Drug Development & Delivery

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Prefilled Syringes & Biologics: The Perfect Partnership

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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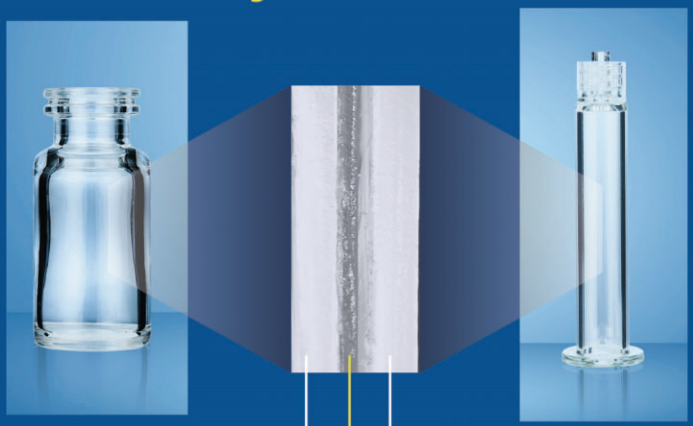

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Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
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"Today, through the research efforts of dedicated gene therapy pioneers, huge knowledge gaps have been closed concerning virus biology, vector dynamics, immune interaction, and vector safety. This intense research has resulted in science's ability to remove the harmful/pathogenic components of virus genomes, enabling applications that would not harm the organism or patient, and turning the tide on viral vectors as a historic opportunity, rather than a threat."

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Stephanie Raines
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"Sectors of the CDMO market – sterile injectables, prefilled syringes, biologics APIs, and viral vectors – are expected to expand quickly, driven by an accelerating shift in the pharmaceutical market toward innovative biologic and cell and gene therapy products. Nonetheless, small molecules will continue to represent the majority of prescribed drugs for the foreseeable future and thus are the major growth driver for the CDMO market."

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Real World Challenges
in *Drug Delivery and Formulation*

The Objective

Need to understand the changing dynamics of clinical-stage pipelines by indication, molecule type and most advanced phase to present to senior management

The Challenge

How do I obtain this information in a format that will allow me to quickly evaluate overall trends in pharmaceutical development?

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Microfluidics Enables Reliable siRNA Drug Delivery for Inflammatory Diseases & Tumor Targeting

Researchers in the Department of Pharmacy at the Ludwig Maximilian University of Munich are using chips from Dolomite Microfluidics to reliably and consistently produce monodisperse particles for targeted delivery of small interfering RNA (siRNA) therapeutics. This microfluidic encapsulation technology is ideal for gene silencing applications in cancer immunology and inflammatory diseases, where siRNA can potentially be used to down-regulate genes associated with these pathologies. Prof. Dr. Olivia Merkel, Professor of Drug Delivery, explained: "Nanoencapsulation is a highly efficient way to deliver siRNA to targets across the cellular membrane, protecting it from degradation prior to endocytosis. It is important to deliver the therapy in a controlled and reproducible manner; the particle size has a huge impact on in vivo work, affecting the rate of uptake and clearance."

"Previously, we produced our nanoparticles manually, which was both time consuming and uncontrolled, and resulted in a range of particle diameters. We needed a solution to overcome this challenge and, in 2017, discovered Dolomite Microfluidics. We've been using Dolomite chips ever since, consistently downsizing our particles from around 200 to 100 nanometers and below. Our batch-to-batch reproducibility has improved immensely, and we are confident that the nanoparticles we prepare will have low polydispersity and be the optimal size for our work, which is important. We are very pleased with what we have achieved so far using the Dolomite chips, and are excited about what we still have to come."

Established in 2005, Dolomite Microfluidics has grown to be the world leader in the design and manufacture of high quality innovative microfluidic products. The company offers a range of microfluidic systems, components, and specialist chemicals – including pumps, chips, connectors, temperature controllers, sensors, accessories, and custom-made components – as well as software for analysis or automation.

Modularity, ease of use, innovation, and scalability are common to all Dolomite Microfluidics products, which are used across a broad range of applications in biology, drug discovery, chemistry, food, cosmetics, and academia.

Dolomite is a part of the Blacktrace group of companies, a world leader in Productizing Science®, and has offices in the USA, Japan, India, Brazil, and Hanoi as well as a worldwide network of distributors. For more information, visit www.dolomite-microfluidics.com.

Ajinomoto Bio-Pharma Services Signs Manufacturing Agreement With Humanigen for Lenzilumab, Currently in FDA-Approved Phase 3 Study for COVID-19

Ajinomoto Bio-Pharma Services, a leading provider of biopharmaceutical contract development and manufacturing services, recently announced it has entered into a manufacturing agreement with Humanigen, Inc., for the fill finish supply of lenzilumab, currently being studied in a Phase 3 clinical trial in adult, hospitalized patients with COVID-19.

"We are extremely pleased to partner with Humanigen in the fight against COVID-19 and to use our unique position as a US-based manufacturer to help simplify and secure a key part of their supply chain," said Kristin DeFife, PhD, Sr. VP of Operations & Site Head at Ajinomoto Bio-Pharma Services. "Through this collaboration we uphold our mission to improve the health of humankind, and our employees take great pride in knowing that our efforts may ultimately help patients survive this devastating disease."

Under the terms of the agreement, Aji Bio-Pharma will provide drug product aseptic fill finish services for Humanigen at its San Diego facility. Lenzilumab, Humanigen's proprietary Humaneered anti-human granulocyte macrophage-colony stimulating factor (GM-CSF) monoclonal antibody, is being administered as part of a US multi-center, randomized, placebo-controlled, double-blinded Phase III study for COVID-19 patients. Lenzilumab neutralizes GM-CSF, a key cytokine in the initiation of a cytokine storm.

"We are excited to be working with Aji Bio-Pharma for the fill finish production of lenzilumab," said Dr. Cameron Durrant, Chairman and CEO of Humanigen. "This partnership allows us to utilize Aji Bio-Pharma's drug product expertise and infrastructure to provide a timely supply of lenzilumab."

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization with sites in Belgium, US, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities for preclinical and pilot programs to commercial quantities, including Corynex protein expression technology, oligonucleotide synthesis, antibody drug conjugations (ADC), high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing, and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our client's needs. For more information, visit www.AjiBio-Pharma.com.

Humanigen, Inc. is developing its portfolio of clinical and pre-clinical therapies for the treatment of cancers and infectious diseases via its novel, cutting-edge GM-CSF neutralization and gene-knockout platforms. The company's immediate focus is to prevent or minimize the cytokine storm that precedes severe lung dysfunction and ARDS in serious cases of SARS-CoV-2 infection with lenzilumab, the company's proprietary Humaneered anti-human-GM-CSF immunotherapy, for which a US multi-center, randomized, placebo-controlled, double-blinded Phase 3 study for COVID-19 patients is underway. The company also is working to combine FDA-approved and development stage CAR-T therapies with lenzilumab. A clinical collaboration with Kite, a Gilead Company, to evaluate the sequential use of lenzilumab with Yescarta, axicabtagene ciloleucel, in a multicenter clinical trial in adults with relapsed or refractory large B-cell lymphoma is currently enrolling.

KBP Biosciences Completes Enrollment of BLOCK CKD Phase 2b Study

KBP Biosciences recently announced it has completed patient enrollment of BLOCK CKD (Blood Pressure in Chronic Kidney Disease), its Phase 2b study of its lead product candidate, KBP-5074, a highly-selective and potent non-steroidal mineralocorticoid receptor antagonist (MRA), in patients with moderate-to-severe chronic kidney disease (CKD) and uncontrolled hypertension. The company expects to report top line data from BLOCK CKD in the fourth quarter of 2020.

BLOCK CKD is a randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy, safety, and pharmacokinetics of KBP-5074 in patients with moderate-to-severe CKD and uncontrolled hypertension. The study enrolled around 160 patients with an estimated Glomerular Filtration Rate (eGFR) of 15-44 mL/min/1.73m2 and systolic blood pressure (SBP) >140 mm Hg. Following a screening period of up to 4 weeks, participants received placebo for a 2-week run-in period. Upon completion of the placebo run-in, subjects were randomized to receive either placebo, 0.25 mg or 0.5 mg of KBP-5074 once daily for 12 weeks. At the conclusion of the dosing period, subjects will undergo a post-treatment observation period for 4 weeks. The primary endpoint of the study is change from baseline in SBP, with secondary endpoints evaluating diastolic blood pressure, ambulatory blood pressure change and change in urine albumin to creatinine ratio (UACR).

"Completion of enrollment marks an important milestone in the KBP-5074 development program," said Thijs Spoor, Chief Executive Officer of KBP Biosciences. "We are highly encouraged by the data generated from previous studies of KBP-5074 and look forward to the data readout from BLOCK CKD later this year. This data will help inform the design of the planned Phase 3 clinical study of KBP-5074, for which we are targeting a 2021 initiation. I would like to thank our investigators, patients and their families for their support throughout the study. There is a critical unmet need for new therapies to treat these patients, and we believe that our drug has the potential to become a best-in-class treatment option."

James McCabe, MD, Vice President, Medical Director of Clinical Development and Medical Affairs of KBP Biosciences added, "As a practicing nephrologist, I am excited about the potential of KBP-5074. Currently approved therapies, including others in the MRA class, are characterized by severe and in some cases life-threatening side effects and contraindications, most notably the risk of hyperkalemia. KBP-5074 could provide a safe and efficacious treatment option to this large, underserved patient population."

KBP Biosciences is a global, clinical-stage biopharmaceutical company focused on the research and development of new chemical entities with known mechanisms of action targeting underserved patient populations. Headquartered in Princeton, NJ, KBP Biosciences has strong capabilities from Discovery and CMC through global clinical development and registration. The company principally devotes its resources to the therapeutic areas of major organ protection and anti-infectives.

eGenesis Strengthens Production Capabilities With Acquisition of ICBiotec

eGenesis recently announced the acquisition of the assets and operations of ICBiotec (ICB), one of its key production partners. ICB is one of the few companies in the US with advanced cloning and large animal transgenic production capabilities integral to the xenotransplantation supply chain.

Under the terms of the transaction, eGenesis will acquire ICB's existing facilities, equipment, and land. ICB's research and operations staff will continue as employees of a wholly owned subsidiary of eGenesis. The acquisition will provide eGenesis with full control of its xeno-organ supply chain.

"eGenesis is committed to advancing therapies for patients in need of organ, tissue, and cell transplants," said Paul Sekhri, President and Chief Executive Officer of eGenesis. "The acquisition of ICB is a key part of our strategic development plan and enables us to vertically integrate our research, cloning, and production capabilities."

Luis Queiroz, DVM, Chief Scientific Officer of ICB, added "For the past several years, we have been working closely with eGenesis to develop engineered organs to support their xenotransplantation programs. We are thrilled to join eGenesis and continue supporting their critical production needs as they advance their approach to helping solve the organ shortage."

William Westlin, PhD, Executive Vice President of Research and Development noted, "In addition to ICB's state-of-the-art production facilities, eGenesis will have the opportunity to work seamlessly across Research and Development and build synergies with ICB's team of highly experienced scientists and production specialists. This transaction is an important step as we accelerate our xenotransplant programs toward the clinic with the aim to address the serious shortage of transplantable organs for patients in need."

The demand for life-saving organs far outnumbers available supply. In the US today, 20 people die every day due to lack of available organs for transplant and every 10 minutes an additional name is added to the national transplant waitlist. There are more than 110,000 people in need of an organ transplant in the US alone.

The concept of xenotransplantation, or the transplantation of organs, tissue, and cells from one species to another, has been explored for several decades, with the pig considered the most suitable donor for humans. However, until the development of modern gene-editing tools, hurdles related to virology and immunology have prevented porcine organ xenotransplantation from advancing beyond early preclinical research.

eGenesis' goal is to advance the field of transplantation and make available safe and reliable xeno organs, tissues, and cells to patients in need. eGenesis uses gene-editing technology, such as CRISPR, to directly address the key virology and immunology hurdles that have impeded xenotransplantation to date. eGenesis is advancing an initial product toward the clinic for kidney transplant, with the longer-term potential of addressing a broader organ recipient population and expanding the applicability of xenotransplantation into other areas such as cell therapy. Learn more at egenesisbio.com.

Catalent Announces Acquisition of Japanese Facility to Provide Local & Global Clinical Supply Solutions

Catalent recently announced a deal to acquire a clinical packaging facility in Minakuchi, located in the Shiga prefecture of Japan, from Teva-Takeda Pharmaceuticals, Nagoya Aichi, Japan. This purchase will establish a new clinical GMP manufacturing and distribution hub to support clinical studies. Financial details of the deal, which is expected to close on July 1, 2020, have not been disclosed.

The 60,000-sq-ft facility will be the largest in the company's Asia Pacific clinical supply network. The new facility will offer customers access to Catalent's FastChain demand-led supply services, primary and secondary packaging capabilities, a range of temperature options for storage and distribution, as well as clinical returns and destruction services. It will operate in partnership with Catalent's existing Japanese clinical supply facility at Kakegawa, serving both local customers as well as global biotech and pharmaceutical companies.

"This new facility provides much-needed capacity as we look to expand our capabilities across the Asia-Pacific region, and follows on from recent expansions and investments we have made in our clinical supply business in China and Singapore," said Ricci Whitlow, President, Catalent Clinical Supply Services. "Our strategy has been to build expertise and capacity in this region as demand for local clinical supply services increases, to provide support to customers with global programs, and to meet the growing demand in biologics and cell and gene therapy studies."

With sites in the US, UK, Germany, Singapore, Japan, and China, and an extended network of over 50 depots, Catalent's clinical supply services can handle a broad range of international compliance and distribution requirements to support global clinical trials. For further information on Catalent's Clinical Supply Services business visit https://www.clinical.catalent.com.

Catalent is a global leader in clinical supply services, with comprehensive and flexible solutions for small molecules, biologics, and cell and gene therapies and integrated solutions to accelerate speed to clinic. Catalent offers a full range services including clinical supply management, comprehensive packaging solutions, comparator sourcing, cold chain storage and global distribution and specialized supply chain services including direct-to-patient and demand-led supply. With nine GMP clinical packaging facilities and over 50 strategically located depots on six continents combined with more than 25 years' experience across thousands of studies in more than 80 countries, Catalent has the comprehensive services, global scale and expertise necessary to reliably supply clinical trials of all sizes and complexity anywhere in the world.

Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, cell and gene therapies, and consumer health products. With over 85 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable global clinical and commercial product supply. Catalent employs over 13,500 people, including over 2,400 scientists and technicians, at more than 40 facilities, and in fiscal year 2019 generated over $2.5 billion in annual revenue.

Alethia Biotherapeutics Announces Receipt of FDA Authorization to Begin Phase 2 Development

Alethia Biotherapeutics recently announced the US FDA has cleared its Phase 2 Investigational new drug (IND) application for AB-16B5, a potent inhibitor of the epithelial to mesenchymal transition (EMT). This allows the company to initiate a multi-center trial of AB-16B5 in combination with docetaxel in previously treated subjects with metastatic non-small cell lung cancer (NSCLC) who have experienced disease progression following treatment with a platinum-containing doublet treatment and an anti-PD1 or PD-L1 immune checkpoint antibody.

"We are extremely pleased to have achieved this important milestone in the development of AB-16B5 and to continue to advance the clinical development of this promising antibody" said Yves Cornellier, President and CEO of Alethia. "EMT is a central enabler for solid tumor progression because it triggers metastatic invasion, resistance to several classes of anti-cancer drugs and contributes to immune evasion. There is also increasing evidence that EMT contributes to resistance to immune checkpoint inhibitors. AB-16B5 may play an important role in overcoming these problems", added Dr. Mario Filion, Chief Scientific Officer.

This multicenter, open-label, Phase 2 study of AB-16B5 in combination with docetaxel (NCT04364620) will enroll approximately 40 subjects with advanced NSCLC who have previously been treated with a platinum-containing doublet treatment and an anti-PD1 or PD-L1 immune checkpoint antibody, a patient population with very limited options. The primary objectives are to assess the anti-tumor efficacy of AB-16B5 in combination with docetaxel as measured by objective response rate and to determine the safety and tolerability of the combined drugs. Secondary objectives of the study include clinical benefit rate, percentage of subjects with complete response or partial response, duration of stable disease, progression-free survival and overall survival.

AB-16B5 is a humanized IgG2 monoclonal antibody that selectively binds and inhibits tumor-associated secreted clusterin, a protein expressed in many cancers. Tumor-associated secreted clusterin is induced early in the EMT cascade and its inhibition with AB-16B5 stops and reverts EMT in animal models. A Phase 1 study in subjects with advanced carcinomas demonstrated that AB-16B5 was safe and well tolerated and provided clinical benefit to several subjects. Stable disease was observed in several patients for up to one year. There was also evidence of EMT inhibition in tumor biopsies. Alethia is a privately held clinical stage biotechnology company located in Montreal. Alethia develops immunotherapeutics for the treatment of cancer.

Vaxart Announces Selection of its Oral COVID-19 Vaccine Lead Candidate

Vaxart, Inc. recently announced it has selected its lead COVID-19 vaccine candidate and has contracted with KindredBio to manufacture bulk vaccine under cGMP to complement the manufacturing capacity of partner Emergent BioSolutions.

"All our COVID-19 vaccine constructs were highly immunogenic in preclinical testing, and we are taking the candidate forward that is expected to generate the broadest immune response in humans," said Sean Tucker, PhD, Chief Scientific Officer of Vaxart. "In a Phase 2 efficacy study that was recently published in the Lancet Infectious Diseases, we have demonstrated that our oral H1 flu tablet vaccine protected against influenza infection after just one dose. Based on these results, we believe our vaccines are ideal to protect against mucosal respiratory viruses such as SARS-CoV-2, the virus that causes COVID-19."

In January 2020, Vaxart initiated a program to develop a COVID-19 vaccine based on its VAAST oral vaccines platform. The company evaluated multiple vaccine candidates in its preclinical models and has chosen the lead candidate for cGMP manufacturing and clinical testing based on the magnitude and the breadth of the immune response. Vaxart has contracted with Emergent BioSolutions (Emergent) and Kindred Biosciences, Inc. (KindredBio) to produce bulk vaccine under cGMP for upcoming clinical trials. The vaccine tablets will be manufactured at Vaxart.

"We are very pleased to have an experienced partner such as KindredBio to help us meet global demand for our COVID-19 vaccine," said Wouter Latour, MD, Chief Executive Officer of Vaxart. "The program with Emergent BioSolutions is progressing very well, and we expect KindredBio will add additional capacity to help produce bulk vaccine. An important benefit of our platform is that our vaccines are produced in tablet form and we don't need the sterile fill and finish that is required for the production of injectable vaccines. Manufacturing of our COVID-19 vaccine is on track to start a first phase 1 study in the second half of this year, possibly as early as the summer."

Vaxart is a clinical-stage biotechnology company primarily focused on developing oral recombinant protein vaccines based on its proprietary oral vaccine platform. Vaxart's vaccines are designed to generate broad and durable immune responses that protect against a wide range of infectious diseases and may also be useful for the treatment of chronic viral infections and cancer. Vaxart's vaccines are administered using a convenient room temperature-stable tablet, rather than by injection. Vaxart believes that tablet vaccines are easier to distribute and administer than injectable vaccines and have the potential to significantly increase vaccination rates. Vaxart's development programs include oral tablet vaccines that are designed to protect against coronavirus, norovirus, seasonal influenza, and respiratory syncytial virus ("RSV"), as well as a therapeutic vaccine for human papillomavirus ("HPV"). For more information, visit www.vaxart.com.

Almac Discovery Enters Into Licensing Agreement for the Development & Commercialization of ALM301

Almac Discovery, a member of the Almac Group, recently announced an out-licensing partnership with an undisclosed biotechnology company in order to advance the development and commercialization of one of its portfolio projects – ALM301.

ALM301 is a novel, patent-protected, potent, subtype selective Akt kinase inhibitor with good pharmacokinetic properties across multiple species, and an excellent selectivity profile. It has demonstrated robust efficacy in preclinical prostate, breast, and other cancer xenograft models, both as a single agent and in combination with standard chemotherapeutic agents, where synergy has been observed.

The molecule is currently in late-stage preclinical development, and the partner will complete this before progressing into the clinical development phase.

Dr. Stephen Barr, Managing Director & President, Almac Discovery, said "This new out-licensing agreement represents a further example of the business model we have pursued at Almac Discovery in action – namely the discovery of new, innovative drug candidates for development through external partnerships and collaborations."

This announcement comes just 2 weeks after Almac Discovery disclosed a new strategic collaboration with MSD on selected Deubiquitinase (DUB) enzyme therapeutic targets for neurodegenerative disease. In addition, in March, the company also announced the clinical advancement by its partner Debiopharm (Switzerland), of Debio 0123, an oral, potent and highly selective WEE-1 inhibitor, in combination with carboplatin in patients with advanced solid tumors. The molecule was initially discovered and developed by Almac Discovery, before being out-licensed to Debiopharm in 2017.

Almac Discovery has grown from strength to strength with four significant agreements signed in the past 5 years. It continues to build its internal pipeline through partnerships and collaborations to drive forward a dedicated effort towards the development of novel therapeutics for the treatment of disease, and to make a real and lasting contribution towards the advancement of human health.

Almac Discovery is an innovative research driven biotech company dedicated to the discovery and development of First-in-Class therapeutics across a range of therapeutic areas including neuroscience, muscle-wasting, oncology, and inflammation. Almac Discovery focuses on the discovery to preclinical stage, seeking to licence programs early with a pharmaceutical partner for further development. For more information, please visit www.almacgroup.com/discovery or e-mail alan.lamont@almacgroup.com.

The Almac Group is an established contract development and manufacturing organisation providing an extensive range of integrated services across the drug development lifecycle to the pharmaceutical and biotech sectors globally. Its innovative serv-

SeraNovo Enters Second License Agreement With Carna Biosciences

SeraNovo B.V. recently announced it has signed a second License Agreement with Carna Biosciences, Inc., a company engaged in the drug development of kinase inhibitors. Under the agreement, the companies will expand their existing collaboration and jointly develop an oral formulation of a new active ingredient with an enhanced bioavailability. Utilizing its proprietary Deep Eutectic Solvent (DES) formulation platform, SeraNovo is formulating one of Carna's proprietary drugs to increase its oral bioavailability. The DES formulation platform is based on GRAS excipients that are used for oral administration and broadly used in the industry.

Niall Hodgins, Chief Executive Officer of SeraNovo, said "After our initial licence announcement in October 2019, we are pleased to extend our relationship with Carna to include the formulation of another promising active ingredient. This expansion of our partnership with an industry leader is a great development towards wide spread adoption of our breakthrough formulation technology."

SeraNovo is an innovative formulation company improving the oral bioavailability of active ingredients. The focus of the company is on solving the problem of poor drug solubility by designing DES formulations to increase the oral bioavailability when administered as a capsule or tablet. For each of these poorly soluble or high melting point APIs, a DES-based formulation is designed that is proven to increase the oral bioavailability substantially more than competing techniques. SeraNovo is a privately owned company located in Leiden, the Netherlands, and as technology inventor owns all know-how and IP. For more information, visit www.seranovo.com.

Carna Biosciences is a biopharmaceutical company focused on the discovery and development of kinase inhibitor drugs to treat serious unmet medical needs in oncology, autoimmune, and neurological diseases by inhibiting kinases that are important drivers for those diseases. Carna Biosciences was founded in Kobe, Japan, in 2003 as a spin-off of Japan Organon (Nippon Organon KK). Carna's initial focus was to develop an extensive number of state-of-the-art, highest quality reagents for kinase drug discovery, and has since established a leading drug discovery program with a significant collection of proprietary chemical libraries. For more information, visit www.carnabio.com.

