tubing Partners, Less is More

By: Andrew Filachek, Global Head of Design & Development – Interventional Devices

INTRODUCTION

Increasingly, MedTech companies are seeking contract design and manufacturing partners that can accompany them on comprehensive product journeys – from initial concept to validation to large-scale manufacturing, and everything in between. The ability to combine ideation and early stage development with materials science and process technologies has, in recent years, become a differentiator across a variety of device categories.

This relatively recent dynamic runs decidedly against the historical grain. In a globalized supply chain that frequently relies upon numerous design and production partners providing separate components for sophisticated, mission-critical medical devices, a single-partner approach seems almost quaint. But the advantages offered by truly turnkey partners – ones that can steer a complicated, often multi-component medical device from materials selection and prototype engineering straight through ramp-up production and broader commercialization, with participation in critical steps along the way – have never been more evident.

This value is magnified when the medical device in question is a "niche within a niche." As the healthcare solutions landscape becomes more intricate, more MedTech companies are eschewing "stay in your lane" specialists for multilane partners capable of running from starting gun to finish line. This "under one roof" mindset favors contract development and manufacturing organizations (CDMOs) with holistic strategic skillsets rather than piecemeal tactics that must be stacked upon elsewhere.

If too many chefs can ruin an entrée, too many design, engineering, and production partners can limit and delay the realization of a complex medical device. Nowhere is this consolidation-centric concept truer than with advanced stents, catheters, and tubing products.

STENTS & CATHETERS: PRODUCTS INFORMED BY PROCESS

A comprehensive dissertation encompassing the myriad varieties of stents and catheter combinations would require a book rather than a few pages, so instead let's explore one sliver of this market – a "niche within a niche within a niche," so to speak. For starters, let's take a deep dive into a category known for its heightened levels of design, engineering, and manufacturing challenges: neurovascular stent systems.

All stents are miniscule; neurovascular stents are exceedingly so, frequently measuring just two or three millimeters. The tiny tubular devices are implanted within blood vessels in the intracranial cavity to treat a vascular abnormality, such as those resulting from aneurysms or strokes.

Here, the bird's eye view becomes the proper perspective. Neurovascular stents are an exceptionally intricate device that, after being coupled with another device (a catheter), will be the focal point of a delicate, difficult medical procedure. The entire process – not only design through manufacturing but design through implantation – must be as optimized as possible. This optimization requires not just individually perfected steps but the synchronization of those steps.

Here, categorization comes into play. Whereas many stents come preloaded into their complementary catheter delivery sys-

tems, neurovascular stents occupy too limited a landscape for such conveniences. Given the narrow, twisting tortuous path that must be navigated for successful placement, preloading a neurovascular stent in a catheter would make the latter too stiff for the task at hand.