2019 Global Drug Delivery & Formulation REPORT

Part Four of a Four-Part Series

Part 1: A Review of 2019 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2019

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2019

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, Vice President Operations, and Selda Candan, Vice President Data Analytics, PharmaCircle LLC

Introduction

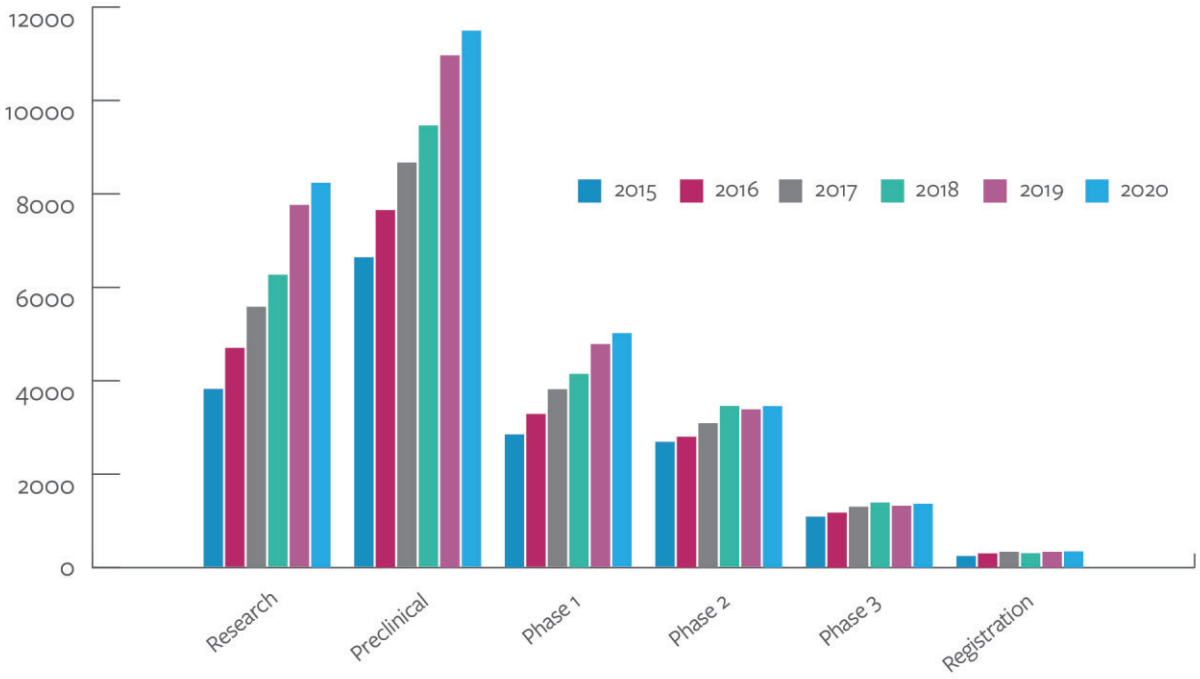
The pharmaceutical industry has certainly seen a major product shift in focus throughout the past decade from large population medical conditions to smaller, orphan type indications. This is exemplified by the US Food and Drug Administration's (FDA) approval of 21 new molecular entity (NME) products in 2019 that had received Orphan Drug designation, representing almost half, 44%, of all NME approvals in 2019. At this point, the FDA has granted 4,352 orphan designations, with 296 alone granted in 2019. There is however much more in the pipeline than orphan products. In fact, the pipeline of products has increased by 65% during the past 5 years, totaling almost 29,000 products and 60,000 programs by early 2020, stretching from Research to Preclinical to Phases 1, 2, and 3 to Registration. This review analyzes the pipeline with an emphasis on clinical-stage products for which there is more product-related information.

The fourth part of this review reinforces the common opinion that cancer therapeutics, often targeted to smaller populations, are receiving increasingly greater investment as expressed in larger numbers of product candidates. It also confirms that more products are being developed using novel molecular scaffolds, typically macromolecules modeled on biological constructs. This new generation of products are not obvious candidates for the majority of the technologies developed and validated for small molecule therapeutics, a suspicion reinforced by an examination of the pipeline in terms of drug delivery and formulation incorporation.

This year's Drug Delivery and Formulation Pipeline analysis uses PharmaCircle's new Pipeline Dynamics companion module to the Pipeline & Products Intelligence module and covers 6 years of pharmaceutical pipeline history. By capturing detailed records annually of what products were at what stage of development from 2015 through to 2020, it is now possible to better understand the dynamic history of product development. The following pages provide a pipeline snapshot according to a number of parameters that are of most interest to drug delivery professionals – Disease Area, Molecule Type, Delivery Route, Product Types, and Drug Delivery Technology Incorporation.

Clinical-Stage Product Growth Has Lagged Behind Preclinical & Research

Pharma Pipeline Product Development, 2015-2020 (Most Advanced Phase)



Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020.

The booming investment in biopharma is reflected in the steady increase of research and preclinical products in the 5-year period between 2015 and 2020, which has not yet been fully reflected by a similar increase in clinical-stage products. As the number of Phase 1 projects has increased substantially in the 2015 to 2020 period, the growth in the number of Phase 2 and Phase 3 projects has not kept pace. While this may in part be accounted for by changes in clinical trial disclosure requirements that have increasingly led to the disclosure of earlier stage clinical-stage products, it could simply be an issue of companies being more selective in promoting only the very best product candidates to later- stage trials. There may also be a lag effect, reflecting the time required from a first investment in research and preclinical products to produce later-stage clinical candidates. The larger number of Phase 1 products seen in 2020 may well work its way through the system, resulting in a bump of Phase 2 and Phase 3 products in 2022 and beyond.

- The relative distribution of Research/Preclinical/Phase 1/Phase 2/Phase 3 products in 2020 is 6/8/4/2.5/1. This compares with a 3.5/6/2.5/2.5/1 ratio in 2015.
- Research-stage products increased by 116% over the 2015-2020 period.
- Preclinical-stage products increased by 73% over the 2015-2020 period.
- Phase 1-stage products increased by 75% over the 2015-2020 period.
- Phase 2-stage products increased by 29% over the 2015-2020 period.
- Preclinical-stage products increased by 25% over the 2015-2020 period.

The Movement to Biologic Therapeutics is Most Obvious in the Earliest Clinical-Stage Products

Molecule Type as a Share of All Clinical-Stage Products, 2020

	Phase 1	Phase 2	Phase 3	Registration	All Clinical Stages	% of Total (2015)	% of Total (2020)
Small Molecule	55%	61%	67%	76%	60%	62%	60%
Antibody	12%	10%	10%	7%	11%	9%	11%
Protein	6%	8%	6%	6%	7%	10%	7%
Peptide	5%	6%	6%	5%	6%	7%	6%
Cell & Gene	15%	8%	4%	3%	10%	8%	10%
Oligonucleotide & RNA	2%	2%	1%	1%	2%	2%	2%
Stem Cell	3%	2%	2%	0%	2%	0%	2%
Carbohydrate	1%	1%	2%	1%	1%	1%	1%
All Other	2%	2%	2%	2%	2%	0%	2%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020.

The generally held belief that Biopharma is increasingly investing in more complex biological molecules is reflected in the clinical-stage product pipeline. The Small Molecule product share of all clinical-stage products has dropped from 62% in 2015 to 60% in 2020. This trend is more obvious when one looks at the relative share of Small Molecule products from Phase 1 to Phase 2 to Phase 3 to Registration-stage products, where the Small Molecule share drops from 76% at the Registration stage to only 55% in Phase 1. These proportions are likely to even out a bit more throughout the next few years as the current Phase 1 cohort advances to Phase 2 and Phase 3 trials.

- Protein products seem to be the only molecule type not sharing the general growth in Biologics. The number of clinical-stage Protein products has actually dropped by 4% in the 2015 to 2020 period.
- Cell and Gene Therapy products have seen the largest gain in the 2015 to 2020 period, up 68%, with the largest bump seen at the Phase 1 stage.
- Clinical-stage Antibody products have seen a 58% increase in the 2015 to 2020 period with 909 identified clinical-stage products, 116 of them in Phase 3.
- Stem Cell products present the most surprising increase in clinical-stage products. From no identified clinical-stage products in 2015, the number has grown to 195 products in 2020, with 19 in Phase 3 development.

Cancer & Eye Diseases Have Shown the Greatest Growth Throughout the Past 5 Years

Active Clinical-Stage Programs by Disease Area, 2015-2020

	2015	2020	Change 2015-2020
Cancer	1,642	2,911	77%
Infections	886	1,215	37%
CNS	686	985	44%
Endocrine / Metabolism	519	631	22%
Inflammation / Immune	461	612	33%
Skin Disorders	295	452	53%
Cardiovascular Diseases	306	383	25%
Pain Management	263	324	23%
Respiratory	257	288	12%
Eye Diseases	164	314	91%
All Other	1,103	1,701	54%
Total	6,582	9,816	49%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020. (Note: the figures here represent Programs rather than Products. It is possible for one Product to be in more than one Program in more than one Disease Area.)

Clinical-stage programs have grown almost 50% in the 2015 to 2020 period. The Disease Areas showing above average growth include Cancer (+77%), Eye Diseases (+91%), and Skin Disorders (+53%). The increase in clinical-stage Cancer programs is not really surprising given the significant need, the large number of new disease mechanisms discovered throughout the past decade, and the many new molecular constructs available. More surprising is the large increase in the number of Eye Disease programs at the clinical stage. The overall number of clinical-stage Eye Disease programs is now on par with Cardiovascular, Respiratory, and Pain Management programs. While there continues to be a consensus that Infectious Disease deserves more investment, the growth of the pipeline has dropped relative to the average with increasing contributions from vaccines and reformulations of previously approved actives.

- The Phase 1/Phase 2/Phase 3 distribution of Cancer programs is 1,800/861/255. In 2015, the distribution was 864/571/187 programs, respectively.
- Respiratory represents the greatest laggard in the Top 10 group, up 12%, with 35 Phase 3 programs and a combined 255 programs in Phase 1 and Phase 2.
- Among All Other, only Gastrointestinal (+77%) showed above average growth between 2015 and 2020. The greatest laggards were Genitourinary (+4%) and Male Health (+14%).

Less-Invasive Delivery Routes are Dropping in Favor of Injection

Delivery Route Products as a Share of All Clinical-Stage Products, 2020

	2015	2020	Change 2015-2020
Injection	46%	49%	6%
Oral	40%	39%	-2%
Topical	5%	5%	-7%
Ophthalmic	2%	2%	-7%
Inhalation	3%	2%	-19%
Nasal	2%	2%	-11%
Transdermal	2%	1%	-40%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data as of April 2020. (Note: in the case of early stage clinical programs, notably Phase 1, products often do not provide information regarding Delivery Route. These products are not included in the analysis. While the absolute numbers of products at each stage are as a result somewhat limited, the relative proportions of Delivery Routes for each development stage should be valid, as should the Phase 3 numbers.)

The development of products as a function of Delivery Route for the most part parallels development by Disease Area. Injection, the only Route to show an increase in share, largely owes its increased share to the growing number of treatments for Cancer, an indication often restricted to parenteral routes of delivery. In the opposite sense, the drop in Inhalation as a Delivery Route is consistent with the very limited expansion of Respiratory programs throughout the 2015 to 2020 period. The biggest drop in terms of Delivery Route was with Transdermal delivery. This probably reflects both a relative lack of novel molecules appropriate for transdermal delivery and the commoditization of the many transdermal technology platforms..

- A total of 552 Injection Route products were identified as being in Phase 3 development as of 2020.
- Oral Route still maintains a high prevalence/importance. Increase in Injections is due to both molecules developed (eg, biologics) and disease (eg, Cancer).
- Inhalation, Nasal, and Transdermal had only 27, 20, and 13 products identified as in Phase 3 development.
- Topical Route will always be needed for dermatology-related conditions in which non-invasive delivery is therapeutically feasible.
- Ophthalmic is increasingly focused on improved convenience with better application devices and reduced dosing frequency.

The Clinical Development Pipeline is Less Dependent on New Formulations & Combinations & Drug Delivery in General

Active Clinical-Stage Products by Product Type, 2015-2020

	2015	2020	Change 2015-2020
New Formulation	1,365	1,881	38%
New Combination	245	315	29%
Biobetter	23	16	-30%
All Other	5,233	7,976	52%
All	6,866	10,188	48%

Active Clinical-Stage Products Incorporating Drug Delivery Technology, 2015-2020

	2015	2020	Change 2015-2020
DD Technology	36%	33%	-9%
No DD Technology	64%	67%	5%

Source: PharmaCircle Pipeline & Products Intelligence Module (Pipeline Dynamics). Pipeline data for 2020 is as of April 2020.

Following a heavy emphasis on developing improved formulations of previously approved actives in the 80s, 90s, and 00s, almost all small molecules, the past decade has seen more investment in the development of new molecular entities and products that are not simple formulation enhancements. While the overall 2015 to 2020 growth of clinical-stage products was 48%, New Formulations lagged at a 38% growth. The development of Biobetters, improved versions of previously approved biologics, at no point particularly active, has dropped even further with greater industry interest and emphasis on novel innovative therapeutics. The number of New Combinations has increased in the 2015 to 2020 period although the growth has lagged overall pipeline growth. All Other, the largest group, includes products that do not fall into the New Formulation, New Combination, or Biobetter groups. This group does not include Generics or Biosimilars.

Pipeline products can incorporate drug delivery and formulation technologies as a means to either enable and/or enhance the performance of a pharmaceutical active. The term DD Technology refers to products that incorporate some sort of definable drug delivery or formulation technology. This can mean technologies to enhance the bioavailability of an active, extend the duration of action of a product, or improve stability. Drug Delivery in this context does not include simple oral or injectable components and excipients that do not intentionally impact the pharmacodynamics of a product. The trend seen between 2015 and 2020 with respect to DD Technology is a general drop in its application, from 36% to 33%. The reason may be the general change in pipeline emphasis to biologics, many of which are first-generation products employing basic formulation methods and excipients. It may also reflect the increasing sophistication of small molecule discovery programs leading to product candidates that are optimized structurally with respect to bioavailability and pharmacodynamic properties. You don't need to "add on" if it's already "baked in." This overall trend away from drug delivery and formulation technologies is likely to reverse itself in the next decade as new biologicals are introduced and competitive pressures require companies to differentiate their products using more than simple molecular manipulation.

Final Thoughts

PharmaCircle's Pipeline Dynamics, with 6 years of information, provides a concise summary of what most people already suspected about the evolution of the pharmaceutical pipeline, a greater industry emphasis on Cancer-related products. Obvious, but perhaps a little further back in terms of development, is the increasing number of non-small molecule therapeutics in the clinical-stage pipeline. For those folks who have been looking at how drug delivery and formulation technologies are being applied to new products, the data largely confirms the suspicion that there is more emphasis on molecules not requiring further drug delivery and formulation optimization, and products for which appropriate technologies are not yet available. This latter point suggests an opportunity for future drug delivery technology development. With time, market pressures will encourage companies to look beyond "good enough" to gain a competitive advantage. For many of these new macromolecules, the answer to date has been increasingly sophisticated patient-friendly devices. This is unlikely to suffice when patients can get the same therapeutic benefits with simple once-a-day oral dosing. Novo Nordisk's Rybelsus suggests how this might be accomplished and its success, or lack thereof, will have major ramifications for the development of next-generation technologies.

A common theme of this year's series of reviews has been the relative stasis in drug delivery and formulation deals, technology development, investments, and efforts. This stasis seems to be less an issue of creativity but more of the general lack of technology-focused investments. The consensus "smart money" is currently chasing novel molecules, novel mechanisms, and orphan indications. These are opportunities that will in the near term be increasingly exhausted. What should follow is the optimization of these products through the development of similar, but incrementally enhanced, new molecular entities, or the optimization of the existing and new therapeutics with novel drug delivery and formulation technologies.

Among the hopeful signs in 2019 was the investment in RNA inhibitors. The secret sauce for these new therapeutics largely lies in their efficient and effective delivery. They need to be targeted to the appropriate cellular components with the necessary "permission slips" to gain entrance and avoid the body's defense systems. But don't call this optimization of delivery and targeting Drug Delivery. Drug Delivery is now old, passé, and not worthy of investment. This new stuff, it's much the same in terms of intent if not the technologies, is exciting and worthy of investment.

Appreciate 2019 as a necessary step forward in terms of approvals, pipeline growth, technology development, and improved patient outcomes. Products and pipelines are running ahead of the necessary technologies to support their optimization. The solution for this is more investment. That will come, but it will require business models that are more than the traditional license fee, milestones, and royalties. What is working for this new generation of experimental and risky therapeutics is the promise of acquisition at crazy premiums. It's more immediate than eventual milestones and royalties and keeps the "smart money" happy and ready to invest.

About the Authors

Kurt Sedo, Vice President of Operations, PharmaCircle LLC

Kurt Sedo earned his BS in Chemistry and Mathematics from the University of Wisconsin Stevens Point. Prior to joining PharmaCircle in 2003, he held various R&D Scientist positions within Searle/Pharmacia's Pharmaceutical Sciences Department in Analytical Development and Drug Delivery. Mr. Sedo's responsibilities with PharmaCircle include oversight of data integrity, product development, project management, and customer service. In addition to authoring articles, Mr. Sedo regularly presents overviews of the state of drug delivery and formulation at industry conferences.

Selda Candan, Vice President Data Analytics, PharmaCircle LLC

Selda Candan is responsible for data management and customer service. She earned her BS and MS in Chemistry at Middle East Technical University (METU) in 2007 and 2008, respectively. Prior to joining PharmaCircle, she worked as a research assistant at METU.

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Contact us today:

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

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

drug-dev.com

Formulation Forum

Rational Design of Oral Nanosuspensions for Insoluble Drugs

By: Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceuticals

Jim Huang, PhD
j.huang@ascendiapharma.com

A pharmaceutical nanosuspension is a fine dispersion of nanosized, insoluble API solid particles in a liquid medium. The particle diameter in a nanosuspension is usually less than 0.5 μm. Nanosuspensions are an important class of pharmaceutical dosage forms, particularly for pharmaceutical compounds with solubility and bioavailability challenges. Nanosizing is a widely used formulation method for sparingly soluble compounds as nanosuspensions offer an attractive option to enhance the rate of dissolution and solubility of poorly soluble drugs replaced by those compounds. The saturation solubility of the nanocrystals is highly related to the particle size, and solubility increases with particle size decrease due to the increased surface area, especially when the nanocrystals are below 300 nm. Consequently, the concentration gradient between gut lumen and blood is increased, resulting in improved absorption by passive diffusion. In these nanosuspension formulations, the rate-limiting step for drug absorption is normally the insoluble drug particle dissolution in the fluid surrounding the drug formulation.

The advantages of nanosuspension dosage forms include improving bioavailability, eliminating food effect, increasing drug loading, eliminating cosolvents, masking of bad API taste, improving API stability, dose reduction, better dose flexibility and accuracy, and easy swallowing for pediatric or geriatric populations. Examples for oral nano-dosage form are showed in Table 1.

FORMULATION DEVELOPMENT OF NANOSUSPENSIONS

Successful nanosuspension formulation development depends on careful evaluation of compound physical chemical and biopharmaceutical properties, such as solubility, pKa, solid surface properties, permeability, meting point, and crystal lattice structure. A good candidate for nanosuspension has the characteristics of BCS Class II compounds: low solubility, high melting point, high permeability, and a strong tendency of food effects. A formulation screening study is normally conducted under a small scale to find the suitable stabilizer(s), ie, a polymer, a surfactant, or a combination of polymer/surfactant for the nanosuspension. Different surface properties of API, such as surface charge, hydrophobicity, functional groups responsible for ionic, hydrogen bond, and Van der Waal interactions, may demand different types and level of stabilizers. The performance of nanosuspensions should be confirmed by in vitro studies, such as stability, re-dispersibility, and in vivo performance in animal models. Figure 1 is a high-level flow chart for nanosuspension prototype formulation development.

PROCESS FOR NANOSUSPENSIONS

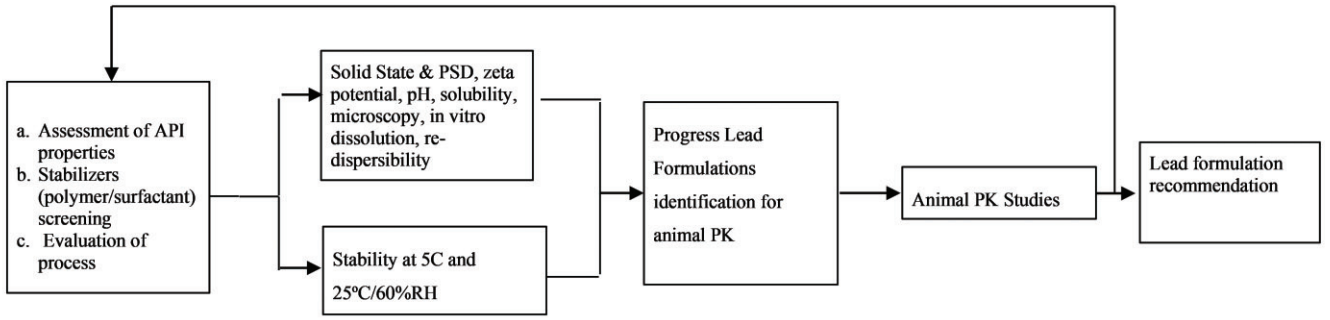
Two commonly used methods for nanosuspensions include: "Bottom-up technology" and "Top-down technology." Bottom-up technology is an assembling method to form nanoparticles by dissolving the

TABLE 1

Product Name	Manufacturer	Excipients	Manufacturing Process
Aprepitant (Emend®)	Merck	HPC polymer	Top down process
Fenofibrate (Tricor®)	Abbvie	Lecithin/PVA/PVP	Top down process
Fenofibrate (Triglide®)	Aevona France SA	Egg Lecithin/Na CMC	Combined process
Megestrol Acetate (Megace® ES)	Par Pharma	HPMC/Docusate sodium	Top down process

Example of Oral Nanoformulations

FIGURE 1



Oral Nanosuspension Development Flow

API in a carrier, and then undergoing a process like precipitation or emulsification; whereas, Top-down technology involves the disintegration of larger particles into nanoparticles, examples of which are high-pressure homogenization, micro-fluidization, sonication, and wet milling methods, etc.

Wet Milling Technology

Wet milling (top-down process) is a relatively effective milling technique for nanocrystal preparation. The process is done in a media milling, and it treats a dispersion of concentrated drug in an aqueous or non-aqueous liquid medium with milling balls. It has several advantages in its economic value and ease in scaling up. With the right media milling equipment, manufacturers can cost-effectively create uniformly fine particles with limited or no contamination. However, due to the intensive mixing forces in the vessel, erosion of the milling balls is a common occurrence.

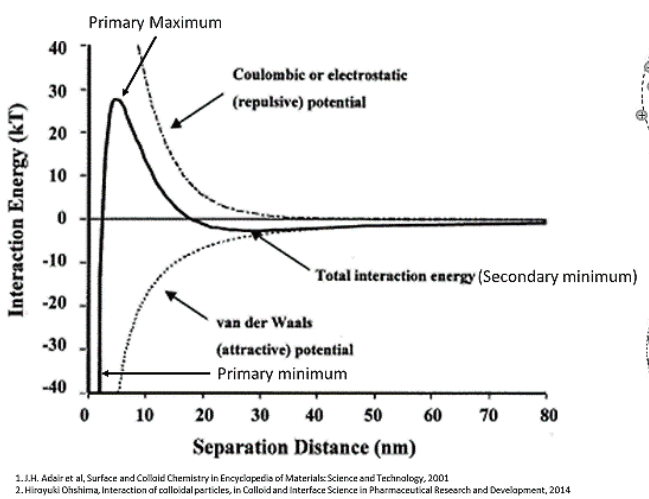
High-Pressure Homogenization Technology

High-pressure homogenization or microfluidization can also achieve suspension with narrow particle size distribution. It is a purely mechanical process, which is evoked by forcing a fluidic product through a narrow gap (the homogenizing nozzle) at high pressure. The liquid product is subjected to very high shear stress causing the formation of very fine particles. It can effectively process large volumes of liquid suspension sample thoroughly and reproducibly. Because it doesn't use milling balls, contamination of the final product is much less; however, the high pressures applied cause a temperature increase because of the heat of compression, this needs to be controlled in case of heat-sensitive drug products. Alternatively, a combination of the bottom-up and top-down process, ie, solvent dissolution of API, crystallization by non-solvent, and then homogenization of freshly formed particles, could be utilized.

STABILITY OF NANOSUSPENSIONS

Nanosuspensions also possess some disadvantages relative to other dosage forms. The primary disadvantage is their physical instability, which can be overcome by thorough formulation design and development. According to the DLVO theory (Figure 2), the thermodynamic equilibrium state may be reached when the particles are in deep primary minimum, wherein attractive forces overpower the repulsive forces at short molecular distances less than 10 nm and the coagulation process is irreversible, leading to a breakdown of the suspension. However, if

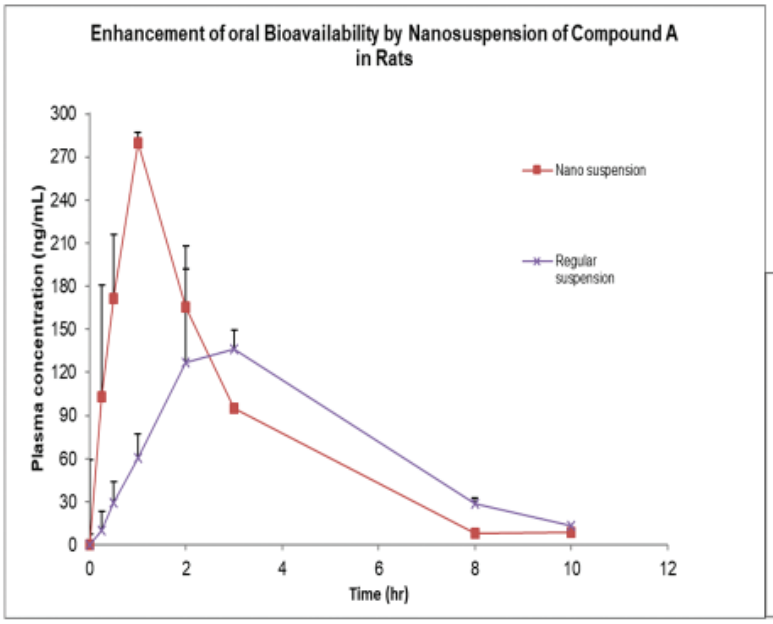
FIGURE 2



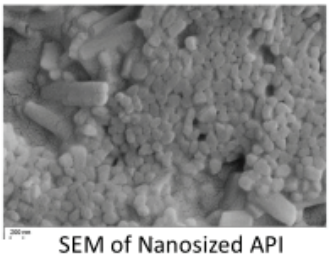
1. J.H. Adair et al, Surface and Colloid Chemistry in Encyclopedia of Materials: Science and Technology, 2001
2. Hiroyuki Ohshima, Interaction of colloidal particles, In Colloid and Interface Science in Pharmaceutical Research and Development, 2014

DLVO theory of Particle Dispersion

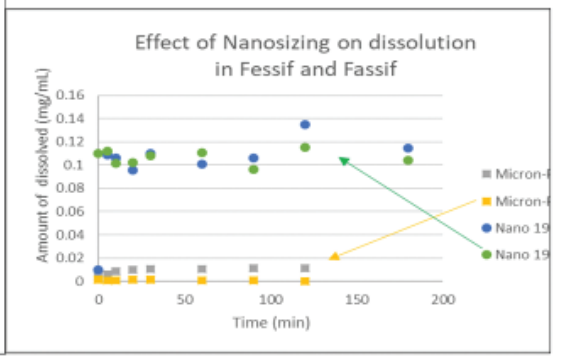
FIGURE 3



~2 folds higher bioavailability and faster onset for nanosuspension



SEM of Nanosized API



~10 folds higher solubility for nanosuspension, showing similar solubility in Fassif and Fessif

Enhancement of API Solubility & Bioavailability Via Nanosuspension With a Potential in Food Effect Reduction

we design the nanosuspension formulation well so that when the primary maximum energy barrier is too high to overcome, the nanosupension particles may stay in the secondary minimum, wherein particles are held together by a weaker force than the primary minimum, and those loose aggregates can be re-dispersed. Utilization of particle charge, coating of the nanoparticles with polymer and surfactants, and selection of pH and buffer make it possible that the thickness of the electric and coated double layers of the nanoparticles could be expanded so that the total interaction energy between nanoparticles is located in the secondary minimum, and a stable nanosuspension is formed.

A CASE STUDY

A compound was classified as BCS II (low solubility and high permeability), which had a log P of ~4 and a meting point of ~130°C. Its aqueous solubility was extremely low, <0.2 µm/mL. The compound crystalline micronized suspension (mean particles size between 1-10 microns) had very low bioavailability in humans with a strong food effect. It was desirable to obtain a human formulation that had enhanced bioavailability and had no food effect. Based on the assessment of the compound properties, Ascendia's Nanosol® Technology was utilized for nanosuspension formulation screening and in vitro assessment. Three nanosuspension prototype formulations were developed and tested for stability and animal PK studies. The lead prototype nanosuspension with a particle size below 200 nm resulted in a ~2-fold increase in bioavailability (Figure 3); and the nanosuspensions showed similar solubility in Fassif and Fessif and were stable for at least 3 months when stored at room temperature.

SUMMARY

Nanocrystal suspensions are a versatile and important class of pharmaceutical dosage form, particularly for pharmaceutical compounds with solubility and bioavailability challenges at the preclinical and early clinical development phase. The advantages of nanosuspension dosage forms include improving bioavailability, eliminating food effect, increasing drug loading, eliminating co-solvents, masking bad API taste, improving API stability, dose reduction, better dose flexibility and accuracy, and easy swallowing for pediatric or geriatric populations. It is critical to understand the colloidal properties of the API nanoparticles in order to formulate, process, and stabilize the nanosuspensions. In addition, the taste-masking, preservatives, sweeteners, and viscosity of nanosuspensions should also be considered for commercial product development. ◆

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PFS MANUFACTURING

Prefilled Syringes & Biologics: The Perfect Partnership of Medicine & Delivery

By: Anish Parikh

INTRODUCTION

It is no coincidence that the booms in prefilled syringes (PFS) and biologic medicines are happening at the same time – the two are intrinsically linked. Innovative biologic medicines demand innovative delivery systems to match, and as the utility of "living" medicines explodes, so has the challenges associated with their packaging and administration. When seeking to overcome those challenges and bring these complex products to a competitive marketplace as soon as possible, collaboration is king. Successful, timely development rests on the ability of drug innovators and PFS contract development manufacturing organizations (CDMOs) to pool their expertise and work side by side for the good of the patients they seek to serve. The modern CDMO has a key part to play, offering multidisciplinary experts and integrated services, creating the agile environments needed for efficient delivery of those partners' project objectives.

The following charts the twin rise of biologics and PFS and outlines some of the common challenges associated with filling and dispensing.

It also discusses how a patient-centric partnership approach, based on a culture of collaboration and communication, can help biopharmaceutical companies shorten the development pathway and ensure a reliable supply of safe, effective medicines for the people who need them.

BIOLOGICS: THE MEDICINES OF THE FUTURE

Recent years have seen some of the biggest leaps in medical science in history. Researchers, driven by rapidly evolving technology and an ever-greater understanding of the underlying mechanisms of disease, have developed a growing number of products that have proved to be nothing short of life-changing.

Much of this progress can be attributed to the rise of biologics, or drug products derived from the components of living organisms. Molecular biologists have been able to isolate and purify naturally occurring proteins, such as hormones and antibodies, and then administer them to those whose bodies lack them.

The first genetically engineered form of insulin, which replicated the form of the protein found in the human body, was approved in 1982.[1] By the mid-1990s, scientists had improved upon this early insulin by altering the protein's amino acid sequence and changing its properties.[1]

Around this same time, the first antibodies were approved for use in humans, opening the door to the possibility of new drug products that could block the function of specific proteins. Since then, progress has been swift and, today, antibody-based drug products are common in the treatment of several long-term conditions.

The previously untreatable progressive neurological condition multiple sclerosis (MS) is one such example. While scientists have yet to find a cure for the condition, disease-modifying drugs, many of which are biologics, are routinely used to slow the progression

of the disease and reduce relapse rates, allowing patients to remain active longer than originally anticipated.[2]

We are now set for the next giant leap, as the tremendous promise of next-generation gene and cell therapies begin to bear fruit. Clinical trials have suggested that cell therapies could play a revolutionary role in cancer treatments, and that gene editing could even reverse blindness caused by specific genetic mutations.

In 2018, the FDA had 500 active investigational new drug applications involving gene therapy products, and $2.3 billion in funding has been pumped into private gene therapy companies throughout the past 10 years.[3]

As many "first-wave" biological products reach the end of their patent period, biosimilars are becoming increasingly common – approximately 50 have been launched since 2010, and many more are in the pipeline.[4] Their development highlights their complexity.

Biosimilars, or follow-on biologics, are not generics. Every batch of a biologic medicine, whether it is a vaccine, blood component, allergenic, somatic cell, gene therapy, or recombinant therapeutic protein, is biologically different to the one that came before. Simply recreating it, as would be seen in traditional, large molecule drug production, is not an option.

In the US and European Union, manufacturers must demonstrate that there are no clinically meaningful differences in terms of quality, safety, and effectiveness between their product and the reference product.[5] This involves a robust testing process.

The success of biological products overall is demonstrated in the data. Since the first genetically engineered insulin was marketed in 1982, almost 300 biologic drugs have been developed, patented and approved.[4] In 2018, the biopharmaceutical industry was worth $210 billion, and an estimated 60 to 70% of drugs currently in development are biological products.[4,6]

All this makes for a fiercely competitive marketplace, but the drugs themselves are not the sole marker of success. Far from being an afterthought, delivery systems are an integral component of the biological drug development pathway.

FIGURE 1

Syringe nesting undergoing filling and stoppering on AMRI's prefilled syringe line.

PFS: THE DELIVERY SYSTEM OF THE FUTURE

While it is fair to say that biologics have driven, and continue to drive personalized care, administering these medicines presents a challenge. They are complex products that require complex delivery systems.

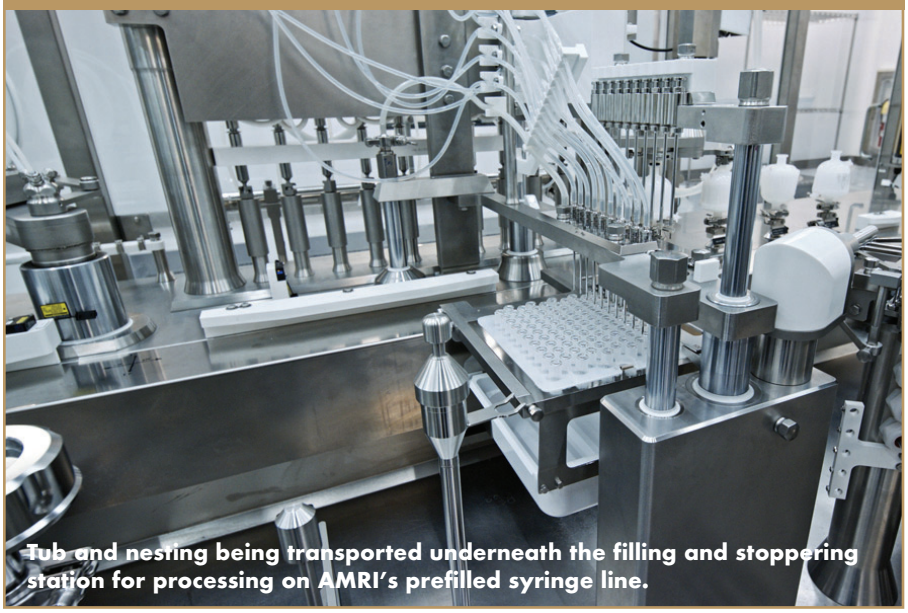
Tablets, capsules, and pills, the mainstay of traditional, small molecule medicine, are not suitable for biological medications due to high levels of degradation in the gut. This class of medicine must be delivered parenterally, usually intravenously, subcutaneously, or intramuscularly.

When compared with needle and vial systems, PFS has emerged as the preferred delivery method for biologics for a variety of reasons. Delivery via PFS is better suited to emergency situations and remote areas and is ideal for the self-administration required for the delivery of many monoclonal antibodies used in, for example, long-term conditions.

They also can reduce dosing errors by facilitating the provision of exact doses. In addition to the obvious compliance and safety benefits, this also plays into cost considerations. Multi- and single-dose vials typically have a drug overfill of between 20% and 25% to account for human error — a significant cost implication when manufacturing large quantities of expensive proteins and peptides.[7]

What's more, the high viscosity of biological products, and therefore the pressure needed to inject them, makes the use of traditional vial-based syringes extremely challenging. This is particularly pertinent when the medication is being used at home by someone with a condition that

FIGURE 2



Tub and nesting being transported underneath the filling and stoppering station for processing on AMRI's prefilled syringe line.

can affect dexterity, such as MS.

As the number and range of biological treatments have grown, so has the utilization of PFS as an effective delivery system. As of 2017, nine of the top 10 PFS-delivered drug products were biologics, a trend that is expected to increase as next generation gene and cell therapies come online.[8]

CHALLENGES: PREFILLED, NOT EASILY FILLED

The synergy in the rise of biological medicines and PFS is clear, but the relationship between product and delivery system isn't without its challenges.

Simply put, prefilled does not mean easily filled. Each complex protein or peptide medication is unique in its formulation, use, and safety profile, necessitating bespoke manufacturing, sterilization, filling, and compliance procedures. To build such processes, PFS manufacturers need to consider all factors, including efficacy, active pharmaceutical ingredients (APIs), the product's characteristics and safety profile, and the preferences of the end-user.

Ironically, one of the most widely discussed challenges in formulating and filling PFS with biologics centers around one of the primary reasons they are so compatible – product viscosity. The high-dose requirements of many monoclonal antibodies (MAbs), for instance, mean they must be formulated at high concentrations, increasing their viscosity.

A major challenge with filling such a highly viscous product is being able to cleanly dispense the product into the syringes. The solution will often stick to the tip of the filling needle, creating a trail of product along the syringe as the needle withdraws after dispensing.

A common method to overcome this problem is reducing viscosity through heat. However, this is not valid for many biologics, including MAbs of which solution stability is temperature dependent.

Other approaches have looked at fill needle movement. Some use a short, quick downward motion before needle retraction to break surface tension. However, this approach is problematic when filling products over 1,000 centipoise into polymer syringes.

AMRI's own solution involves using a high-speed camera to film the needle motion, then aligning the retracting motion of the needles to the velocity of the pump motion dispensing of product. This process, which implements a short pause above the final liquid level, ensures the remaining product disconnects from the needle tip. It's an effective method, but it must be adapted to suit each medicine we work with.

Another PFS consideration is the choice between glass or plastic syringes, which are typically made from either cyclo olefin polymer (COP) and cyclo olefin copolymer (COC).

Plastic has become increasingly common in recent years – not least in biologics of which viscosity means products need to be stored in packaging that allows for a consistent gliding force during administration. However, it is not always the right solution for the product.

Several factors need to be considered, and drug and PFS manufacturers will often work together to holistically assess the three Ps: Product, Process, and Patient. The importance of design flexibility, tighter tolerance, and break resistance, whether the PFS will be integrated with a safety device or autoinjector, and patient comfort will all be considered.

Where polymer is the preferred route, filling can be difficult. Improperly programmed machine movements or even minor equipment defects can cause scratches and increase the unit rejection rate. Much of the industry attempts to overcome this with vacuum stoppering, though it is important to note that this solution doesn't work with all products or container closure systems.

Instead, AMRI has developed expertise to assess each case across a variety of syringe sizes and implement custom solu-

tions. AMRI has also developed custom tools that verify all critical components are mechanically aligned before each filling campaign, which minimizes scratching.

Extractables and leachables (E&Ls), which can interfere with the drug molecules and compromise the product's effectiveness, present another challenge to the pairing of biological medications and PFS.

Whereas products in vials only come into contact with glass and rubber, those provided in PFS are exposed to most of the delivery system's materials and components, multiplying the likelihood of interactions.

Hence, the PFS market is heavily regulated, with the FDA and EMA, representing the world's two biggest markets for biologics, setting strict guidelines on the filling and dispensing of PFS to enforce risk reduction.

It is another example of how there is no off-the-shelf solution to PFS. The selection of materials and components involves a detailed assessment of biocompatibility, formulations and risk profiles, as well as an encyclopaedic knowledge of the relevant compliance processes.

AMRI's in-house analytical team's expertise in extractables and leachables, container testing, and heavy metal detection significantly aids in optimizing container closure design for any given product, and is a valuable resource for our clients.

THE VALUE OF PARTNERSHIP IN A PATIENT-DRIVEN WORLD

Overcoming the multitude of manufacturing and process challenges associated with biologics and PFS – and fulfilling the potential of this product/delivery system coupling – requires partnership.

FIGURE 3

A tub of filled and sealed syringes exiting the RABS barrier on AMRI's prefilled syringe line.

The biological medicines marketplace is fiercely competitive, and with the average drug development pathway taking 10 years and costing $2.6 billion, there is little room for error.[9] Quite simply, there is no point to developing an innovative, life-changing drug if people cannot use it.

Combining pharmaceutical and drug delivery expertise as early on in the development process as possible can help speed up the pathway, while ensuring new medicines are safe, effective, easy to use, and tackle unmet patient needs.

There is no one-size-fits-all solution. Every product is unique, requiring custom mechanical, technical, and compliance processes. Industry-leading CDMOs can take a more agile approach that adapts to the needs of each product and its end users.

Every patient group will have differing requirements of both the product itself and the packaging it is supplied in. Therefore, the PFS design and development must evolve in parallel to product design and development.

Indeed, many drug developers work with their chosen PFS supplier as early as Phase 1 to ensure the end result meets the needs of the product and patient. The formulation of some solutions, for example, requires the addition of several kilograms of excipients in a low oxygen environment. The whole process, including weighing and transfer, must be conducted within an active nitrogen overlay with low oxygen permeability.

Rather than spend a huge amount on a complicated, automated system that would result in significant residual powder losses, AMRI worked with Solo Containment Ltd and Servolift LLC to engineer a custom solution for our clients.

The resulting system features an isolator unit with docking station for split butterfly valves and powder containment bags. It allows for large amounts of powder to be moved from isolator to tank in a low-oxygen environment, facilitating the precise addition of the powders to the formulation vessel, and minimizing product loss.

SUMMARY

The rise of biologic medicines plays a major role in the growth of the PFS market. These cutting-edge treatments have necessitated a shift from oral to parenteral administration, creating a need for state-of-the-art, innovative delivery systems, and the trend is set to continue as more biosimilars, and next-generation gene and cell therapies, come online.

However, dispensing highly viscous solutions, minimizing E&Ls, and ensuring biocompatibility, all while developing delivery systems that suit individual patient groups, presents unique manufacturing, compliance, filling, and dispensing challenges.

CDMOs with integrated expertise streamline product development and optimization. Close working relationships, both within the organization and with partners and clients, speed up problem-solving and facilitate the creation of bespoke solutions.

By partnering with PFS CDMOs, biopharmaceutical companies can benefit from specialized expertise and expect shorter, smoother development pathways. These strong partnerships, working together to develop custom solutions, are the best way to ensure that innovative biologic treatments are delivered effectively, fulfil their potential and, ultimately, save lives.◆

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BIOGRAPHY

Anish Parikh, AMRI's Vice President, Drug Product Sales & Marketing, has more than 25 years of R&D, sales, and marketing experience in the pharmaceutical industry. He earned his Bachelor's degrees in Molecular Biology and Biochemistry (MBB) as well as Psychology from Rutgers College at Rutgers University in New Brunswick, NJ.

FORMULATION DEVELOPMENT

Formulating Immediate-Release Tablets for Poorly Soluble Drugs

By: Gayatri Khanvilkar, MPharm, Ajit Bhagat, Sangmesh Torne, PhD, Tejas Gunjikar, PhD, and Amina Faham, PhD

INTRODUCTION

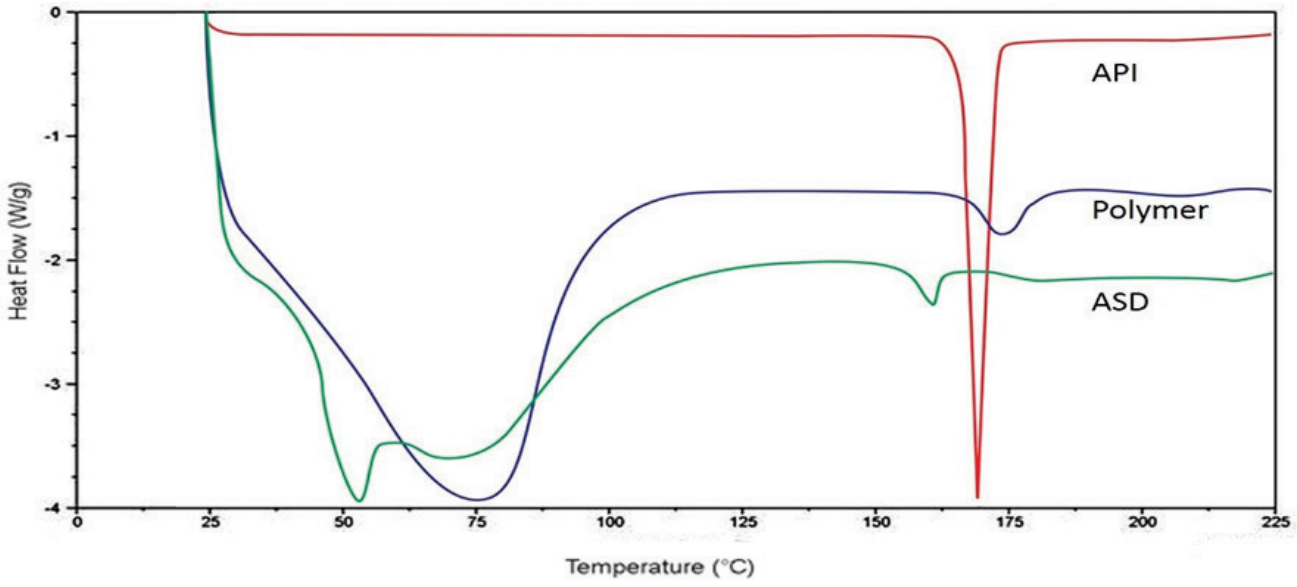
Formulators across the pharma landscape are all too familiar with the challenge of low aqueous solubility, which severely limits the oral bioavailability and commercial viability of new drugs. As a consequence, many products that could potentially improve patients' lives never reach pharmacy shelves. In fact, poor solubility has caused 40% of state-of-the-art products to fall short when attempting to enter the market.[1]

About 70% of active pharmaceutical ingredients (APIs) present a solubility issue of some kind, which limits a manufacturer's pipeline of drug candidates.[2] A concerning amount of life-saving treatments will remain just out of reach unless low solubility is addressed. But these troubling APIs don't have to remain obstacles to securing patient safety, product efficacy, low toxicity, and metabolic clearance.