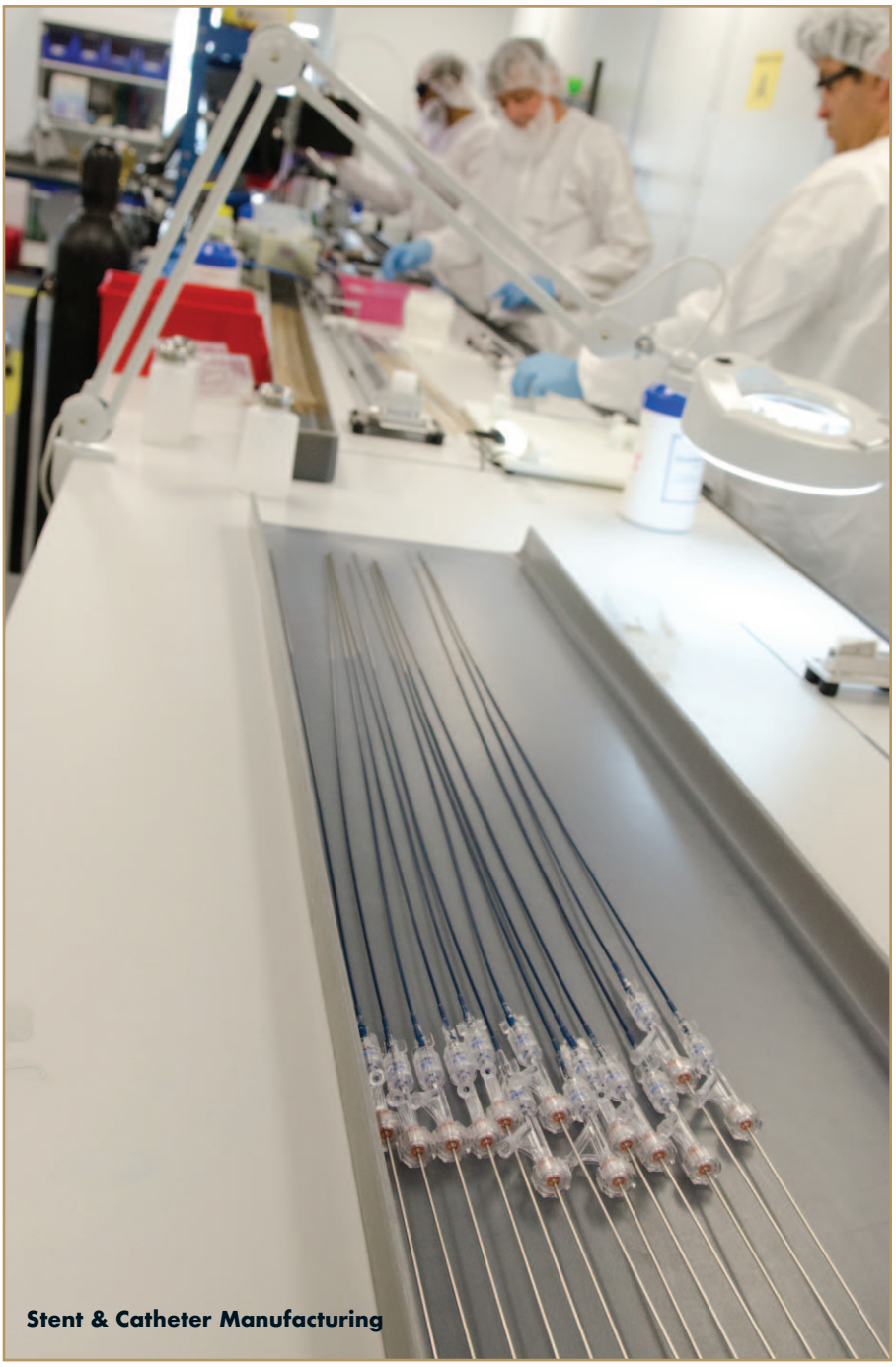
Rather, neurovascular stents are placed by first inserting a small-diameter microcatheter, typically about 150 centimeters in length. Once the microcatheter reaches its destination, the guidewire is removed; the stent is then fed through the distal end and, ever so gently, pushed to the precise implant spot.

This process places a premium on the interaction between a neurovascular stent and its microcatheter. The tracking must be smooth and free of bunching, and the final step – the removal of the stent from the microcatheter's tip – must be seamless.

With neurovascular stent systems, then, we're confronted with intricate systems that must be designed with their payloads in mind. The right catheter will meet its stent's needs for column strength without an overabundance of compliance, because if it stretches too much or too unpredictably, the procedure becomes more complicated and less informed. Deployment accuracy also is critical; for example, a particularly springy stent will need a custom-designed catheter mechanism to prevent premature deployment.

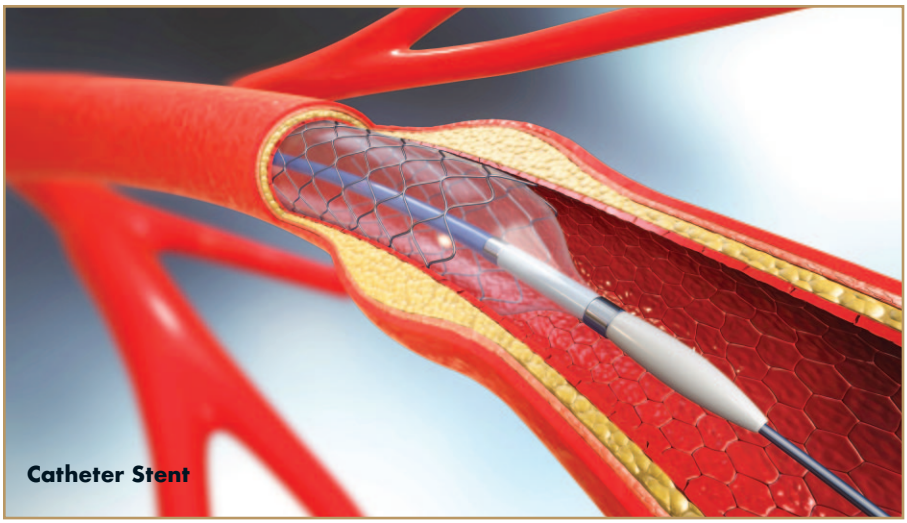
With catheters and stents, there are typically several design tradeoffs when holistically considering the tortuous path, stent radial force, and catheter compliance. Striking the right balance among these attributes will yield an optimized stent-catheter combo whose procedural application is repeatable, and whose ultimate effects are positive and enduring.