Excipients have made a significant impact on the bioavailability of dosage forms, especially when it comes to solubility. Drug manufacturers looking to buck the trend of poor solubility should seek out supplier partners that can offer a one-stop-shop for modified-release technologies — versatile solutions that can be plugged into a wide range of formulations.

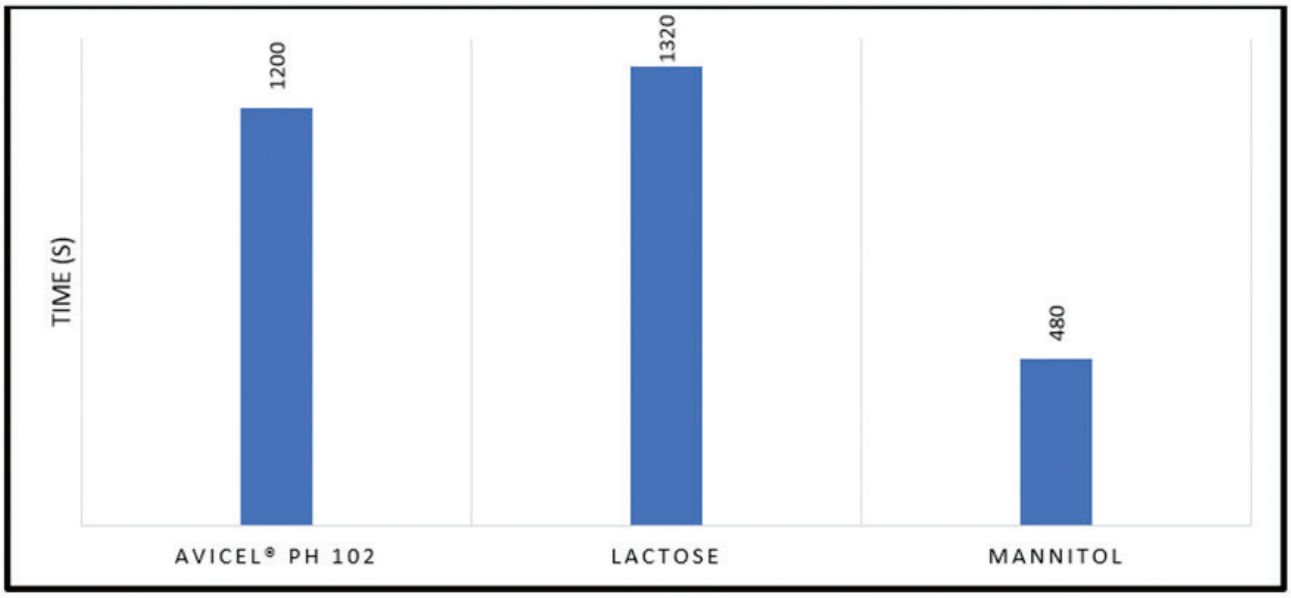
A variety of chemical and physical modifications have been introduced to innovate the way drug products are produced, en-

FIGURE 1



DSC images of API, polymer, and amorphous solid dispersion.

FIGURE 2



Disintegration Time

hancing solubility and dissolution along the way. Some of the more common methods are amorphous solid dispersions (ASDs), complex formation and nano-suspensions. ASDs can be used in a polymeric carrier to increase an API's solubility. This combination also bolsters the ASD in question with high-solids loading, and when in contact with intestinal fluids, the API is effectively stabilized against precipitation or re-crystallization.

As formulators seek to produce drugs with low aqueous solubility, they are simultaneously discovering new, unique approaches in development. For a case in point, look no further than DuPont Nutrition & Biosciences (DuPont) — the company found a way to increase the solubility and bioavailability of APIs through the use of AFFINISOL™ HPMC HME, an excipient specially designed for hot melt extrusion (HME), which factors heavily in successful solubilization. According to a recent case study, DuPont's proprietary form of hydroxypropyl methycellulose (HPMC) proved ideal for formulating immediate-release tablets for a poorly soluble drug.

DETERMINING THE PROCESS OF PRODUCTION

Before embarking on the study, DuPont researchers evaluated their preferred process of production. Though they concluded that HME was the ideal method, the answer wasn't immediately clear. The team evaluated spray dried dispersion (SSD) first, another method of ASD manufacturing, to discover which process was most effective for solubility and bioavailability. SSD has grown in popularity because it not only improves an API's solubility, but also prevents against nucleation of poorly soluble drugs.

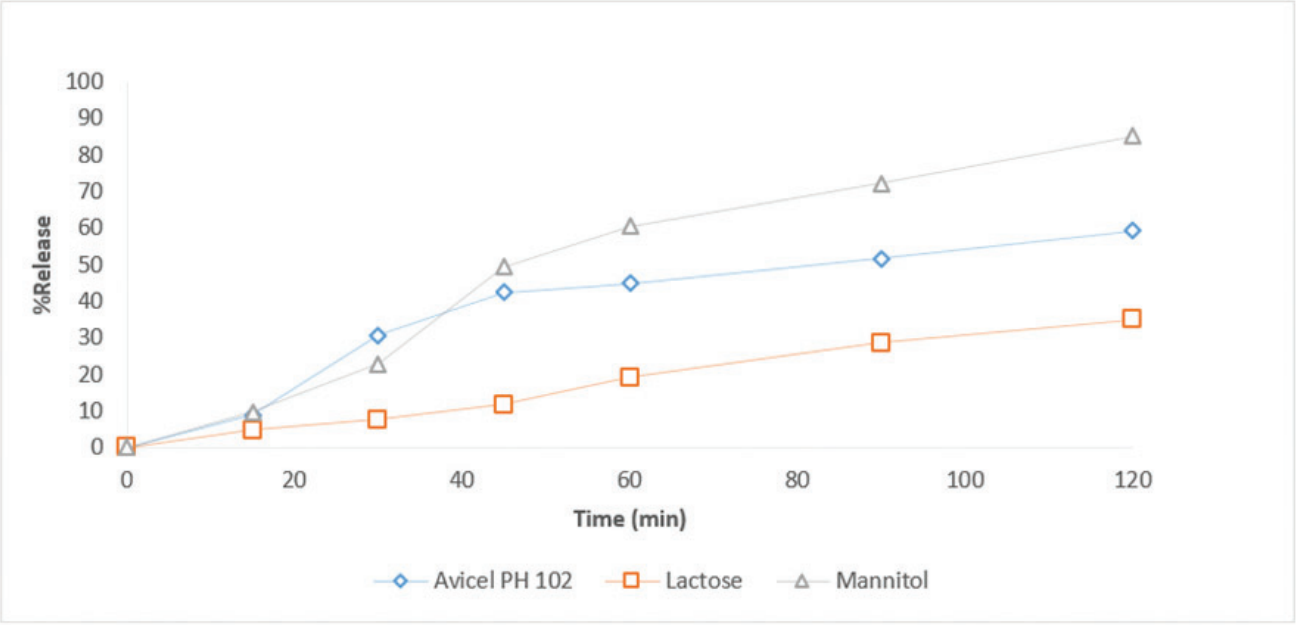
SSD and HME are not created equal, however. Manufacturers should do their due diligence to make sure they align with development goals. For example, SDD is available in smaller scales, but requires solvent for both the API and the excipient; HME does not require solvents, but it is limited to pharmaceuticals that can withstand high temperatures. Nevertheless, HME is a versatile, continuous, solvent-free process that enables the formulation of APIs that often face issues during processing and delivery. HME also boasts increased solubility in ASDs without sacrificing permeability, which leads to increased bioavailability.

Though HME is poised to become a leading technology in the manufacturing of ASDs, the most compelling reason the company used HME in this study is its unique ability to disrupt the crystal lattice of the active ingredient to render it amorphous, promoting its incorporation in to the polymeric carrier to yield a homogenous dispersion (a product of the manner in which thermal and mechanical energy are input during the process). As shown in the following case study, the results are noteworthy.

OBJECTIVES

With its production process established, DuPont set out to evaluate the formulation of a poorly soluble antifungal BCS class 2 drug using AFFINISOL™ HPMC HME to convert the API into a more soluble form. DuPont also investigated the

FIGURE 3



***In vitro* dissolution profile comparing effect of different bulking agents.**

effects of different excipients for formulating AFFINISOL™ HPMC HME-based drug extrusions into immediate-release tablets.

The study was conducted with a mixture of APIs and polymers that were blended, milled, and combined with other excipients, then compared to the original drugs to determine the differences in solubility and API release. The team came to a preferable conclusion, with the end result showing that processing poorly soluble drugs with HPMC in HME can formulate high-dose tablets with improved solubility.

METHODOLOGY

To begin the case study, the team used a mixture with a ratio of 1:1 of API and AFFINISOL™ HPMC HME 15 LV, based on previous screening trials. They then blended the API and polymer for 10 minutes, and passed the blend through a 30# mesh sieve. The blend was then fed through a Thermo Fisher Pharma 11 twin-screw extruder at 190°C to obtain extrudates.

The extrudates were cut into pellets (1-2 mm) using Varicut Pelletizer, and the pellets were further milled using a Retsch Ultra-Centrifugal Mill ZM 200 to achieve extrudates with particle size of < 250 µm. The milled extrudates were further blended with various bulking agents (Avicel® PH 102, lactose and mannitol) and tablet disintegrants (PVP CI, SSG, Ac-Di-Sol® and Amberlite™ IRP 88). The various blends were then compressed into tablets and evaluated for hardness, disintegration time, and *in vitro* drug release.

The tablets were compressed on an 8 Station Kambert tablet compression machine (KMP-D-8) using standard concave 12-mm round punches and evaluated for hardness, disintegration time, and in vitro drug release.

All compaction profiles of the compositions were analyzed on standard ESH compaction simulator equipment. Disintegration tests soon followed, and the study concluded with samples drawn at regular intervals from the dissolution apparatus.

EFFECTS OF BULKING AGENTS & DISINTEGRANTS ON TABLET PROPERTIES

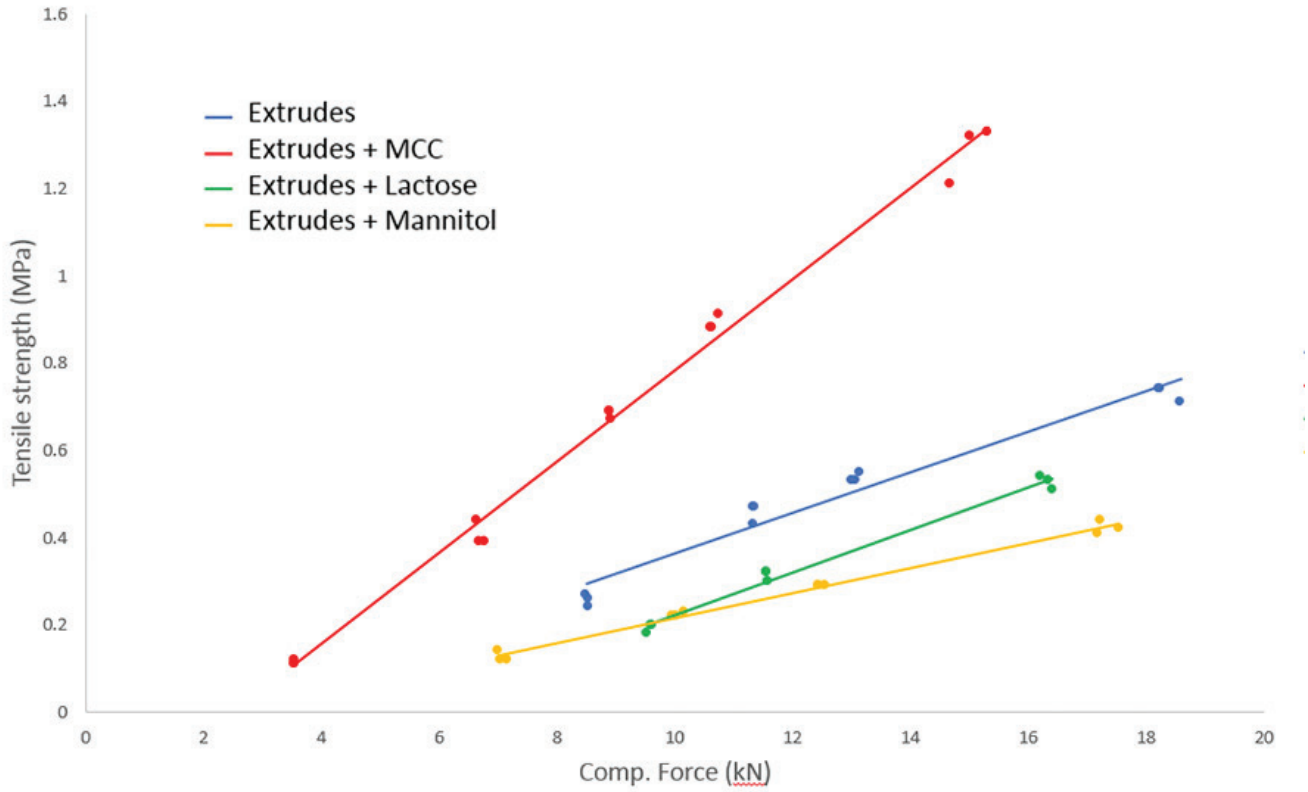
Researchers also evaluated the effects of bulking agents and disintegrants on drug performance over the course of the study. The following is the methodology and results of this evaluation.

For the disintegration test, the team used an Electrolab EDT-2L disintegration tester from as per USP method in HCl 0.1 N.

As shown in Figure 1, researchers saw an absence of drug peak in thermogram readings, which indicated a strong interaction between the AFFINISOL™ HPMC HME 15 LV and a given API, resulting in amorphous solid dispersion.

Tablets formulated with Avicel® PH 102 as a bulking agent showed excellent hardness (70 N) compared to those formu-

FIGURE 4



Compaction study comparing effect of different bulking agents.

lated with mannitol or lactose, which both achieved a hardness of 32 N. Typically, a minimum hardness of 60 N is acceptable criteria, putting DuPont's results well above expected performance.

Figure 2 shows that tablets formulated with mannitol as a bulking agent resulted in a faster disintegration time of 480 seconds, as compared to tablets containing Avicel® PH 102 or lactose as bulking agents.

For the *in-vitro* dissolution studies, researchers used the USP apparatus 2 from Electrolab in 900 ml of 0.1N HCl for 2 hours at 100 rpm. A 5-ml sample was withdrawn at each sampling time point (15, 30, 45, 60, 90, and 120 minutes).

According to Figure 3, the API release of tablets formulated with Avicel® PH 102 was slower than mannitol. API release with lactose as a bulking agent was extremely slow and incomplete.

Interestingly enough, the results from the compaction simulator — shown in Figure 4 — indicated that compacts containing Avicel® PH 102 exhibited better compactibility than lactose or mannitol. Avicel®, with its unique crystalline and paracrystalline microfiber structure, provides the best compactibility in tabletting, while formulations containing mannitol or lactose were lacking. Moreover, the hydrogen bonding available on the surface of cellulose particles further increases the strength of tablets.

Formulations with Avicel® PH 102 demonstrated significantly better tensile strength and compactability, which made them an easy choice for further formulation optimization.

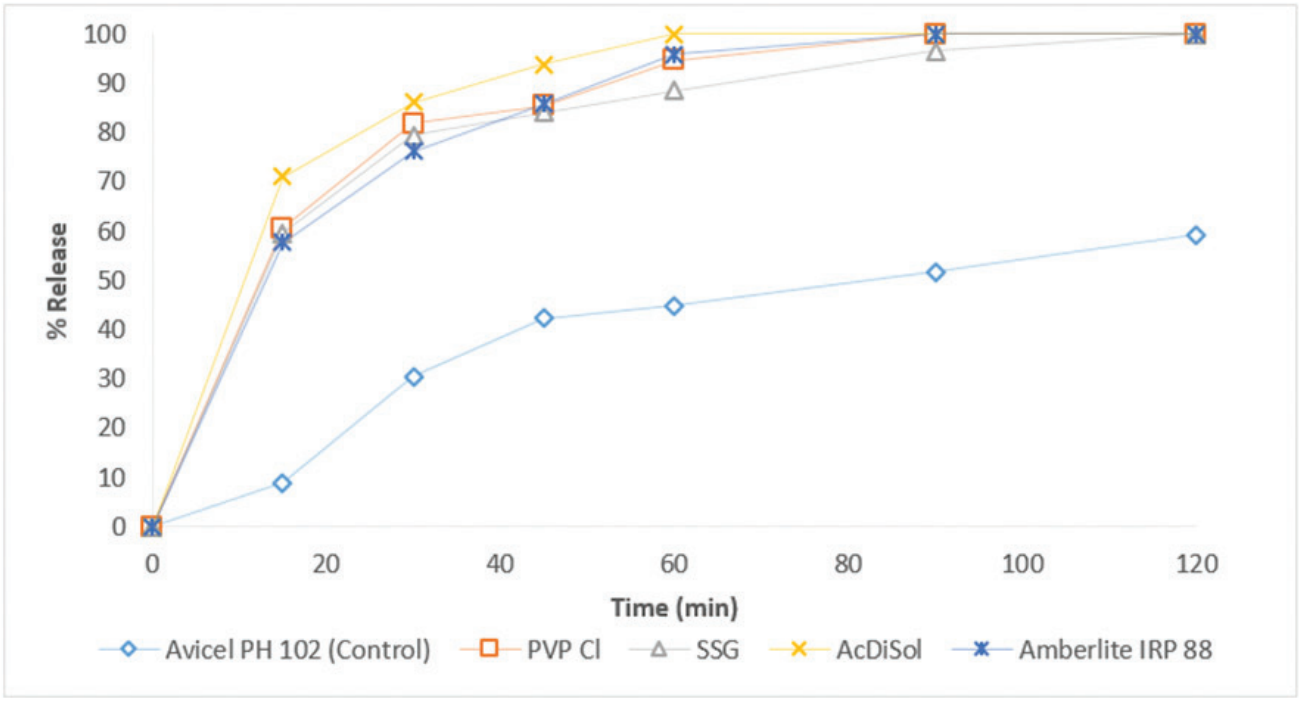
Tablet disintegration time was significantly lowered by the inclusion of disintegrants in the formulation as compared to the control sample, which contained only Avicel® and disintegrated after 1,200 seconds. Of all tablets tested, those with Ac-Di-Sol® and Amberlite™ IRP 88 achieved the fastest disintegration time (10 seconds) while tablet hardness remained acceptable for all of the formulations investigated.

The formulation with Ac-Di-Sol® resulted in the fastest API release followed by the formulation with Amberlite™ IRP 88, according to Figure 5.

FAVORABLE RESULTS

The study shows that high-dose (200 mg) tablet formulation of a poorly water-soluble drug was developed with excellent tablet properties and API release by processing with AFFINISOL™ HPMC HME 15

FIGURE 5



***In vitro* dissolution profile comparing the effect of different disintegrants.**

LV using HME technology. The results show that AFFINISOL™ HPMC HME 15 LV can help in formulating an ASD into immediate-release tablets of a poorly soluble drug.

In addition, bulking agents and tablet disintegrants could have a profound effect on tablet properties and API release across the pharmaceutical industry. For example, tablets containing Avicel® PH 102 as a bulking agent and Ac-Di-Sol® as a tablet disintegrant result in tablet formulations with excellent physical tablet properties and quick disintegration.

DuPont's case study shows that previously unviable APIs can be successfully processed with the right methods, which should give hope to formulators facing similar difficulties. Through the use of bulking agents and tablet disintegrants, researchers created formulations with improved physical-tablet and drug-release properties, all of which can benefit the pharma industry.

It all comes down to HPMC's unique ability to inhibit recrystallization and increase bioavailability when used as a polymeric stabilizer in ASDs. As shown throughout the study, DuPont's proprietary form of the excipient was successfully processed in a wide range of conditions into ASDs, resulting in formulations that provide increased solubility of model compounds.

To put it plainly, poorly water-soluble drugs are no longer exempt from high-dose tablet formulations. Excellent tablet properties and API release are both possible by processing with AFFINISOL™ HPMC HME 15 LV in conjunction with HME technology. For an industry in which so many promising drugs have stalled out in reaching the market because of poor solubility, DuPont's success with AFFINSIOL™ HPMC HME represents a new paradigm for formulators. No longer do limitations in delivery method mean the difference between getting life-changing drugs on the shelf and going back to the drawing board.

MOVING FORWARD

These results suggest that one day soon, almost any drug will be able to hit the market without delay, regardless of solubility. But drug makers looking to implement similar tactics should use caution. The global supply chain for pharmaceuticals can be a complex gauntlet of regulations and risk assessment protocols, all of which vary by region. For a drug manufacturer that spans across borders, developers need to navigate regulations and risk assessments for new delivery methods. More and more regulatory agencies are working to standardize guidelines globally to easily manage raw material and supplier qualifications. In the meantime, close collabora-

tion between raw material supplier and manufacturer is imperative to ensure regulatory standards are held at each phase.

Quality-by-Design (QbD) is key to a thriving pharmaceutical business, so make sure any potential manufacturing partner can adhere to it. By understanding and addressing different components of a product at the beginning of the process — from its formulation process, to manufacturing and quality control — future risk can be mitigated and cost savings achieved. A QbD approach allows manufacturers to evaluate how their product will move through every step in the supply chain to better understand the entire system in product creation. In the end, this structure allows manufacturers to minimize costs by limiting the time and complexities through improving processes, testing, and inventory costs and can even help address regulatory needs. ◆

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BIOGRAPHIES

Gayatri Khanvilkar is a Application Development & Innovation Scientist at DuPont Nutrition & Biosciences focusing her career on pharmaceutics, Good Laboratory Practice (GLP), JMP, R&D, and regulatory affairs. She earned her Master's in Pharmacy, with a focus in Pharmacology, from Bombay College of Pharmacy. Prior to that, she earned her Bachelor's from Mumbai University .

Ajit Bhagat is a Senior Technician at DuPont Nutrition & Biosciences based in Maharashtra, India.

Dr. Sangmesh Torne is the Application Development & Innovation Scientist at DuPont. Throughout his career in the pharmaceutical industry, he has focused on complete drug product development processes and management. He earned his PhD from Vellore Institute of Technology, his Master's in Pharmacy from Swami Ramanand Teerth Marathwada University, and his Bachelor's in Pharmacy from Nanded Pharmacy College.

Dr. Tejas Gunjikar is the Pharma Application and Innovation Leader for South Asia at DuPont, where he helps develop oral fast-dissolving technologies, biopharmaceutical formulations, solid oral dosage forms, and much more. He earned his PhD in Pharmaceutics from University of Mumbai and his Bachelor's in Pharmacy from Savitribai Phule Pune University.

Dr. Amina Faham is DuPont's Global Director of Pharma Application Development and Innovation. She also Chairs the DuPont Diversity & Inclusion Steering Committee. She earned her PhD in Pharmaceutics from Aix-Marseille University, People Leadership certification from INSEAD, and Leadership through financial excellence certification from MIT Sloan school of Management.

NEXT-GENERATION TUMOR TARGETING

Leveraging the Tumor Microenvironment to Change the Standard of Care

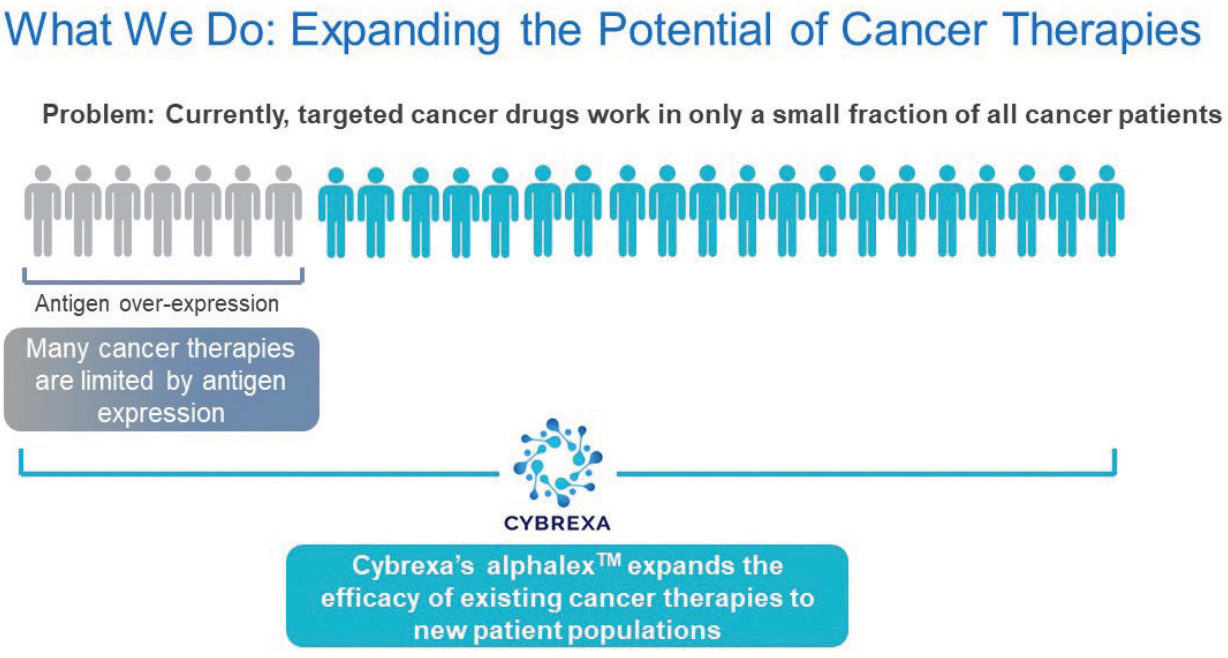
By: Vishwas Paralkar, PhD

ABSTRACT

Most cancer drugs are designed to shrink tumors by killing tumor cells; however, these drugs do not affect tumor cells in isolation. Cancer drugs affect both cancer and healthy cells throughout the body, resulting in off-target adverse toxic effects on the healthy, normal cells. These off-target toxic effects can limit the efficacy of cancer drugs, as side effects caused by off-target drug activity can limit the dose of a drug administered or prevent a drug from being combined with other cancer therapeutics.

This conundrum applies to treatments such as highly potent chemotherapies, including topoisomerase I inhibitors and maytansines. Such treatments are known to be highly effective in killing cancer cells, but toxicities to normal tissue preclude these drugs from being administered systemically. To date, these potent chemotherapies have been targeted to tumors by antibodies, creating a class of therapeutics called antibody drug conjugates (ADCs). ADCs can only be used against tumors that overexpress specific antigens, limiting the number of patients who can benefit. In addition, the chemotherapies, or "payloads" are released ex-

FIGURE 1



"It has been known for decades that the area in and around all tumor cells has a lower pH relative to healthy tissue. Although previously explored, this phenomenon has not been successfully leveraged as part of drug development. Cybrexa Therapeutics is currently developing a unique platform technology called alphalex™ that represents the first technology that has successfully used pH differential to target cancer drugs to tumor cells in animal models, while sparing healthy tissue."

tracellularly, which can result in off-target toxicities. The relatively large size of the ADCs also limits tumor penetration.

In addition, some classes of therapies have been unable to fully unlock their potential because they cannot be combined with DNA-damaging chemotherapies, like topoisomerase I inhibitors. PARP inhibitors, a type of DNA Damage Response (DDR) Inhibitors, are one such class of therapies. Four PARP inhibitors are currently approved by the FDA and EMA. Like other DDR inhibitors, PARP inhibitors require inherent errors in cancer cells' DNA – caused by either genetic mutations (or external factors like chemotherapy or radiation therapy that cause damage to tumor cell DNA). Only 15% to 40% of all cancer patients contain a DDR mutation. Therefore, PARP inhibitors are currently approved only as monotherapies in patients with BRCA mutations or following a response to platinum-based chemotherapy.

PARP inhibitors have shown efficacy in these specific patient populations; however, they can affect normal cells too, including the bone marrow. This particular off-target effect has limited expansion of PARP inhibitors to other populations. Based on preclinical and clinical evidence, PARP inhibitors are known to have synergistic efficacy in combination with topoisomerase I inhibitors across a variety of tumor types without any mutations (wild-type). Unfortunately, these combinations are prohibitively toxic. In clinical trials attempting to expand the use of PARP inhibitors into these wild-type patients in combination with DNA damaging chemotherapy, toxicity forces a reduction of the dose and/or dose intensity of the PARP inhibitor and/or DNA damaging agent to the point at which synergistic efficacy is lost in order to avoid the side effects associated with bone marrow suppression, including anemia and neutropenia. Solving the problem of this synergistic toxicity can expand the potential of PARP inhibitors.

FIGURE 2

Company	Drug	PARPi Monotherapy Daily Dose	Approx. Dose (intensity) Reductions in Combo with TMZ*	Approx. Dose (intensity) Reductions in Combo with Irinotecan*
abbvie	Veliparib	800 mg[1]	↓ 40-fold PARPi[1]	↓ 13-fold PARPi[2] ↓ 20% irinotecan[2]
CLOVIS ONCOLOGY	Rucaparib	1200 mg[3]	↓ 20-fold PARPi[4,5,6]	n/a
AstraZeneca / MERCK	Olaparib	600mg[3]	↓ 12-fold PARPi[7]	↓ 17-fold PARPi[8]
TESARO / gsk	Niraparib	300 mg[3]	↓ 7.5-fold PARPi[9]	n/a
BeiGene	Pamiparib	120mg[11]	↓ 3-fold TMZ[10] *(note: study ongoing, may evolve)*	n/a
Pfizer	Talazoparib	1 mg[3]	↓ 4-fold TMZ[11]	↓ 4-fold irinotecan[11]

* Calculations assume 28 days per month

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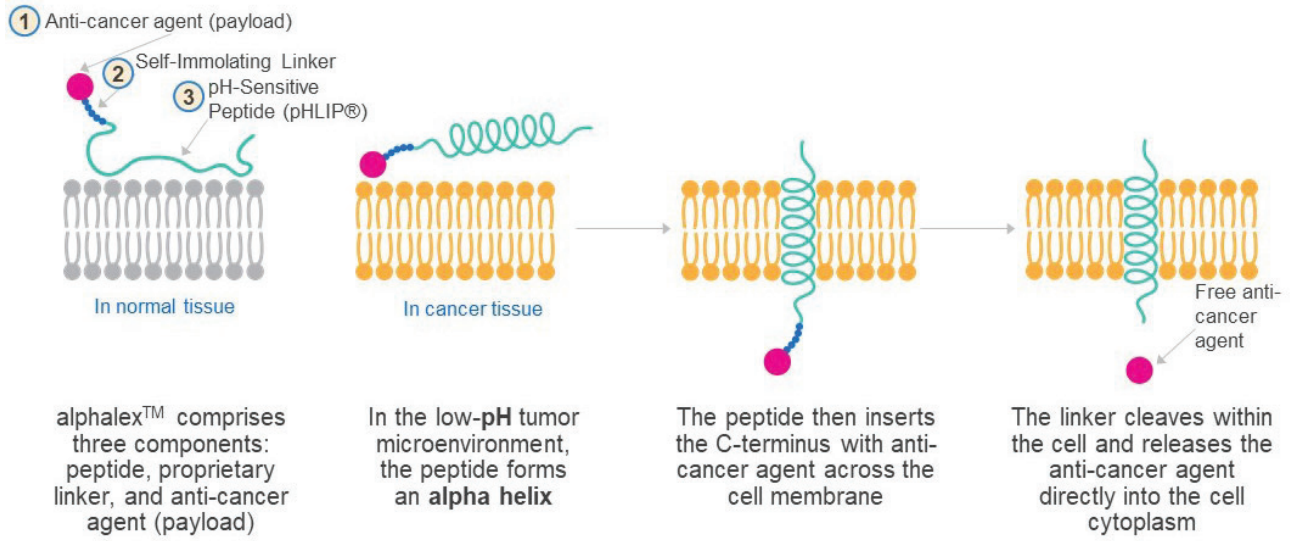
FIGURE 3



AN ELEGANT SOLUTION: alphalex™

It has been known for decades that the area in and around all tumor cells has a lower pH relative to healthy tissue. Although previously explored, this phenomenon has not been successfully leveraged as part of drug development. Cybrexa Therapeutics is currently developing a unique platform technology called alphalex that represents the first technology that has successfully used pH differential to target cancer drugs to tumor cells in animal models, while sparing healthy tissue.

alphalex is the combination of a pH-sensitive pHLIP® peptide, linker, and anti-cancer agent. pHLIP peptides are a family of pH-Low Insertion Peptides that target acidic cell surfaces. pHLIP was developed at Yale University and the University of Rhode Island, and is exclusively licensed to pHLIP, Inc. The complex undergoes a chemical reaction in the low-pH tumor microenvironment: the peptide forms an alpha helix and translocates across the cell membrane to release and deposit anti-cancer agents into cancerous tumor cells. The anti-cancer agents remain inactive while they are part of the conjugate and only become active when they are released into the tumor cell. The platform is exquisitely sensitive to pH differential between tumors and healthy tissue. In addition, alphalex has a relatively simple and scalable manufacturing process.

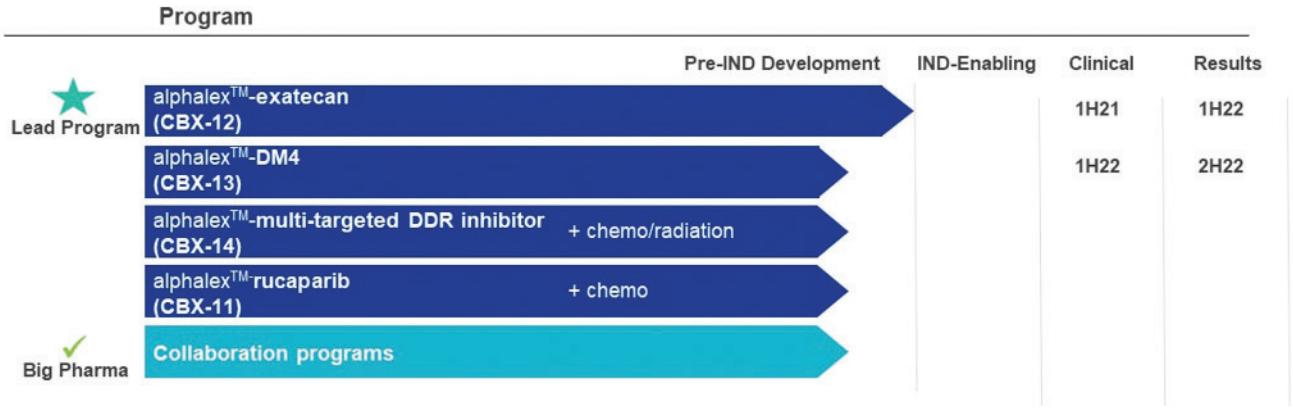
This technology allows for the selective, antigen-independent, intracellular delivery of anti-cancer agents. The antigen independence of alphalex is a major advantage compared to ADCs, like ENHERTU® (fam-trastuzumab deruxtecan-nxki), which contains a potent topoisomerase I payload and is specific to HER2-expressing tumors. ENHERTU was licensed by AstraZeneca in 2019 for a total deal value of $6.9 billion.

alphalex can be applied to a broad range of small molecule drugs, and its potential lies in enabling an enhanced therapeutic index. This allows both highly toxic monotherapies and combinations of therapies with known synergistic efficacy and toxicity to be administered to patients at effective doses.

CHANGING THE NARRATIVE OF TUMOR TARGETING: ALPHALEX POWERS CYBREXA'S PIPELINE

By leveraging existing anti-cancer agents with established clinical evidence, Cybrexa is moving programs into the clinic quickly. This also provides us with a reduced risk profile for development because new molecules are not being designed or developed from scratch. Our lead program, CBX-12 (alphalex-exatecan), leverages a highly potent topoisomerase I inhibitor payload, similar to ENHERTU's payload. Unlike ENHERTU, CBX-12 is not dependent on HER2 overexpression. CBX-12 was selected based on its strong efficacy and solid safety profile in preclinical models, which we look forward to publishing later this year. CBX-12 may have potential synergy with immuno-oncology drugs, such as PD-1s as well as in combination with DDR inhibitors, including PARP inhibitors. CBX-12 could enable the combination of PARP inhibitors with DNA-damaging chemotherapy to effectively kill cancer cells independent of mutation status and without extreme bone marrow toxicity.

FIGURE 4



Our focus is initially on patients with few or no treatment options, where preclinical and clinical data has shown topoisomerase I inhibitors may have particular efficacy. This includes colorectal, ovarian, breast, and small cell lung cancer. Cybrexa plans to advance CBX-12 into the clinic in the first half of 2021. The Cybrexa team is confident that the compound could yield clinical efficacy and safety data by 2022.

BEYOND TOPOISOMERASE I INHIBITORS: EXPANDING TO NEW FRONTIERS

CBX-12 is the first of several programs we plan to advance to the clinic. Cybrexa's pipeline includes programs with other established toxins such as DM4, in which administration of the anti-cancer agent alone is too toxic to be tolerated, and a multitargeted DDR inhibitor-alphalex conjugate. Given the potential of alphalex, we are continuing to evaluate other applications for the platform and expect to announce our second lead program later this year.

SUMMARY

Cybrexa is a privately held biotechnology company dedicated to developing next-generation tumor-targeted cancer therapies using its alphalex platform. The company's lead candidate, CBX-12, an alphalex-exatecan conjugate, is expected to enter Phase I in 2021 in advanced solid tumors. Cybrexa also has other preclinical toxin conjugate programs as well as synthetic lethality programs. Cybrexa was founded by physician-scientists and has an experienced management team that has built numerous successful life sciences companies. ◆

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

BIOGRAPHY

Dr. Vishwas Paralkar is Chief Scientific Officer of Cybrexa Therapeutics. He brings more than 23 years of executive experience in addition to extensive drug discovery and research experience to his role. He most recently served as Chief Scientific Officer of Karos Pharmaceuticals, where he was hired as the first employee and served as the CSO until its acquisition in August 2017. Prior to joining Karos, he was a Senior Director at Pfizer, which he joined in 1995 and left to join Karos in June 2010. Before that, he was a Visiting Research Fellow at the National Institutes of Health in Bethesda, MD. He earned his PhD in Cell Biology/Biochemistry from Howard University.

CAPTISOL®
A Ligand TECHNOLOGY

FORMULATION FORUM

Application of Captisol® technology to enable the formulation of remdesivir in treating COVID-19

By James Pipkin, PhD, Vince Antle, PhD, Rebeca García-Fandiño, PhD

Introduction

The numbers are startling for the outbreak of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Coronavirus disease (COVID-19) is affecting more than 227 countries and territories. Globally, total cases are nearly 5.9 million as of May 29[1] and total deaths surpassed 363,000.[1] In the United States, there are more than 1.74 million confirmed total cases with more than 102,000 deaths. Also, the cumulative hospitalization rate in the U.S. is approximately 73 per 100,000 people; and in the 65+ age group, this rate is more than triple.[2]

On May 1, 2020, Gilead Sciences and the U.S. Government announced an Emergency Use Authorization (EUA) for remdesivir[3], the first antiviral therapeutic for treating COVID-19. A week later, the Japanese Regulatory Authority approved VEKLURY® (remdesivir).[4] Japan, United Kingdom, Taiwan and the U.S are currently the only countries to authorize use of remdesivir for treatment of COVID-19. The European Medicines Agency is continuing its rolling review of remdesivir, and on May 11, 2020, recommended expanding the compassionate use of the investigational medicine remdesivir so that more patients with severe COVID 19 can be treated.[5]

Figure 1

Working to supply remdesivir for COVID-19

"Since the moment the novel coronavirus that causes COVID-19 was identified, Gilead has mobilized every area of our organization to respond to the global health emergency."

https://www.gilead.com/

Every day we are improving processes, shortening timelines and increasing volumes as we work to bring remdesivir to patients as soon as possible. Our goal is to produce a total of:

- More than 140,000 treatment courses by the end of May 2020
- More than 500,000 treatment courses by October 2020
- More than 1 million treatment courses by December 2020
- Several million treatment courses in 2021, if required

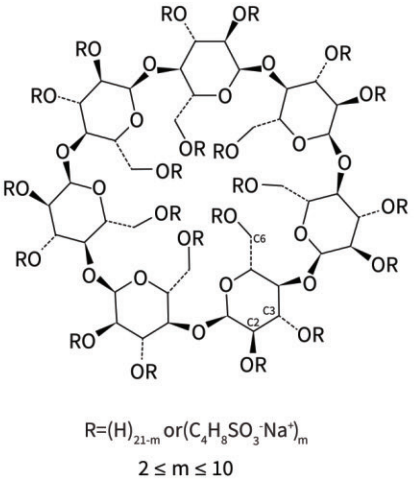
The numbers above are based on a 10-day treatment course

https://gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19

Gilead announced it will donate its entire remdesivir stockpile to the U.S. Government (~1.5 million doses) and boost production to provide more than 1.5 million additional treatment courses by year end.[6] If required, production is expected to continue to ramp up through 2021 to replenish and grow the stockpile (Figure 1). Ongoing clinical trials continue to evaluate remdesivir's safety and efficacy.

To meet the high demand for remdesivir is an immense task and requires extraordinary coordination and cooperation on an unprecedented and global scale. Gilead said it will build a geographically diverse consortium of pharmaceutical and chemical manufacturing companies, and announced signing non-exclusive licensing pacts with five generic drug makers, voluntarily sharing its knowledge to produce remdesivir across the globe. Gilead recognized early that to deliver remdesivir worldwide to the patients in need requires establishing numerous partnerships.[7,8]

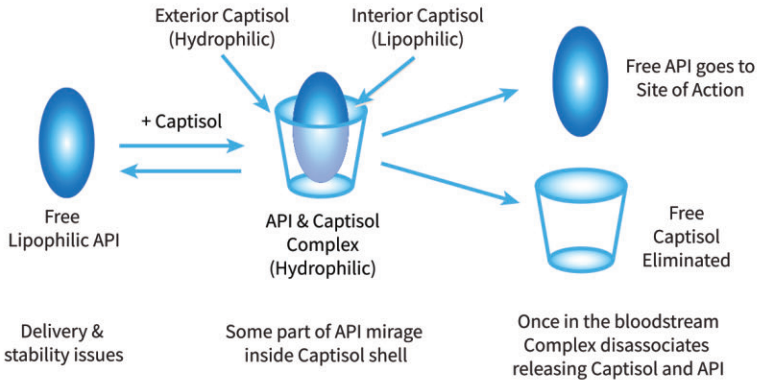
Captisol Technology



$R=(H)_{21-m}$ or $(C_4H_8SO_3^-Na^+)_m$

$2 \leq m \leq 10$

Figure 2 **How Captisol Works**



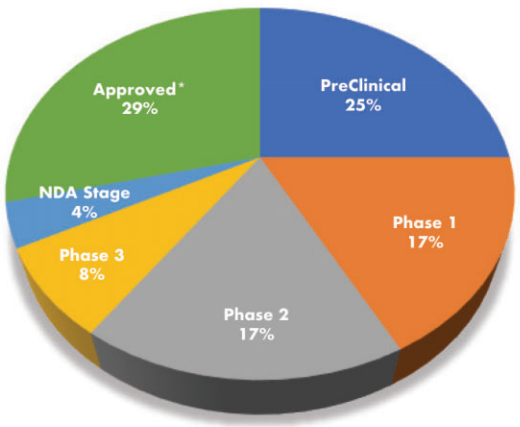
Captisol is a proprietary sulfobutylether-cyclodextrin process-specific composition that is a mixture of regional and positional isomers consistently produced via a patented all-aqueous process originally discovered at the University of Kansas.[9] The motivation for Captisol's discovery was to provide a parenterally safe material broadly applicable across all drug classes for solubilizing and stabilizing intractable drug candidates as opposed to historically used toxic cosolvents and surfactants. It works predominantly by a transient and reversible cyclodextrin (CD) host-guest association complex whereby a hydrophobic region or moiety of a wide range of substrates (drugs) is attracted to the hydrophobic cyclodextrin cavity (Figure 2). This forms the basis for use to increase solubility, stability, and bioavailability of drugs.[10] Captisol can also have extra cavity interactions with the 4-carbon linker or electrostatic with the anionic sulfonate. And more recently, it has been observed that other types of complexes, such as non-inclusion complexes can form, and CDs can self-assemble to form nanosized aggregates; both can contribute to their solubilizing properties.[11]

Fifteen human drug products have been approved using Captisol (including this EUA, tentative approvals, and approvals outside the U.S.). There are many Captisol®-enabled products in all phases of product development (Figure 3).

As the owner of the innovator technology Captisol, Ligand Pharmaceuticals has invested to increase cGMP production capacity, establishing manufacturing at two geographically distinct locations, establishing storage and distribution from multiple sites in the U.S. and overseas, and also establishing relationships with several Contract Research Organizations (CROs) to practice monograph test methods to perform release testing for Captisol partners.

Ligand has also established vast Drug Master Files in the U.S., Canada, China, and Japan, and has a voluminous safety database grown by Ligand and partners investing in preclinical development. Ligand has invested in continuous improvement in the control and cGMP manufacturing of Captisol. Ligand and its manufacturing partners have discovered all-aqueous processes to reduce or remove undesirable impurities such as phosphate, chloride, and color that have resulted in proprietary compositions.

Figure 3
Captisol®-enabled programs by development phase



*Includes US, tentative and exUS-only approvals

CAPTISOL is a Key Functional Excipient in Remdesivir/VEKLURY® [12,13]

Table 1 **Selected Antivirals**

Antiviral	MW g/mole	Water Solubility* mg/ml	Log Po/w*
remdesivir	602	0.339	2.2
favipravir	157	8.7	0.49
ribavirin	244	33.2	-1.9
sofosbuvir	529	0.824	1.6
lopinavir	629	0.00192	3.91
ritonavir	721	0.00126	3.9
galidesivir	265	7.42	-1.2

*Values from https://www.drugbank.ca/

Remdesivir, like some other antivirals listed in Table 1, has poor predicted solubility[14] and poor stability.[15] Molecular Dynamics (MD) was used to perform a preliminary view of the interaction of Captisol with remdesivir (Figure 4).[16] Several sets of MD simulations were performed starting from pre-assembled Captisol-remdesivir complexes in pre-equilibrated-explicit Simple Point-Charge (SPC) water model. Six representative structures of Captisol, using different locations for 6 or 7 sulfobutylether substitutions in the positions 2, 3 and 6 of βCD were employed. Four replicas of each system (50 ns-long each) were performed, using different orientations of remdesivir inside the cavity. For additional technical details for the MD simulations, please see Garrido et.al.[17] or contact Dr. Garcia-Fandiño.