Already, we can see the pitfalls of a multi-partner building block approach. The various parties involved would need constant, ultra-detailed inter-organizational communication to ensure best possible compatibility between the stent and its delivery device. In this example, optimized stent concepting and prototyping must consider more than the attributes of the stent itself. While stent-specific elements like size, radial force and crimping characteristics are invaluable, equally invaluable is understanding how that stent will conform to its delivery vessel: the catheter.



Stent & Catheter Manufacturing

Notably, such intricacies apply not only to stent-catheter combos but also a wide array of adjacent and next-generation solutions. For example, it's becoming increasingly common for complex catheter systems to include stent-like devices like stentrievers and other devices for thrombectomy. Such sophisticated constructions also benefit greatly from extensive experience in traditional stents,



catheters, tubing solutions and other interventional medical devices.

DRUG DELIVERY: THE DESTINATION DICTATES THE JOURNEY

Unsurprisingly, this dynamic of interconnectivity stretches beyond device delivery into the realm of targeted drug delivery. Let's briefly touch upon a few of these categories.

For a variety of reasons, a growing number of drugs are locally deployed through catheters, on catheters, and on medical devices. Many of the catheters utilized for such purposes require special or even one-of-a-kind properties to reliably and compatibly handle a specific drug – a process whose complexity increases in parallel with the corresponding medicine's intricacy.

Here's an example: A few years ago, a novel perfusion catheter capable of delivering liquid paclitaxel was the focus of a first–in–human study. Dubbed the Occlusion Perfusion Catheter (OPC), the tubing solution was designed as a universal drug–delivery catheter for delivering liquid paclitaxel to the medial layer, treat multiple lesions with a single device and, critically, minimize drug loss. A report published by the National Institutes of Health showcases the catheter's hyper-customization.[1]

The OPC delivers paclitaxel by creating a treatment chamber between two occlusion balloons through which the agent is delivered. The delivery of liquid paclitaxel is mechanically driven using pressure, measured in real–time. Local liquid delivery provides a novel approach to deliver paclitaxel uniformly into the vessel wall and potentially overcomes the shortcomings of current procedures to treat [below-the-knee] arterial stenosis.

Notably, paclitaxel also can be delivered via drug-eluting stents, another area where overarching design, prototyping and production control can be beneficial. As the stent must be paired with its corresponding drug, so must the catheter be paired with its corresponding stent.

Drug-eluting stents also may be employed to deliver drugs like sirolimus, everolimus, zotarolimus and biolimus, which help prevent the arterial narrowing that can occur following stent implantation. In any application, developing the comprehensive system becomes a chain – and the fewer links along that chain, the lower the chances for costly, time-consuming inefficiencies or even oversights that send engineers back to the drawing board.

Several other oncology drugs are similarly applied hyper-locally. As a result, those catheter developers and suppliers with established expertise designing tubing solutions for the high-potency drugs typical to this field have a leg up. A deep bench of experts and an ample knowledge bank can narrow down what can otherwise be a protracted trial-and-error process. With oncology APIs always highly potent and often in short supply, the advantages to finding the right tubing solution expediently become obvious, as does the value in keeping the process under one corporate roof.

Tangentially, it's also worth noting that catheter design also must consider compatibility with other devices besides stents and drugs, including interactions with ancillary, non-proprietary components such as guidewires, introducers and guide catheters. A singular entity with the knowledge set to consider the myriad variables is in a decidedly advantageous position.

GREATER THAN THE SUM OF ITS PARTS

All this leads to one destination: the operating room. While the stents and drugs may be the stars, the stage is just as important. Considering the complex catheter-dependent applications – delicate neurovascular stent implantation, painstaking high-potency oncology drug delivery, medicines that mitigate transplanted organ rejection – healthcare personnel conducting such procedures take on crucial supporting roles. Everything from stent design to catheter compatibility

to skillful implantation and drug delivery must coalesce in support of one goal: successful acute deployment and, in the case of stents, long-term device viability.

Can this process be successfully conducted through a multi-partner approach? Certainly. But there are indisputable insights and best practices that can be more thoroughly developed and honed with an overarching view of how both stents, catheters and other tubing solutions are designed, produced and utilized. The whole of the process is greater than the sum of its parts.

One substantial benefit to containing the entirety of the development and prototyping process in one facility is expedient trial and error. Savvy designers often have in-house simulation labs that precisely mimic how doctors would utilize (for example) a stent-catheter combo. This can inform potential modifications to stents, catheters or both.

Compatibility simulations and the foresight they afford are but one area in which medical device CDMOs can showcase value to potential MedTech customers. Further upstream from such prototype trials, CDMOs with in-house materials testing and analysis programs help MedTech companies understand parameters and potential pitfalls before component construction even commences. Here, experience matters; an outsourcing partner with firm roots in stent-catheter and drug delivery systems development can draw upon a deep well of knowledge and seasoned team of engineers who've successfully designed, produced and launched unique yet similar combinations.

Indeed, even in scenarios involving novel, patented designs, ingrained niche knowledge helps a stent-catheter or drug delivery system development process hit the ground running for enhanced speed to market. For example, new stent and catheters concepts typically require approval from regulatory authorities. This includes design stress tests, such as how a stent will handle the strain of crimping. Here, expertise becomes an expediting agent, because even new designs share similarities with existing ones. This means that certain device modeling parameters can be largely informed from an established knowledge base of stent development.

The human body is an exceptionally complicated, interconnected design. Companies producing targeted direct-delivery drugs, or providing invasive or implanted medical devices, naturally must develop their products in relation to this – and, crucially, according to the operatory procedures used to introduce or employ them. With so many considerations to juggle, more MedTech companies are finding reassurances with turnkey partners, whose comprehensive product and process expertise make them less likely to drop the ball. ◆

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BIOGRAPHY

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Drug Development
EXECUTIVE

Ofer Gonen
Chief Executive Officer
MediWound

MediWound Ltd.: Developing a New Class of Biologic Enzymatic Therapeutic Products to Debride Wounds

MediWound (Nasdaq: MDWD) specializes in the development, production and commercialization of rapid and effective biologics that improve existing standards of wound care. The company aims to enhance patient experiences while reducing costs and unnecessary surgeries. *Drug Development & Delivery* recently interviewed Ofer Gonen, Chief Executive Officer of MediWound, to discuss the company's innovative approach to debridement.

Q: Tell us about the importance of debridement and the founding of MediWound.

A: Debridement is the process of removing dead or non-viable tissue from burns and wounds and is essential for healing. While there are multiple different techniques for debridement, surgical removal of the dead tissue is the most common. However, for many patients, surgery is not always the best or most preferred option.

A drug for enzymatic debridement has been available for over 50 years, and while it is widely used in the United States, it is not considered to be very effective, limiting its utilization. MediWound is changing that, offering a novel biologic drug that provides quick, safe, and effective debridement.

Research has explored various enzymes for debridement, with Bromelain — an enzyme derived from pineapple stems — proving to be one of the most effective. However, due to its high activity and volatility, it was historically challenging to stabilize and package. Therapeutic treatments typically require a stable shelf life to ensure they are ready for use when needed and can be easily applied.

Due to these challenges, Bromelain was largely overlooked as a commercially viable product. However, the founders of MediWound saw its potential and developed a patent portfolio focused on lyophilizing Bromelain and other enzymes from pineapples into a stable powder. It took us over 10 years just to be able to develop the process to manufacture this powder in a way that resulted in the level of batch-to-batch consistency required for regulatory approval of a drug. We then perfected the process of reconstituting this powder at the site of care. This breakthrough formulation proved highly effective for debridement of non-viable tissue, creating a powerful, ready-to-use commercially viable treatment.

After another 10 years, our first drug, NexoBrid®, was approved and became one of the few purely botanical drugs in the market.

NexoBrid is an FDA and EMA-approved orphan biologic for eschar removal for deep partial-thickness and/or full-thickness thermal burns in both adults and children. Next up for us is using the same drug product but in a lower concentration and a different formulation as a debridement treatment for various chronic wounds.

Q: How is NexoBrid used to treat burns?

A: Although burns make up a relatively small portion of the global wound care market, the need for effective treatments is immense due to the severity of burn injuries. We have dedicated substantial resources to addressing this critical unmet need, recognizing the profound impact it can have on patients' lives. In surgical burn tissue debridement, physicians often face the challenge of distinguishing between what is viable and non-viable, leading to the removal of all the tissue down to a certain level. This process can remove tissue that doesn't need to be removed, often leads to excessive blood loss, and of course has all the other negatives of surgery to go along with it.