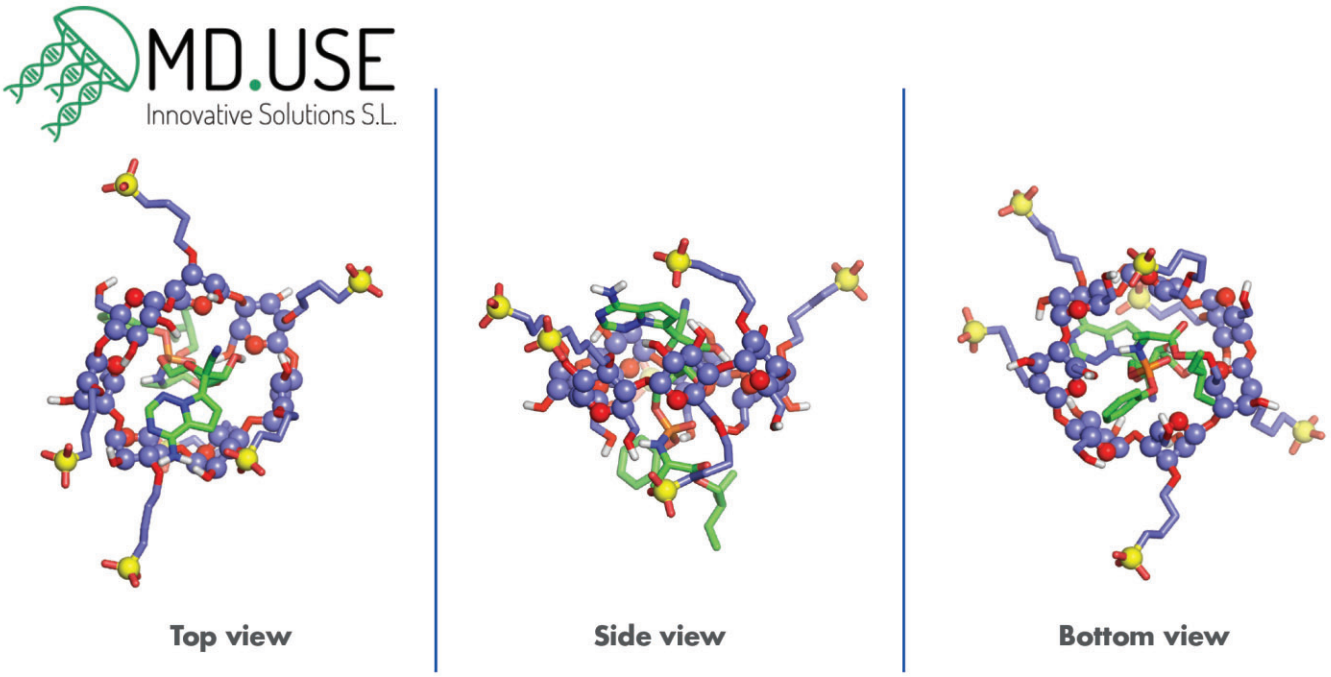


Figure 4

MD Simulation Snapshots

Remdesivir (in green) stable inside Captisol

The interactions of Captisol with remdesivir readily produce a clear solution (Figure 5) or lyophilized solid presentations of remdesivir, i.e. Lyophilized Powder and Injection Solution with drug – Captisol amounts in Table 2 as described in the EUA Fact Sheet for Health Care Providers[12] and Gilead Remdesivir Pharmacy Guide.[13]

Figure 5

Simple demonstration illustrates Captisol's ability to dissolve remdesivir

Each vial contains 100 mg of remdesivir, without (left) or with (right) Captisol (3 g). Internal demonstration performed by WuXi AppTec following a procedure adapted from Example 1 in US 2019 / 0083525 A1 Larson; Pub. Date: Mar. 21, 2019.

As a ready-made solution, the EUA Fact Sheet and Pharmacy Guide states to store remdesivir injection solution (contains 6 grams Captisol) at refrigerated temperature, whereas for the lyophilized powder (contains 3 grams Captisol), store at room temperature below 30°C.[12,13]

Table 2

Remdesivir Compositions [EUA FACT SHEET FOR HCPS[12] and Pharmacy Guide[13]]

Component	Lyophilized Powder	Injection Solution
remdesivir	100 mg	100 mg
Captisol	3000 mg	6000 mg
Ratio Captisol/remdesivir	30:1	60:1

Drug/active (Approval Year)	Captisol to API* (weight : weight
BAXDELA®/ delafloxacin (2017)	8:1
NEXTERONE®/ amiodarone (2010)	10:1
VFEND®/ voriconazole (2002)	16:1
NOXAFIL®/ posaconazole (2014)	22:1
KYPROLIS®/ carfilzomib (2012)	50:1
ZULRESSO®/ brexanolone (2019)	50:1
EVOMELA®/ melphalan (2016)	54:1

The use of high Captisol to API ratios in Captisol®-enabled products is not unusual (Table 3), but does dictate bulk requirements. Given the large amounts of Captisol used in the formulations, quality, purity, and reproducibility are all very critical.

Table 3

Formulation Ratios of Selected Captisol®-enabled Commercial Products

*References: Product Labels

Summary

Ligand supports Gilead and the remdesivir manufacturing consortium with Captisol. More Captisol than ever is required to meet Gilead's bold goals of making remdesivir available to COVID-19 patients in the U.S. and to hundreds of countries around the world. Ligand announced it plans investment in capital equipment that may possibly allow the cGMP annual production capacity for Captisol to increase to as much as 500 MT. Captisol production is supported by other raw material suppliers. For example, Wacker Chemie AG supplies native β-cyclodextrin that undergoes further processing by Ligand. Critical links throughout the Ligand supply chain are being maintained and managed to expand the supply of Captisol.

Ligand, along with a network of suppliers and manufacturers, is among the critical supply chain links to support Gilead and its partners to urgently produce remdesivir.

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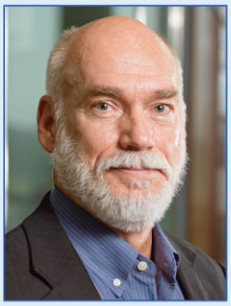
About the authors



James Pipkin, PhD, Vice President, New Product Development

Dr. Pipkin joined Ligand in 2011, following Ligand's acquisition of CyDex Pharmaceuticals. He joined Cydex in 2001. Dr. Pipkin supports Captisol partners and directs internal development of new applications, and products utilizing Captisol, whether applied to new molecular entities (NMEs), or reformulations of existing drugs via traditional and the 505(b)(2) regulatory pathways. Prior to joining the Company, he was Executive Director for CMC Services at Oread Laboratories, Research Fellow with Merck Research Laboratories in the INTERx Research Division and West Point PR&D facilities where he was involved in the design and evaluation of controlled release devices for ophthalmic and oral delivery, and he was at The Squibb Institute for Medical Research, where he directed preformulation activities. He has contributed to numerous presentations, monographs/chapters, publications and patents and holds a M.S. and Ph.D. in Pharmaceutical Chemistry from The University of Kansas.

Vince Antle, PhD, Senior Vice President, Technical Operations

Dr. Antle joined Ligand in 2011 following Ligand's acquisition of CyDex Pharmaceuticals. He joined CyDex in 2005. Dr. Antle is currently responsible for quality assurance, internal drug product quality, operations, distribution and logistics for Captisol. From 1999 to 2005 Dr. Antle was Technical Operations Manager and Head of Process Development at EaglePicher Pharmaceuticals Services. Prior to 1999, Vince was the Group Leader for the Combinatorial Chemistry Department of MDS Panlabs in Bothell Washington. Dr. Antle has contributed to publications, presentation and patents and holds a Ph.D. from the University of Cincinnati in Medicinal Chemistry, and a B.A. in Chemistry from the University of Minnesota, Morris.

Rebeca García Fandiño, PhD (rebeca.garcia.fandino@usc.es)

Rebeca Garcia-Fandino is a computational chemistry researcher working at the Center for Research in Biological Chemistry and Molecular Materials (CiQUS), at Santiago de Compostela University (Spain). She is one of the main co-founders and CEO of MD.USE Innovations. She is author of more than 30 research articles on Molecular Dynamics and Quantum methods applied to different systems, from small reactive molecules to supramolecular systems, including cyclodextrins. She is also author of several book chapters, a patent and software register. The aim of her research is the design of new and improved antibacterial/antineoplasic agents based on understanding their action mechanism, both in solution and at the level of membranes using computational tools.

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GENE THERAPY

The Role Viral Vectors Play in Current Gene Therapy Development

By: Dieter Lingelbach, MBA

INTRODUCTION

Viruses, among the smallest organisms on earth, have gone through literally eons of natural selection to make them one of the most advanced gene delivery mechanisms imaginable, for any and all kinds of tissue and cell types.

Today, through the research efforts of dedicated gene therapy pioneers, huge knowledge gaps have been closed concerning virus biology, vector dynamics, immune interaction, and vector safety. This intense research has resulted in science's ability to remove the harmful/pathogenic components of virus genomes, enabling applications that would not harm the organism or patient, and turning the tide on viral vectors as a historic opportunity, rather than a threat.

EARLY SETBACKS LEAD TO INSIGHTS & CLINICAL TRIAL EXPANSION IN MULTIPLE DISEASE AREAS

Gene therapy suffered near catastrophic setbacks when adenovirus vectors were employed for the treatment of the non-life-threatening disease, ornithine transcarbamylase (OTC) deficiency, resulting in the death of a young patient.[1] OTC deficiency is one of the most common urea cycle disorders in humans. An inherited disorder, it causes toxic levels of ammonia to build up in the blood.

Moreover, although success was achieved in the treatment of children with severe combined immunodeficiency (SCID), the integration of the retrovirus-delivered therapeutic gene into the LMO2 proto-oncogene region triggered development of leukemia in some individuals.[2]

Following these high-profile failures and the subsequent worldwide efforts to mitigate against them, the field has recovered, and gene therapy has continued to progress, as evidenced by the more than 2,600 clinical trials conducted through 2017.[3] The largest percentage of these trials, 64.6%, focused on cancer therapy, while 10.5% focused on monogenic diseases, 7.4% on infectious diseases, and 7.4% on cardiovascular diseases.

About 70% of the trials have utilized viral vectors. And although developments in gene manipulation methods, such as CRISPR, and more efficient delivery methods for non-viral vectors have been introduced, viral vectors remain attractive.

The growing number of clinical trials using viral vectors indicates enthusiasm for their potential. Clinical efficacy and safety shown in recent gene therapy trials have prompted significant investments from both biotech and pharma companies, opening the door for widespread investments into acquisitions and clinical developments of gene and cell therapies, all using viral vectors.

CURRENT ADVANCES IN VIRAL GENE THERAPY

Recombinant DNA technology can now generate viruses that incorporate modifications in a specific viral gene or locus and that have a broad tropism allowing gene expression in a wide range of host cells. Recombinant viruses are currently being ex-

"SIRION Biotech has developed a Lentiviral vector enhancer called LentiBOOST™, which increases the gene transfer efficiency and long-term gene expression in patients. Moreover, the use of LentiBOOST™ increases the efficiency of this process and lowers manufacturing costs due to the significant reduction in vectors needed for production."

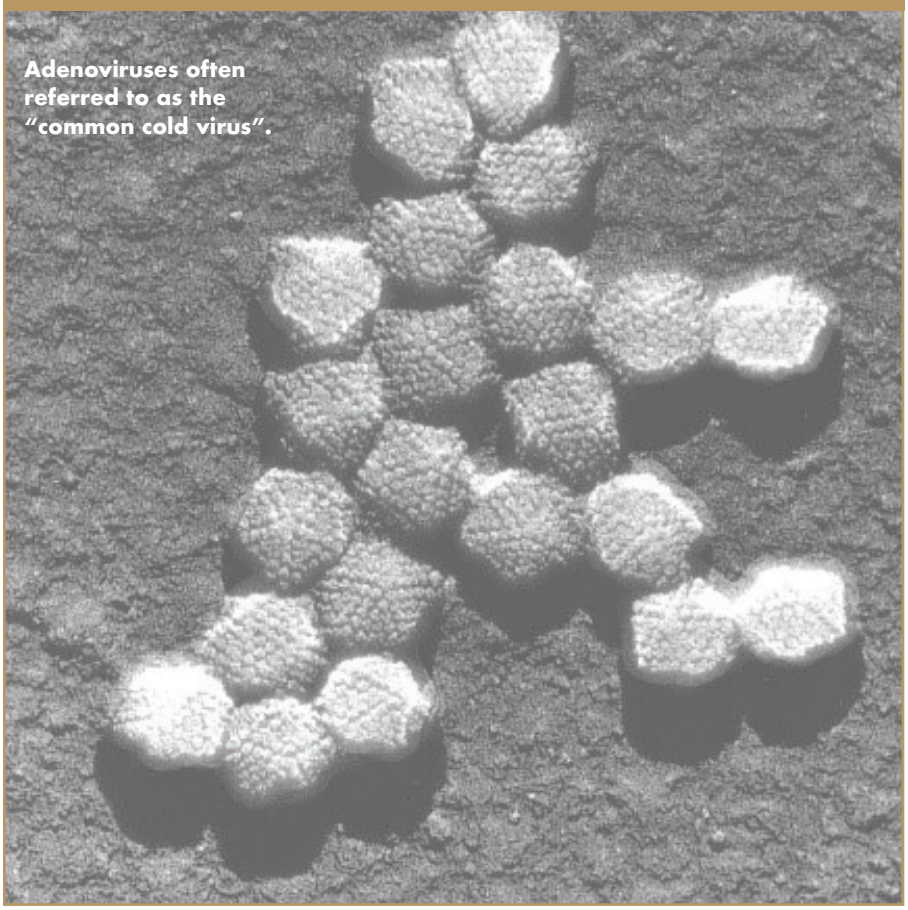
tensively investigated in preclinical and clinical studies in such disease areas as neurodegenerative, central nervous system, rare genetic diseases, and cancer.

Currently used recombinant viruses include Adenovirus, Lentivirus, and Adeno-associated virus (AAV). These virus types differ in their transduction and expression profiles as well as other key elements that are important for the application of viral vectors.

ADENOVIRAL VECTORS

Adenoviruses, often referred to as the "common cold virus," are double stranded DNA viruses with a wide range of vertebrate hosts. In humans, more than 50 distinct adenoviral serotypes have been found to cause a wide range of illnesses, from mild respiratory infections in young children to life-threatening multi-organ disease in people with a weakened immune system.

FIGURE 1



Adenoviruses often referred to as the "common cold virus".

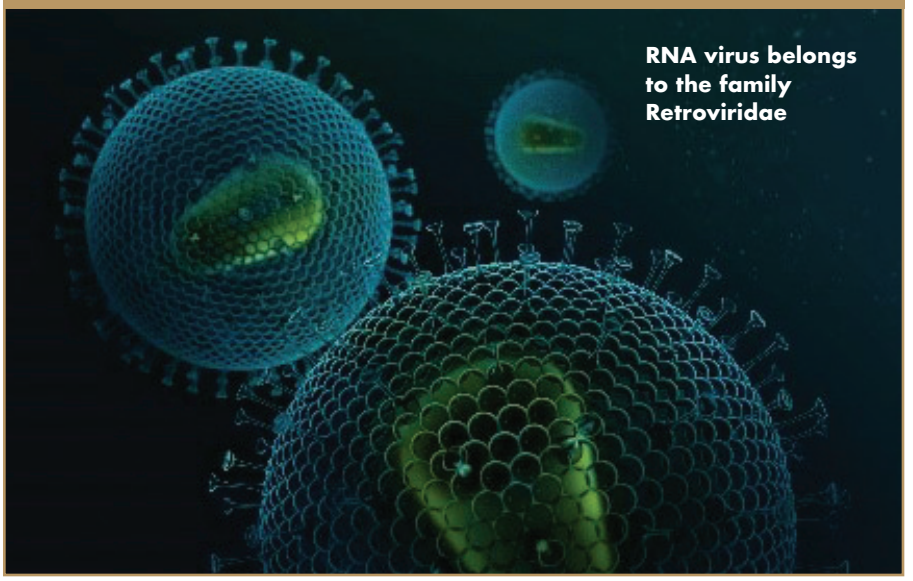
Adenoviruses are highly effective in transducing cells *in vivo*, eliciting a rapid onset of gene expression and inducing a strong immune response. Adenoviral immunogenicity has been excited in development of vaccines against human papillomavirus (HPV) and a novel class of tumor antigens using the rare, highly immunogenic adenovirus Ad19a/64 vector. And while some scientists do not believe adenovirus should be pursued for permanent replacement of genes, their utility for vaccination, they say, should be further explored.

Exemplifying the approach of using adenovirus as a potential cancer vaccine, Neukirch et. al. explored a cancer vaccine strategy using the murine model system of the murine melanoma associated retrovirus (MelARV), which is expressed in different murine cancer cell lines and that can be used to study mechanisms and therapeutic approaches against endogenous retroviruses (ERVs) in cancer.

The investigators designed a vaccine, (Ad5-MelARV), adenoviruses encoding the MelARV proteins Gag and Env, which assemble *in vivo* into virus-like particles displaying the cancer-associated MelARV Env to the immune system. The novel vaccine was designed to induce both humoral as well as cellular immune responses in order to attack ERV-expressing tumor cells.

While antibodies were not induced in

FIGURE 2



response to vaccination, elicited T-cell responses were strong enough to prevent colorectal CT26 tumor growth and progression in BALB/c mice after a single vaccination before or after tumor challenge. A combination with the checkpoint inhibitor anti-PD-1 further increased the efficacy of the vaccination leading to complete tumor regression.

The authors further noted that immune responses in vaccinated mice were not restricted to only one cancer cell-line, but vaccinated animals were also protected from a re-challenge with the distinct breast cancer cell line 4T1. Thus, the developed vaccine strategy could represent a novel tool to successfully target diverse ERV-bearing tumors in cancer patients.[4]

LENTIVIRAL VECTORS

Lentiviruses are an RNA virus that belongs to the family Retroviridae. A significant advantage to retroviruses as vectors for gene therapy is that they can accommodate a large insert size (7-8 kb) for the gene of interest and produce high titers.

Investigators have reported the replication-defective vectors from the lentivirus human immunodeficiency virus (HIV) and showed they transduce target cells independent of mitosis. The vectors proved highly efficient for *in vivo* gene delivery and achieved stable long-term expression of the transgene in several target tissues, such as the brain, the retina, and the liver and muscle of adult rats. A persistent remaining concern, however, is the biosafety of vectors derived from a highly pathogenic human virus.

These so-called "third-generation" HIV-1-derived lentiviral vectors have been highly engineered, and this third-generation Lentiviral vector system has many advantages, including high packaging capacity, stable gene expression in both dividing and post-mitotic cells, and low immunogenicity in the recipient organism. They also lack a potentially harmful promoter activity originating from their long terminal repeat sequences (self-inactivating (SIN) vector).

The most significant disadvantages are lack of cell specificity and the possibility of insertional mutagenesis.[5] The enzyme "integrase" inserts copies of the retroviral genome into the host cell chromosomes, but there is a risk of inserting the genome copy into an unfavorable location, such as a tumor suppressor gene or an oncogene, which would lead to uncontrolled cell division.

The most advanced gene or cell-therapy applications use Lentiviral vectors to transduce cells, most commonly hematopoietic cells, *ex vivo* before injecting them back into a patient. This approach is used to manufacture the most advanced genetically modified cell products (ATMPs) like CAR-T and gene-modified CD34+ cells.

FIGURE 3

SIRION Biotech has developed a Lentiviral vector enhancer called LentiBOOST™, which increases the gene transfer efficiency and long-term gene expression in patients. Moreover, the use of LentiBOOST™ increases the efficiency of this process and lowers manufacturing costs due to the significant reduction in vectors needed for production.

ADENO-ASSOCIATED VIRUSES (AAV)

A member of the Parvoviridae family, these are the new superstars in the gene therapy sector. Wild-type AAVs do not elicit any disease in humans and can elicit long-term gene expression.

AAV capsids can be engineered and targeted toward specific cell or tissue types. All these features make them ideal tools for modern gene therapy applications, and the rise in interest for this technology has been significant.

AAV is a small virus that allows packaging of 4.7-kb inserts. The virus has low toxicity, lacks pathogenicity, and provides long-term transgene expression.

The AAV genome contains two genes, rep and cap, that encode polypeptides essential for its replication and encapsidation. These two genes are flanked by viral Inverted Terminal Repeats (ITRs).

AAV requires co-infection with another helper virus (adenovirus or HSV) to mediate its replication. AAV serotype 2 (AA2) is the first and best characterized infectious clone to have been widely used to transduce neurons. Specific advantages of AAV vectors include their relatively broad host range, their ability to transduce both dividing and non-dividing cells, its lack of pathogenicity, and with their ability to elicit stable gene expression.

FIGURE 4

SIRION has collaborated with a network of leading partners in the development of novel evolved AAV vectors. Ongoing collaborations include the development of an optogenetic gene therapy for patients with Retinitis Pigmentosa and the development of a therapeutic gene delivery platform for CNS disorders.

To date, AAV has won clinical success as the FDA granted marketing approval to Spark Therapeutics for its Voretigene neparvovec (Luxturna™), to treat biallelic RPE65 mutation-associated retinal dystrophy, a rare genetic eye disease that gradually leads to severely impaired sight in childhood and, in some cases, blindness by adolescence. Luxturna has been shown to stop and even in some cases reverse the effects of the condition. Luxturna is the first directly administered gene therapy approved in the US that targets a disease caused by mutations in a specific gene, the RPE65 gene that encodes an enzyme that is essential for normal vision.

WHAT THE FUTURE HOLDS FOR VIRAL VECTORS

The future of viral vectors will need to focus on both increasing vector efficiency and manufacture productivity. The first factor and current bottleneck is the cost-of-goods when these vectors are produced under GMP conditions. uniQure's now famous $1-million gene replacement shot using AAV comes to mind immediately.

Similar challenges can be seen in CAR-T cell therapies, where the manufacture of genetically modified cells to combat cancer drives therapy prices up significantly. At every conference, companies tackle the question of increasing manufacturing productivity, new production cell lines, and manufacturing systems. For lentivirus-based gene therapies, SIRION has developed the LentiBOOST™ platform to increase gene delivery efficiency using lower amounts of LV and concomitantly lowering manufacturing costs.

Increasing vector efficiency, and, in particular, enabling gene transfer across the blood brain barrier is also important in addressing new treatment options, not only because less is more, but also in terms of addressing new treatment options for CNS disorders like Alzheimer's and Parkinson's Diseases with high unmet therapeutic needs.

Certainly, current efforts are directed toward reducing the immunogenicity of AAV vectors and neutralization by antibodies present in the population by preventing a vector re-administration. This aspect also drives developments and research in non-viral delivery technologies. A common theme for all gene delivery platforms is delivering the therapeutic gene to the right cells, which is at the core of SIRION's AAV development platform.

The growing number of clinical trials using viral vectors is proof of their boundless potential. Clinical efficacy and safety shown in recent gene therapy trials using SIRION technology have prompted significant investments from both biotech and pharma companies. Pioneering companies like Avexis, Baxalta (acquired by Shire and now Takeda), Biogen, bluebird bio, Celgene, GSK, Kite Pharma, Juno, uniQure, Shire, and Voyager among many others, opened the door for widespread investments into acquisitions and clinical developments of gene and cell therapies, all using viral vectors.

Despite the huge potential and clinical benefits of gene therapy, challenges remain regarding immunogenicity, duration of treatment, and specificity of gene transfer; however, the benefits of the therapy outweigh the potential risks, and offer new treatment options and real hope for patients. ◆

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BIOGRAPHY

Dieter Lingelbach is Chief Operating Officer and Executive Director of SIRION Biotech GmbH. SIRION Biotech possesses one of the world's most comprehensive viral vector technology platforms addressing all three major vector types – Lentivirus, Adenovirus, and AAV. Services range from custom virus design to virus vector productions and cell modelling projects, including multicistronic expression systems and superior gene-knockdown strategies (RNAiONE™). Mr. Lingelbach earned his MBA in Business Administration from Indiana University - Kelley School of Business.

CHIMERIC COMPOUNDS

"Dopastatins": One Molecule Targeting Two Receptors for the Treatment of Pituitary Tumors

By: Heather Halem, PhD, and Michael D. Culler, PhD

THE PITUITARY GLAND

The pituitary gland sits near the base of the brain and is responsible for the production of many different hormones, chemical messengers that circulate through the bloodstream to carry signals throughout the body. The pituitary gland is sometimes referred to as the master gland because it plays an important role in regulating multiple pathways and processes in the human body. For example, certain cells in the pituitary gland produce growth hormone (GH), which regulates growth and tissue repair throughout the body. Other examples include the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), two hormones key to reproduction and the development of sexual characteristics. Hormone production by the pituitary is continuously regulated by chemical signals from the brain, and by feedback from the target organs throughout the body.

AN INTRODUCTION TO PITUITARY ADENOMAS

Pituitary adenomas are tumors that arise from and grow within the pituitary gland. These tumors can be divided into two categories based on size: micro- or macroadenomas. Microadenomas are smaller than one centimeter, whereas macroadenomas are larger.

FUNCTIONING VERSUS NON-FUNCTIONING PITUITARY ADENOMAS

Pituitary adenomas are also classified as "functioning" or "non-functioning."[1] If pituitary adenomas produce active hormones, they are classified as "functioning," and result in diseases caused by hormonal excess. In addition, the growing tumor can cause symptoms due to pressure on surrounding structures (brain, optic nerves, normal pituitary tissue, etc). Other pituitary adenomas are "non-functioning," meaning they only secrete inactive hormone fragments and thus don't affect the normal processes in the human body.[2] Despite the lack of active hormone production, non-functioning adenomas are still dangerous due to their size. In fact, they can be inherently harder to treat than functioning adenomas. Because they generally do not cause symptoms while the tumor is small in size, they can remain undetected for extended periods. Consequently, at the time of diagnosis, these tumors are typically very large. They may also invade nearby critical brain structures, such as the optic nerve or other nerves and important blood vessels, leading to debilitating symptoms, including vision loss, severe headaches, loss of pituitary function, and diminished quality of life for a patient.[2] While the initial therapy for both types of pituitary tumors is usually some form of neurosurgery, in the majority of cases, surgery fails to completely eliminate the tumor. If the tumor is functional, surgery often fails to control the associated disease. Subsequent treatments aim to control excess hormone secretion (in functional tumors) and may be combined with repeated surgeries and radiation therapy to control tumor growth, which can result in permanent damage to

surrounding structures. Consequently, efforts are under way to develop a drug therapy to shrink or stabilize pituitary tumors.

TWO IMPORTANT RECEPTORS: SOMATOSTATIN & DOPAMINE

It has been established that receptors for the hormones dopamine, and somatostatin, which are natural regulators of pituitary function, are expressed at varying levels by many pituitary tumors. These hormones can also play an important role in tumor suppression and have been a target of interest for drug development for several decades. Most drug development efforts have focused on controlling hormone production by a functioning pituitary adenoma. One of the most studied diseases is acromegaly, a condition resulting from excess GH secretion.

A CLOSER LOOK AT ACROMEGALY

Patients with acromegaly produce an excess of GH, which in turn causes excess production of a hormone called insulin-like growth factor (IGF-1). When the disease occurs in children prior to puberty, the excess IGF-1 causes accelerated growth and abnormally tall stature, referred to as gigantism. In adults, the excess IGF-1 results in enlargement of the jaw and skull, bones, soft tissues, and certain organs. If left untreated, the excessive tissue enlargement may lead to serious life-threatening complications.[3,4]

It is now well-established that somatostatin suppresses GH secretion by acting through two different somatostatin receptor subtypes, SSTR2 and SSTR5. The pituitary adenomas that lead to acromegaly consistently express high levels of both. Given this, long-acting somatostatin analogues like octreotide and lanreotide have become accepted treatments for controlling GH secretion in patients with acromegaly.[5]

However, these widely used somatostatin analogs are only fully effective in normalizing GH and IGF-1 in roughly 35% of patients.[6] This is due to the fact that lanreotide and octreotide were developed prior to the identification of the somatostatin receptor subtypes, and before knowledge of the receptor subtypes involved in suppressing GH secretion in humans. Consequently, the currently available clinically used analogs of somatostatin are highly potent at SSTR2, but have only limited activity at SSTR5, which is now known to play an important role in suppressing GH secretion in humans.[6]

Developing an agent with high potency at both SSTR2 and SSTR5 demonstrated that combined activation of both SSTR2 and SSTR5 results in much greater efficacy in suppressing of GH; however, it was discovered that SSTR5 activation also directly suppresses insulin secretion from the pancreas and results in hyperglycemia. This negative side effect has limited the development of therapies that are highly active at SSTR5. Nevertheless, these studies established the concept that activating multiple receptors may offer enhanced therapeutic options for pituitary tumors, including those that cause acromegaly as well as other endocrine diseases.

A CLOSER LOOK AT PROLACTINOMAS

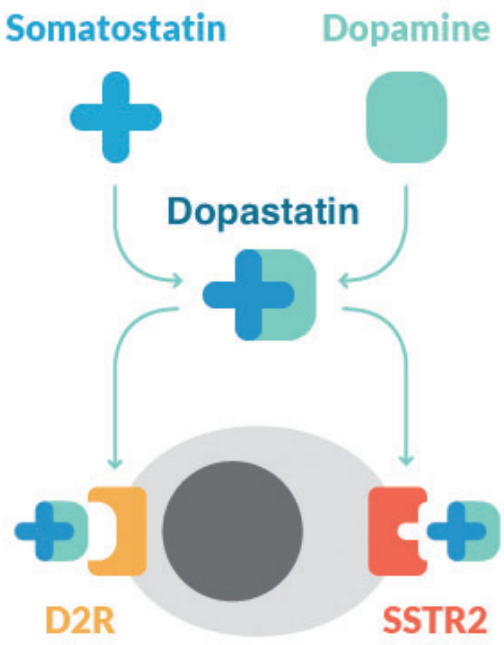
Another important regulator of pituitary function is dopamine. Among other roles, dopamine normally inhibits the secretion of prolactin, a hormone with many functions, including milk production in women after childbirth. A prolactinoma is a non-cancerous pituitary tumor that secretes excess amounts of prolactin, which can cause dysregulated breast milk production, reduced sex drive, and impaired reproductive function in affected individuals. Pre-menopausal women may also experience irregular menstrual cycles.[7] Prolactinomas are the most common pituitary tumors, with a prevalence ranging from 0.3 to 0.5 per 1,000 in the general population.[8]

Because prolactinomas express a subtype of dopamine receptor known as D2R, dopamine agonists specific to this receptor are widely used to treat these tumors.[9] Dopamine agonists selective for D2R, such as cabergoline, are also sometimes used to treat other pituitary adenoma types.[10]

A COMBINATION APPROACH

As somatostatin and dopamine-based medical treatments for acromegaly and prolactinomas became available, it was eventually demonstrated that a combination of somatostatin and dopamine receptor agonists results in greater control of GH and IGF-1 in acromegalic patients than the use of either agent individually.[11] These observations led to the idea of developing a single chimeric compound that interacts with both somatostatin and dopamine receptors (Figure 1).[12] When tested directly on tumor cells from acromegalic patients,

FIGURE 1



A dopastatin is a single chimeric compound composed of somatostatin and dopamine agonists.

the combination of individual somatostatin and dopamine analogs was no more effective in suppressing GH secretion than either agent alone. However, when the somatostatin and dopamine activities were present in the same, single compound, there was a tremendous increase in both potency and efficacy in suppressing GH secretion. Through additional studies, it was determined that the optimal chimeric drug compound should have potent SSTR2 and D2R activity with moderate activity at SSTR5, given the negative side effects observed with potent SSTR5 activation.[12]

USE OF SOMATOSTATIN-DOPAMINE CHIMERIC COMPOUNDS FOR THE TREATMENT OF ACROMEGALY

While an actual mechanism for the enhanced efficacy of the chimeric compound versus the use of individual agonists remains elusive, it has been hypothesized that somatostatin and dopamine receptors interact to form heterodimers (new receptors formed from the physical joining of the somatostatin and dopamine receptors) that lead to a greater effect when activated in comparison with activation of the individual receptors.[6]

Arising from optimization studies that tested a number of different chimeric compounds, the first lead chimeric compound identified was BIM-23A760 (now TBR-760), which demonstrates greatly enhanced potency and efficacy in suppressing GH and prolactin from cultured human pituitary cells collected from acromegaly patients who were resistant to conventional somatostatin analogue therapy. TBR-760 has also been tested in healthy primates and demonstrated to induce a dose-dependent suppression of GH and prolactin, without affecting either insulin secretion or glycemic control.

Human clinical trials demonstrated that TBR-760 induces prolonged suppression of prolactin levels in healthy individuals and suppression of GH in acromegaly patients without significant side effects.[12] When administered chronically, however, the compound's efficacy decreased over time. To investigate why, researchers analyzed patients' blood samples for major breakdown products (metabolites) in the body. They found a major metabolite with high affinity for the dopamine receptor that had a significantly longer duration in the blood than the parent compound, TBR-760. It is believed that the metabolite gradually accumulates and may bind to available dopamine receptors, reducing the number of available dopamine receptors available to bind to TBR-760. This, in turn, may have reduced the interaction of TBR-760 with somatostatin-dopamine heterodimers; however, TBR-760 was still able to bind to somatostatin receptors and thus still had some impact on GH. The result was that the added potency observed *in vitro* that is attributed to the effect of the chimeric was dampened.[6,13]

Nonetheless, the concept of a chimeric dopastatin compound as a treatment for acromegaly was demonstrated to be valid, and additional work exploring applicability and potential use with other pituitary tumors is well under way. Of particular interest is the use of TBR-760 as potential treatment for another pituitary tumor, non-functioning pituitary adenomas (NFPAs), in which the formation of the metabolite with potent dopamine activity could be a major advantage. If one considers the receptor ratio of relatively equal levels of dopamine and somatostatin receptors in acromegaly versus NFPA, the high level of dopamine and lower level of somatostatin receptor found in NFPA is well-suited to TBR-760 and its potent dopaminergic metabolite.[11,13] The metabolite will bind to dopamine receptors, but with the high level of expression, there will still be dopamine receptors available to allow TBR-760 to bind, as well as allowing the potential for it to interact with somatostatin-dopamine heterodimers and realize the added potency.

NON-FUNCTIONING PITUITARY ADENOMAS (NFPAs)

NFPAs only secrete biologically inactive subunits of hormones, so they do not produce any associated hormone excess syndrome. Because of this, NFPAs often grow very large by the time of diagnosis and may lead to debilitating symptoms if left untreated.[14] For example, the pituitary gland sits close to the optic nerves that connect the brain to the eyes. A growing NFPA can put pressure on these nerves, causing patients to experience vision loss. Additionally, because the pituitary is also situated near branches of the carotid artery, a key vessel that provides blood to the brain, pressure on the carotid arteries can compromise the blood supply of the brain. Other symptoms associated with NFPAs include intractable headaches from pressure on the brain and hormone deficiencies from crushing the surrounding normal pituitary tissue.[13]

Without available drug therapy, transsphenoidal surgery (TSS), an invasive type of neurosurgery to remove or reduce the tumor mass, remains the mainstay of treatment. While effective in rapidly relieving pressure on the surrounding structures, patients often experience regrowth of the tumor, which occurs in about 50% of cases as a result of residual tumor.[13] When regrowth occurs and threatens surrounding structures, at present, the only options available are repeated transsphenoidal surgery and/or radiation therapy, both of which significantly increase morbidities, such as the risk of hormone deficiencies, and there is even a small risk of mortality from radiation therapy. In addition, radiation therapy significantly increases the risk of stroke and neurocognitive dysfunction. Magnetic resonance imaging (MRI) scans are routinely used to monitor tumor recurrence and tumor growth. The need for continued monitoring and the risk of related disease complications creates a lifelong psychological and financial burden for both patients and caregivers.

A drug therapy that is able to shrink or stabilize NFPAs and that has the potential to prevent the need for surgery or radiation would be a welcomed, radical treatment paradigm change for patients with NFPA, their families, and physicians.[12]

USE OF SOMATOSTATIN-DOPAMINE CHIMERIC COMPOUNDS FOR THE TREATMENT OF NFPAS

NFPAs consistently express very high levels of dopamine receptors and express variable levels of somatostatin receptors.[12] Just as the enhanced efficacy of activating both receptors was demonstrated in acromegaly patients, this type of approach is also being considered as a therapeutic option for NFPAs. Although the chimeric dopastatin did not prove to be more effective than somatostatin analogs alone in acromegaly patients due to the formation of a potent metabolite that bound to dopamine receptors, it is hypothesized that the much higher ratio of dopamine receptors versus somatostatin receptors in NFPAs will allow both dopastatin and its metabolite to realize their full therapeutic benefit, by acting through both the dopamine and somatostatin pathways.

TBR-760 has been shown to suppress the growth of primary cultures of human NFPA cells.[12] In addition, in a mouse model that develops highly aggressive NFPAs, treatment with TBR-760 has been demonstrated to completely arrest tumor growth. These findings provide reason to believe that chimeric dopastatins, and specifically TBR-760, may represent the first effective drug therapy for the treatment of NFPAs.

LOOKING FORWARD

To date, there are only limited, invasive, and high-risk treatment options available for patients with NFPAs. Even after neurosurgery and radiation, many of these tumors recur. The need for continued monitoring and risk of developing complications also creates a significant burden for patients and caregivers and leads to increased healthcare costs.

Additional clinical studies are needed to determine the extent of tumor shrinkage or stabilization possible using dopastatins, and, ultimately, to understand whether this therapeutic approach can impact these tumors and potentially change the treatment paradigm. A Phase 2 clinical trial investigating the use of TBR-760 in NFPA patients is set to launch this coming year.

Dopastatins with different properties may also prove effective for the treatment of acromegaly or prolactinomas. Developing a compound with receptor affinities that closely match the receptor profile of the specific tumor type will be key in this endeavor.

Ultimately, this novel class of compounds represents a potential treatment for neuroendocrine tumors that are vulnerable to the synergistic dual activation of somatostatin and dopamine receptors. The potential to replace repeated surgeries, radiation therapy, and even first-line, initial surgery with a drug therapy that shrinks or stabilizes tumors is incredibly attractive. ◆

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BIOGRAPHIES

Dr. Heather Halem serves as Vice President, Research at Tiburio Therapeutics. She brings more than 17 years of pharmaceutical experience to Tiburio with strong expertise in rare endocrine and metabolic diseases, oncology, and in developing pharmacology models of disease. A senior, cross-functional project team leader, she has direct experience leading research programs that have taken molecules from early identification to clinic candidates. Prior to joining Tiburio, she spent 15 years at Ipsen Bioscience, serving most recently as Director, Endocrine Modeling. In the role, she led research project teams from early stage target identification and concept assessment through lead optimization and into the clinic. She also initiated and directed *in vivo* biology research efforts and strategies for all endocrine projects. Previously, she was a senior scientist at Genome Therapeutics where she identified novel gene targets for neurodegenerative diseases and she also served as a postdoctoral research fellow at Massachusetts General Hospital. Dr. Halem earned her BA in Biology from Macalester College in St. Paul, MN, and her PhD in Biology from Boston University. She holds two patents and has authored numerous papers in leading peer-reviewed journals.

Dr. Michael D. Culler is the Scientific Founder and Chairman of the Scientific Advisory Board at Tiburio Therapeutics. He brings over 35 years of research experience and is an internationally recognized expert in endocrinology, metabolic disorders, and peptide therapeutics with over 200 publications and 22 patents. He was formerly Vice President of Endocrinology Research for Ipsen, where he led programs in diverse endocrine/metabolic areas that resulted in five compounds reaching clinical development. He is a Co-founder of Rhythm Pharmaceuticals, and he led the preclinical programs that produced the key assets for both Rhythm (relamorelin and setmelanotide) and Radius Pharma (abaloparatide; Tymlos). Prior to joining industry, he conducted basic research in neuroendocrine physiology as a staff scientist at the National Institutes of Health.

Drug Development
EXECUTIVE

Ajay Damani
VP, Pharmaceutical Technologies Business Unit
Adare Pharmaceuticals, Inc.

Maria Flynn
President & CEO
Orbis Biosciences, Inc.

Adare Pharmaceuticals: A Virtual Acquisition is Possible

This past April, Adare Pharmaceuticals, Inc., a technology-driven specialty CDMO focused on oral dosage forms for the pharmaceutical, animal health, and OTC markets, in Lawrenceville, NJ, acquired the pharmaceutical technology company, Orbis Biosciences, Inc. of Lenexa, KS. The acquisition of Orbis will enhance Adare's Pharmaceutical Technologies business, which provides turnkey product development through commercial manufacturing for global markets.

Unlike traditional acquisitions made up of in-person meetings, this acquisition was completely virtual. The integration kick-off call, introductions, subsequent meetings, etc. were all done via Skype. It was not uncommon for these virtual meetings to last up to 4 hours at a time.

Orbis, which was founded in December 2007, always intended to merge with a larger company. Its Precision Particle Fabrication® technology produces uniform particles in a range of sizes for use in injectable, otic, and oral dosage forms.

While the latter is Adare's sweet spot, and Orbis' oral technology platform will expand Adare's offering in this space, the otic and injectable formulations offer additional market opportunities to Adare, which is privately owned.

Drug Development & Delivery recently spoke with Ajay Damani, Vice President of Pharmaceutical Technologies Business Unit, Adare, and Maria Flynn, President and CEO, Orbis, about how both companies will benefit from the acquisition, future product development, and the challenges of a virtual acquisition.

Q: Briefly describe Adare and Orbis and how the two came together. What are your commonalities? How will your differences benefit one another?

Ajay Damani: We are very excited to add Orbis to Adare. Adare has a suite of platforms primarily in the taste masking and controlled-release space for oral dosage forms. Adare's technologies include: Microcaps® for taste masking via a solvent- or aqueous-based coacervation process; Diffucaps®, which incorporates release-controlling polymers or protective coatings onto drug-layered cores, granules, or crystals; and the MMTS™ Multi Mini Tablet System in which functional membranes are applied to 1- to 2mm cylindrical tablets to control release rates. We found Orbis had a wonderful complementary set of technologies. Both companies are focused on taste masking and controlled release; both are focused on pharmaceuticals and OTC market segments; both companies utilize intellectual property (IP) in formulation to drive product development. So there are a lot of commonalities. Orbis also operates in the injectable space, which is an interesting market opportunity for us because none of Adare's technology platforms were able to address that before adding Orbis to the portfolio.

Maria Flynn: The companies have known each other for about 8 years. We saw a nice alignment between what both companies were doing. When Orbis was formed, it was always in the plan to merge into a larger company. We always intended to prove our technology, prove its application, develop IP, and integrate it into a larger company. We never had an eye toward building large-scale manufacturing capability. The integration definitely took longer than we expected, but everything always takes longer than you expect. This acquisition is a really good outcome and fulfills the vision of what the founders set out to do. We studied Adare's history and saw a pattern of them being able to bring in different technology and establish deep expertise and market presence in those areas, and really industrialize in those areas, and that was attractive to Orbis.

Q: How will Orbis and Adare benefit from this acquisition?

Ajay Damani: This acquisition is really for our customers. This is about broadening the footprint that we can provide to our customers that they can utilize to develop products that meet their patients' needs. We are looking forward to globalizing Orbis' technology and add to the established technologies that Orbis has in place, and make it better known and available to customers around the world. Adare operates in 100 countries, and we want to make sure the world knows about what the technologies are and how they can be used for product development. We also see a big opportunity in thinking about commercial manufacturing. Orbis' business model was really focused on early-stage product development and now, with Adare's expertise in scale-up commercial manufacturing, we are excited to provide that as an additional capability for customers. This makes us more of an end-to-end solution.

Maria Flynn: The global footprint that Adare has, and the deep expertise from formulation through manufacturing, will allow us to give our customers a complete turnkey offering. This is something we heard time and time again from customers and now we can do this for them as part of Adare.

Q: Please describe Orbis' platform technology, why it was attractive to Adare, and what makes it unique.

Maria Flynn: Orbis provides enhanced technologies in a scaled, single-step manufacturing process. Its core Precision Particle Fabrication technology is the only technology currently on the market that can produce uniform particles in size ranges suitable for use in injectable, otic, and oral dosage forms. We can control how the drug releases from the particles. The platform technology is flexible, reproducible, scalable, and customizable to accommodate a range of active ingredients, including small molecules, peptides, and proteins. Orbis' proprietary technology includes three platforms: Optimμm® for oral delivery; Stratμm™ for injectable delivery for extended release; and Unisun® for otic delivery. Optimμm aligns with what Adare does in the oral drug space. We bring in new areas for Adare with the injectable Stratμm platform and the Unisun platform.

Q: What new therapeutic areas will Adare pursue with these technologies?

Ajay Damani: We typically think about our tech platforms as being therapeutic-area agnostic. We look at small molecules and protein/peptide targets. We see ourselves enhancing what is in our pipeline and developing new product formulations with the Orbis technologies. Adare has a long history of developing and supplying multiparticulate-based products into OTC markets around the world. We see high levels of synergy with our platforms. We are exploring Orbis' oral platform in combination with our AdvaTab® OTC technology, and with our Parvulet™

technology, which is a platform we acquired last year that is targeted toward patients with dysphagia. We see a good opportunity in stand-alone technology, but also in combinations, including the Orbis multiparticulates with Adare's existing technology platforms. Customers are looking for a good taste masking solution and are pleased by the fact that they can now actually evaluate not one, but two, potential approaches using either Orbis' Optimum or Adare's microcapsule approach.

Q: What advice can you offer to other companies pursuing or undergoing an acquisition?

Maria Flynn: I compare this to heeding a mom's advice about choosing your spouse or partner wisely. It's a very individualized process. For Orbis, we needed to pick a company that had a real appreciation for differentiated technology, one that would value it and know what to do with it. Adare definitely does know what to do with it. We looked for alignment in mission and culture. The mission is what we are working to accomplish, and culture is how we accomplish that. Regarding mission, Orbis and Adare have really nice overlap. We talk about the same pain points for patients. Regarding culture, I have seen in the past how differences in culture can present problems when integrating acquisitions. In this case, we did a project together before the acquisition so Adare could "kick the tires" and see what our technology is like and how it differs from technologies they had in house. And it offered Orbis an inside look at what it would be like to work together. It's important to be honest about what you are bringing to the table. Orbis needed a manufacturing pathway to offer clients, and we had technology platforms that were attractive to Adare.

Ajay Damani: We were grateful for being able to execute a deal like this in the middle of a global pandemic. We learned it is possible to have a virtual integration. It's a new world, and we had to think creatively and differently about how to proceed on an integration plan and navigate through constraints such as travel restrictions. We have been diligent and proactive about being ahead of the curve. I believe our employees showed flexibility and resolve to make the connections we needed to make without seeing each other in-person, as is done traditionally. It is a testament to our teams. The only thing we could not do was go out to celebrate with a nice dinner after the closing. Nevertheless, we did have a virtual toast to the good things to come! ◆

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Special Feature

Outsourcing Formulation Development & Manufacturing: Specialized Capabilities for Small & Large Molecules

By: Cindy H. Dubin, Contributor

The demand for outsourcing pharmaceutical formulation development and manufacturing is on the rise for drug developers at all levels.[1] A new report predicts that the global contract development and manufacturing organization (CDMO) outsourcing market will to reach $44.17 billion during 2020-2024.[2]

Sectors of the CDMO market – sterile injectables, prefilled syringes, biologics APIs, and viral vectors – are expected to expand quickly, driven by an accelerating shift in the pharmaceutical market toward innovative biologic and cell and gene therapy products. Nonetheless, small molecules will continue to represent the majority of prescribed drugs for the foreseeable future and thus are the major growth driver for the CDMO market.[3]

Experts see a strong correlation between size of a company and its likelihood to outsource.[3] In 2017, manufacturing of 20% of newly approved drugs was outsourced by Big Pharma; this increases to 80% of all manufacturing being contracted out by small biotech/pharma. And all 15 newly approved drugs in 2017 owned by small companies were supplied by CDMOs.[4]

A Höfliger ModuleC LS is the centerpiece of precision filling capabilities at Experic, Cranbury, NJ.