NexoBrid offers an important alternative. As a topical treatment, it selectively targets and removes only dead tissue, preserving healthy tissue in the process. This not only minimizes the need for extensive surgery but also reduces blood loss and helps reduce scarring. Moreover, NexoBrid can be applied immediately by health teams without the need for an operating room or general anesthesia, thereby shortening hospital stays and associated costs.

NexoBrid is administered in up to two applications, each lasting four hours. The first application can cover up to 15% of total body surface area (TBSA). A second application of NexoBrid can be applied 24 hours later for a combined total coverage of 20% of TBSA.

NexoBrid is especially valuable in mass casualty events, as we've witnessed around world, including Ukraine, Israel, Italy and other locations. The treatment is also included in the US national emergency stockpile, highlighting the significant role it can play in disaster response.

Notably, NexoBrid recently received an FDA label extension for eschar removal in pediatric patients aged newborn through eighteen with deep partial- and/or full-thickness thermal burns. This young demographic is important as a crucial benefit of enzymatic debridement is the reduction of scarring that often comes with surgical debridement. From a humanistic perspective, use of NexoBrid removes the trauma associated with surgery, and for young children and their families who are already dealing with the trauma of the burn itself, this is incredibly important.

Q: What is the competitive landscape for NexoBrid?

A: NexoBrid has a very compelling competitive profile in the debridement market, where there are few non-surgical options. With regard to enzymatic debridement, the existing product would only be used on less severe burns, so is not considered a competitor for NexoBrid. The main competition is surgery, which has been the standard of care for 100 years. In clinical trials, NexoBrid delivers effective results 93% of the time with just a single four-hour application. Moreover, much Health Economics Outcomes data has been collected, which demonstrates that when considering the total cost of care, including hospitalization and operating room expenses, NexoBrid offers substantial savings relative to those related to surgery. It not only reduces direct surgical costs but also lowers associated expenses, making it a cost-effective solution for treating severe burns.

Given the relative benefits of our non-surgical solution, we are seeing that where it is used, it is becoming a standard of care.

Q: What other products are in the pipeline?

A: Utilizing this core biotherapeutic bromelain-based enzymatic platform technology, MediWound has developed a strong R&D pipeline, including our lead drug under development,

EscharEx®. EscharEx® is a Phase 3-ready biologic for the debridement of chronic wounds, offering significant potential advantages over the dominant $360+ million product and an opportunity to expand the market.

Chronic wounds are common among patients with diabetes and those with vascular conditions that impair blood circulation, leading to diabetic foot ulcers and venous leg ulcers. These patients typically have other comorbidities, making wound healing challenging. Their wounds often become complicated by necrotic tissue, which can harbor harmful bacteria. The standard of care focuses on shifting these wounds into an acute healing process, and much of the time this all starts with debridement. Chronic wounds represent a significantly larger market compared to burns.

Additionally, we are working on a treatment for basal cell carcinoma, where we've seen early success in Phase 1/2 testing. We are currently perfecting the drug delivery with the goal that this treatment could potentially replace surgery for certain patients.

Q: What feedback have you received from the market?

A: NexoBrid is approved and used in more than 42 international markets. We have received positive feedback from physicians and patients alike, having helped to save lives during wartime while providing a surgery-free option to everyday people who unfortunately suffer severe burns.

With regard to EscharEx, for our venous leg ulcer Phase 3 we've entered into research collaborations with important global medical players including Molnlyncke, Solventum (formerly 3M) and MiMedx, who appreciate the quick and effective nature of our technology in debriding chronic wounds, which leads to faster healing. We expect to enter into additional collaborations as we start preparing for our diabetic foot ulcer study.

Q: What are the next milestones for MediWound?

A: We recently completed the construction of our new, state-of-the-art GMP-compliant manufacturing facility in Israel. With full operational capability planned for 2025, this expansion will increase manufacturing capacity sixfold to meet the growing global demand for NexoBrid.

In the US alone, due to the efforts of our distribution partner Vericel, around 70 burn centers have completed submissions to Pharmacy and Therapeutics (P&T) committees, with more than 40 centers already obtaining approval, and nearly all of those placing initial product orders.

We are also continuing our work with the U.S. Department of Defense to advance NexoBrid as a non-surgical treatment for field care burns.

Regarding EscharEx and debridement of chronic wounds, our Phase 3 trial on venous leg ulcers (VLUs) is on track to begin imminently. We also recently received €16.25 million from the European Innovation Council to fund our second indication – diabetic foot ulcers (DFUs). This funding supports our continued development of EscharEx and expansion into new markets and indications.

It's certainly an exciting time for the company as we continue to expand our global footprint and develop new needed wound treatments. ◆

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Technology & Services Showcase

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