In this annual *Drug Development & Delivery* magazine report, some of the key players in the CDMO market present case studies about how they are helping pharmaceutical and biopharma companies overcome a variety of formulation and manufacturing challenges.

Ascendia: Three Platforms Enhance Formulations

Ascendia offers tailored formulation approaches, leveraging its suite of technology platforms: NanoSol®, EmulSol®, and AmorSol®. The technologies are used to formulate biological therapeutic entities that could help address delivery issues associated with solubility, stability, and permeability.

NanoSol helps produce nano-sized drug particles; EmulSol is a technology for production of oil-in-water nano-emulsions; and AmorSol is for the production of amorphous solid dispersions.

Jim Huang, PhD, Founder and CEO of Ascendia, explains that the versatility of these technologies for use in both small and large molecules has grown the company's oral and injectable business. In some cases, the technologies have been used to deliver large molecules orally by enhancing GI stability and permeability.

"A client approached us with a peptide that has a high molecular weight for delivery by oral route of administration," he describes. "There were three delivery challenges facing the peptide: solubility, permeability, and GI stability. Using Ascendia's EmulSol technology, we dramatically improved bioavailability of the peptide in animal models to enable further development of the project by oral route," he says.

Catalent: Providing Small-Molecule Options for Expedited Programs

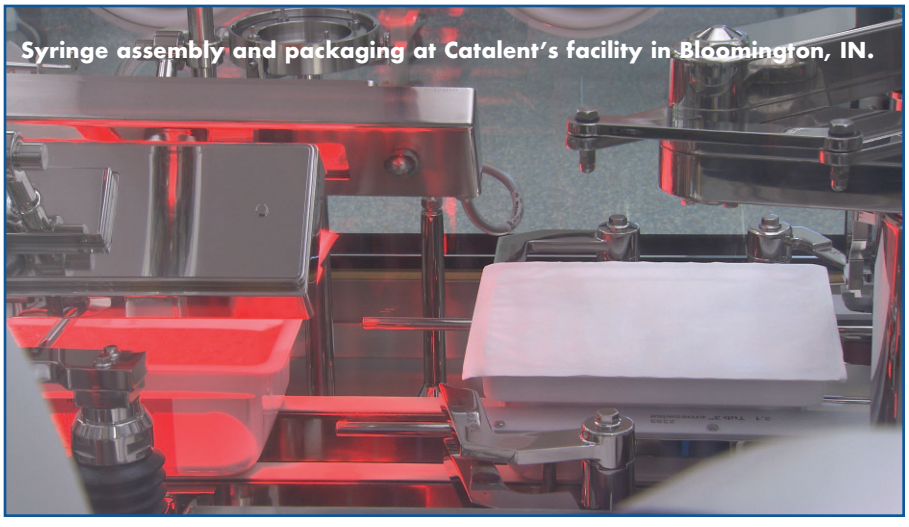
Rare diseases, fast-tracked drugs, and oncology treatments now account for much of pharma's development pipeline, so it is important that CDMOs provide specialized capabilities, technology, expertise, and experience relevant to these types of programs. For expedited pathways, it is important, too, that development partners understand the interwoven and related steps essential to progressing a program efficiently and quickly. To that end, Catalent has invested in technology and capabilities such as hot melt extrusion, spray-dry dispersions, and lipid formulation to provide options for small-molecule development, often to address the all-too-common hurdle of poor solubility and bioavailability.

"By leveraging relevant experience and drug development knowledge, we can demonstrate strategies that maintain the integrity, quality, and timeliness of the development and manufacturing processes at the accelerated pace required of expedited programs," says Elliott Berger, Vice President and Chief Marketing Officer, Catalent.

As an example, MGB Biopharma, a biotech company based in Scotland, is developing a new class of anti-infective medicine based on Minor Groove Binder compounds. MGB-BP-3, a novel small molecule, is currently in Phase 2a in the US and Canada. The drug is being developed for the treatment of clostridium difficile-associated diarrhea. Catalent offered a tablet formulation through its OptiForm® Total Supply solution, incorporating formulation development, clinical trial material manufacturing, and supply and distribution to patients. The first clinical trial kits were successfully delivered to MGB's patients within six months.

Catalent recently announced biologics-related COVID-19 programs, including helping to accelerate the availability of manufacturing capacity for Johnson & Johnson's lead vaccine candidate. Additionally, Catalent partnered with Arcturus Therapeutics to support the drug substance manufacture of its COVID-19 mRNA-based vaccine candidate. "Catalent continues to expand its biologics drug substance capabilities and capacity significantly with a fourth and fifth biomanufacturing train in Madison, WI, and the recent completion of a $14 million commercial packaging expansion, in Bloomington, IN.

In February 2020, Catalent completed the acquisition of MaSTherCell to add cell therapy to its technology-focused cell and gene therapy CDMO capabilities.



Syringe assembly and packaging at Catalent's facility in Bloomington, IN.

The acquisition complements the specialized expertise in gene therapy and adeno-associated virus (AAV) vectors that Catalent acquired with Paragon Bioservices in May 2019.

HERMES PHARMA: ODG Formulation Expanded Sponsor's Brand

Many people experience swallowing difficulties with traditional tablets and capsules, so pharmaceutical companies are looking for ways to address this problem. Sponsors look to HERMES PHARMA to access experience in user-friendly oral dosage forms, for existing products or as part of new product development. As a full-service CDMO, HERMES PHARMA can take a product from technical through to regulatory and clinical development, a capability its customers increasingly require.

As specialists in innovative, user-friendly oral dosage forms – such as effervescent and chewable tablets, orally disintegrating granules (ODGs), and instant drinks – HERMES PHARMA is actually seeing a growing market for such products as patients increasingly exercise choice and manufacturers compete to deliver what consumers want.

"Taste masking is critical to the acceptance of many orally administered products, especially those with a long residence time in the mouth, such as ODGs," says Dr. Martin Koeberle, Head of Analytical Development & Stability Testing, HERMES PHARMA. "We recently deployed a solvent-free hot melt coating (HMC) technology capable of masking even very sour and metallic tastes. HMC involves covering the API solid core with a molten coating at a controlled temperature, which then solidifies to create a homogeneous coating."

He explains that HERMES PHARMA used this technology for a client whose generic, over-the-counter (OTC) drug was formulated as an effervescent tablet, but wanted an additional 'on-the-go' oral formulation to meet consumer demand. "However, the taste characteristics of the API were poor, making the desired re-formulation difficult. Our use of HMC to mask the taste enabled the successful development of a new formulation in the form of ODGs that require no preparation and can be administered directly, extending our client's product range and adding greater value to the brand."

Dr. Koeberle points out that while the ease, convenience, and relatively low manufacturing costs of orally administered formulations means there will always be a strong market for them, there are challenges, such as making sure that regulatory bodies receive and fully understand data that is appropriate for novel approaches.

Hovione: Particle Engineering for Small & Large Molecules

Hovione has strategically decided to explore niche areas that are difficult to tackle and can benefit from its expertise in particle engineering. Examples include the oral delivery of Amorphous Spray Dried Dispersions and the manufacturing of dry powders for inhalation.

Historically, Hovione has mainly focused on small molecules and their pre-formulation, by means of particle engineering, to overcome solubility limitations or to render them suitable for inhalation. In recent years, Hovione has experienced some challenges with large-molecule particle engineering, but intends to increase its activity in this area. "The delivery of large molecules is leading us to novel areas of aseptic particle engineering that we will be introducing in our portfolio," says Teresa Alves, PhD, Senior Director, Science & Technology, Hovione.

Dr. Alves adds that there are opportunities to apply lessons learned with small molecules to large molecules. "We see a trend in the increased delivery of biologics by inhalation, particularly dry powder inhalation, including the delivery of peptides, proteins, hormones, DNA, RNA, etc. We are also actively working to process low bioburden biologics to solve difficulties that our clients experience in limited shelf life, high viscosity, and new areas of administration."

Márcio Temtem, PhD, Site Manager, R&D services, Hovione, explains how the company's sponsors have benefitted from Hovione's experience in spray drying. "Spray drying scale up runs with minimum work at scale," he says. "This is what we call Development by Design. By relying on stasticial and mechanistic models, databases, and scientific know-how, we can save API and time required for CMC process development. We have successfully applied these tools to biologic molecules, namley proteins, antibodies, and fragments of antibodies, and some of these solutions have evolved to commercial manufacturing."

Lubrizol Life Science Health: Early Engagement in Complex Formulations Ensures Scalability

Getting a CDMO engaged in the development process as early as possible avoids spending time exploring the wrong solutions and coming up with suboptimal formulations that need to be corrected be-

fore manufacturing.

"By bringing us in earlier in the process, we can more accurately assess which technologies and approaches can work on a project," says Robert Lee, President of Lubrizol Life Science Health, CDMO Division. "To help with this, we have created feasibility programs for nanomilling and microspheres designed to accelerate product development and provide early-stage support. If a feasibility program proves successful, we are positioned to provide ongoing optimization, scale-up, and manufacturing."

He says Lubrizol's proprietary LyoCell® technology combines a lipid-based approach with nanoparticles, while leveraging the power of a reverse cubic-phase matrix. This assures that the hydrophobic and hydrophilic domains in these nanoparticles are never more than a few nanometers apart, which may lead to unique solubilization properites, he says. Intended for a broad range of applications, LyoCell technology uses Generally Recognized as Safe (GRAS) ingredients and is useful in virtually every route of administration, including injectables.

"Although nanomilling has been around for decades, it is a go-to technique for certain APIs," he says. "The value is especially significant for parenteral dosage forms because this may provide a pharmaceutically elegant formulation, i.e., neutral pH, isotonic, minimal excipients, and the bulk of the composition being water followed by API."

Clients come to Lubrizol with complex development challenges. "Often, these are great product ideas, but their formulations were developed in an R&D environment by organizations without much experience in developing complex dosage forms intended for cGMP manufacturing for clinical use," says Mr. Lee. "We transfer in these lab-scale formulations and create a viable product by using a scalable process in conjunction with optimizing the formulation. This translates it into something that is acceptable for GMP production and ultimately commercial production."

An example is when a client requested that Lubrizol develop a transdermal patch to deliver two APIs – one very potent and at a very low concentration, and the other not as potent, but at a much higher concentration. After evaluating the physicochemical properties of the APIs, loading, and target flux, Lubrizol recommended a gel, rather than a patch.

"At first, our client was not fully convinced, however, due to limitations with the composition of the delivery system, very little of the APIs were released and the levels were unable to reach therapeutic concentrations," Mr. Lee explains. "After this, we were given approval to develop a gel. The gel development program was extremely successful, and our formulation was progressed into Phase 2 studies."

Metrics Contract Services: Full-Service OSD Development

Metrics Contract Services, a division of Mayne Pharma, is a targeted specialist in the novel oral solid dosage (OSD) development space, providing early-stage development through global commercial supply. A recent major expansion of its North Carolina campus brought a new commercial manufacturing facility online, enabling Metrics to offer services under a single FDA registration service, ranging from first-in-human development and clinical trial materials to global commercial supply. Potent handling and analytics round out clinical-to-commercial capabilities.

John Ross, President, Mayne Pharma USA, says the small-molecule OSD segment remains the largest market within pharmaceuticals, and continues to grow at a rate of 6% annually, representing significant opportunity for growth. Occasionally, some large-molecule OSD opportunities exist, and Metrics is currently engaging in some of those.

With regard to small-molecule OSD, a Metrics client had developed a simple direct-blend capsule formulation consisting of three potencies: 2mg, 10mg, and 50mg capsules. The manufacturing process had been scaled up to an automated encapsulation process. While the 2mg capsule drug load was about 1.5%, the drug load of the dose-proportional strengths 10 and 50mg were 10%, respectively, explains Thomas B. "Brad" Gold, PhD, Vice President, Pharmaceutical Development, Metrics Contract Services.

This presented a few problems. First, blend uniformity values for the 2mg potency were unacceptable and were confirmed with content uniformity that likewise did not meet specification. Second, the capsule sizes used were on two extremes (Size 4 and Size 00), which were considered to pose patient compliance issues (size 00) and manufacturing issues (size 4) during the automated encapsulation process.

To resolve these problems, Metrics scientists improved blend uniformity by incorporating a geometric blending strategy with alternate blending and sieving steps. The blend was milled before adding the final geometric portion of excipients. Also, Metrics scientists collected and tested blend uniformity samples at pre-determined points during blending to optimize blending time. Bend uniformity improved significantly with this strategy, says Dr. Gold.

Subsequently, scientists developed a granulation process for a compressed

tablet dosage form, which theoretically would address both blend uniformity and capsule size issues. "The result was a successfully developed and manufactured lead tablet formulation using a dry granulation process," he says. "Blend uniformity improved significantly for the tablets, as did content uniformity. Moreover, scientists made all the required tablet strengths in patient-friendly sizes and shapes." Clinical trial material is scheduled for manufacture in Q3 2020, pending stability results of the tablets.

Quotient Sciences: Translational Pharmaceutics Streamlines Development

"Biotech and pharma sponsors select Quotient Sciences as their formulation and manufacturing partner because they need program acceleration," says Nutan Gangrade, Global Vice President, Pharmaceutical Sciences, Quotient Sciences. "Scientific expertise, technical competence, and quality are paramount, but being able to shorten drug development times for our customers by more than 12 months is a game changer."

One way to improve efficiency and shorten development timelines is to break down the barriers between product manufacturing and evaluation in clinical trials. Quotient Sciences has bridged this gap by establishing an operational platform called Translational Pharmaceutics® that integrates formulation development, real-time product manufacturing, and clinical testing. "By combining the work of CDMOs and contract research organizations (CROs) in one offering, outsourcing and program management are simplified and streamlined, and development times and costs are significantly reduced," he says.

The outcomes from a recent study by Tufts Center for the Study of Drug Development (CSDD) demonstrate that Translational Pharmaceutics creates substantial benefits to pharma and biotech companies compared to traditional multi-vendor development approaches. The Tufts CSDD team evaluated data provided by Quotient for a range of programs conducted over the past decade, including actual dates taken from executed Translational Pharmaceutics project plans. A group of independent industry consultants provided benchmark data for conventional timelines for similar programs to enable comparison and identification of time and cost savings.

Although the Translational Pharmaceutics platform can be applied to nearly any development project, the Tufts study focused on three applications with small molecule oral drug candidates: the transition from first-in-human to proof-of-concept; the development of drug products that required enhanced solubility through formulation control; and the development of modified-release formulations. The Tufts CSDD research concluded that applying the integrated approach of Translational Pharmaceutics to the programs resulted in mean time savings of >12 months and R&D cost reductions of >$100 million per approved molecule.

Mr. Gangrade says that Quotient Sciences has developed state-of-the-art facilities in the UK and US for formulation development, GMP manufacture of clinical trial materials, and for running adaptive development programs. To date, Quotient has completed more than 400 programs using Translational Pharmaceutics with molecules across the development spectrum, including the acceleration of first-in-human to proof-of-concept programs, the optimization of clinical formulation compositions, and as part of late-stage or lifecycle management programs (505(b)(2) projects).

"Biotech and pharma sponsors also achieve other benefits with Translational Pharmaceutics, including formulation screening and bridging within a single clinical protocol, maximizing potential for "right first time" by using clinically driven decisions, seamless supply of drug product(s) into subsequent patient studies, significant reductions in drug substance (API) consumption, and supply chain efficiencies," he says.

Recipharm: Tackling Complexity in Scale Up

There is strong interest in orphan drugs, specialized treatments, and innovative drug products based on existing molecules. Recipharm solves different challenges and manages complexity when developing and scaling up these innovative products, explains Torkel Gren, Science & Technology Officer, Recipharm. "Our end-to-end development and manufacturing offering is one of the advantages of working with Recipharm as it means we can simplify a molecule's journey to market."

As an example, Recipham was selected by the Swedish speciality pharmaceutical company, Lobsor Pharmaceutical AB, to devlop its Lecigon gel designed for the treatment of advanced Parkinson's disease (PD). The gel is administered to the small intestine via a portable pump, overcoming the traditional challenges associated with alternative IV-based solutions. "Throughout the development process, we performed all the formulation work, as well as developing the necessary analytical methods," Mr. Gren explains. "However, the complexity of the formulation meant that we faced several hurdles during the process."

In this instance, combining multiple APIs into a single formulation created some

challenges, primarily because each compound called for specific formulation features to ensure optimal properties, such as stability. There was also a heightened risk that the APIs would affect the stability of each other, especially in a gel formulation. The presence of several APIs also increased the complexity of the analytical methods required, making the development of suitable analytical chemical methods even more complex.

"Our team formed a project group during the initial stages, which brought together experts across various areas in the organization: formulation, manufacturing technology, packaging, analytical chemistry, and quality assurance," he says.

This helped ensure any processes developed remained suitable during the scale-up phase. To initiate the development process, a risk-based assessment of the intended product, including identification and assessment of the Quality Target Product Profile (QTPP) and corresponding Critical Quality Attributes (CQA), was undertaken. Mr. Gren says: "This provided a solid starting point and ensured subsequent work focused on the critical aspects of the product."

Singota: Preserving APIs in Biologics Manufacturing

The biologics market for fill/finish has been growing considerably, and many CDMOs are catering to pharmaceutical companies that have high-value, small batch-filling needs. Handling high-value, complex active ingredients requires an aseptic dosage manufacturer to protect against unnecessary loss of active ingredient.

"Special handling of biologics starts the minute the materials enter the facility by supply chain operators," says Laura Englander, Senior Business Development & Marketing Manager, Singota.

The Vanrx SA25 Aseptic Filling Workcell at Singota Solutions' facility.

Once received at the finished product manufacturing facility, the bulk drug substance is subject to numerous sampling and testing procedures. When manufacturing small batches, the portion of the total bulk active consumed by QC-related activities can amount to a large portion of the overall consumption of active for any given production batch, she explains. "It is important to consider sampling requirements and to minimize the consumption of the precious material while still meeting stringent testing requirements," she says.

An important early task for pharmaceutical companies, often in conjunction with their CDMO, is to produce a prospective estimate of the non-production-related needs for active ingredient to ensure that sufficient material will be available to support the manufacture of the required number of units of finished drug product to meet production goals. "Especially for early clinical trial production, working with a CDMO who understands the areas in which to minimize client material loss can be an effective means of reducing the use of precious active ingredient while remaining compliant with regulatory guidelines," says Ms. Englander.

To help biotechnology and pharmaceutical clients meet the challenges they face in producing small to medium-sized batches of sterile injectable products, Singota invested in the Vanrx SA25 Aseptic Filling Workcell in 2016. The technology combines gloveless isolator technology with high-precision robotic handling and filling equipment.

At Singota, formulation and sterile filtration are typically performed using single-use systems that are connected to the pre-sterilized disposable product filling pathway. Setup of these systems is simple and standardized across a variety of batch sizes and container/closure combinations. Assembly configurations minimize the product hold-up volume between the bag assembly and the filling needle. She explains: "For a batch with a fill volume of 1mL, the initial filling pump calibration consumes only a few doses of product, filtration loss, and end-of-batch holdup volume are negligible, resulting in overall product loss of less than 10mL. The result is a high yield of finished drug product."

Almac: Tailoring Solutions for Individual Drugs

Drug product type is always changing. Almac, a CDMO specializing in the development and manufacture of solid, oral dose, and small molecules, is witnessing a significant growth in developing and manufacturing age-appropriate formulations, especially for pediatrics, mainly multi-particulate formulations such as mini-tablets filled into stick packs.

Although Almac specializes in the clinical and commercial manufacture of solid oral dosage forms, the CDMO also has a range of solutions for labelling and packaging injectable drug products across its commercial facilities in the US, EU, and UK. "We continue to invest in our commercial packaging capabilities from vial and syringe labelling to semi-automated complex kit assembly," says John McQuaid, Vice President Technical Operations, Almac.

Almac supports the launch and market supply of several gene/cell therapies from its European Campus in Dundalk, Ireland. "With each cell/gene therapy product having its own unique handling, packaging, and 3PL distribution requirements, flexibility, responsiveness, and providing a tailor-made solution for every client is paramount," says Mr. McQuaid. "An example of our tailor-made, ultra-low temperature product solutions would be upon receipt of an order, which, depending on the gene therapy, could be as niche as one vial per batch. Our specialist team picks the product from storage, labels, packs over dry ice, and distributes direct to the end user within 24-48 hours."

A recent case study involved a client partner moving from a transactional fee-for-service model to one that enabled dedicated capacity on key Xcelodose technology to support clinical trials. Mr. McQuaid says: "The key element that made the 'reserved capacity' business model a success was the establishment of dedicated teams on both the Almac and client side, underpinned by strong project management. By utilizing this flexible business model, the client partner was able to secure capacity on Xcelodose technology, providing full flexibility of resource utilization to meet any changes in demand for the development of their portfolio of early-phase drug products."

Experic: Process Feasibility Mitigates Process-Related Risks

Many organizations that develop drugs focus primarily on what to make and not how to make it, even though the way in which a product is made can impact its ultimate performance. That is where Experic steps in. "We help companies optimize their products for clinical trials — from manufacturing, packaging, and labeling to clinical supply logistics — and then transition to eventual commercial-scale production," explains Jeffrey P. McMullen, Chairman and CEO, Experic.

Experic currently serves companies with both small and large molecules in their pipelines. While the delivery platforms differ for small and large molecules, Mr. McMullen says Experic complements its oral capsule-based technologies with inhalation- and autoinjector-based manufacturing technologies, and provides packaging, labeling, kitting, and clinical supply management services for both types of molecules.

A primary goal at Experic, he says, is to ensure process feasibility and robustness as clients progress their products from clinical development to commercial-scale production. A Modu-C LS is a modular trolley-based system with fast interchange of dosing systems that can fill up to 25,000 capsules per hour with up to100% inspection via an in-process control check weighing or Advanced Mass Variation sensor. Features include quality checking of capsule integrity, a capsule polisher, and metal detection system.

Understandably, companies want to know how to best manufacture their products. As a recent example, a leading pharmaceutical company contacted Experic about struggling with a new process development project. "We conducted a series of manufacturing experiments to evaluate the characteristics of that client's product," says Mr. McMullen. "From this data, we found that its cohesiveness and propensity to adhere to equipment surfaces created barriers to achieving a robust manufacturing process. This led to revisions in the process that allowed development to progress."

Early development of pharmaceuticals rightfully focuses on efficacy and safety, but delays in optimizing process development of the finished dose can result in some unwelcome late-stage surprises. "That is why we strongly encourage companies to consider manufacturing feasibility assessments early in the development process," says Mr. McMullen. "This allows clients to best capitalize on the investments made in their product and avoid scale-up delays on the pathway to commercialization. Experic's approach combines the application of equipment capabilities, powder handling expertise, and an understanding of the critical quality attributes of a product. This gives us the perspective to solve both manufacturing problems and to identify and mitigate related process risks."

Spray drying of highly potent drugs at Idifarma's facility.

Idifarma: Highly Potent Small-Molecule Capabilities

The growing demand for high potency active pharmaceutical ingredients (HPAPI) in drug manufacturing is fueling the need for high potency handling capabilities. Idifarma has specialized capabilities for niche and highly potent drugs as well as spray drying capabilities. This attracts low-volume projects involving highly potent drugs.

"The capacity to handle highly potent compounds and the flexibility to manufacture small-scale batches are increasingly important for many of our customers and products," says Manuel Leal, Business Development Director at Idifarma. "While many firms offer spray drying, Idifarma is one of only a handful of firms worldwide that can do so for highly potent drugs, such as hormone and oncology drugs, while also integrating the manufacturing of finished drug products in oral solid forms in the same facilities."

Idifarma is catering to a growing segment in the small molecules field: oncology treatments. Within the small molecule space, oral drugs remain one of the preferred options (over 50% of total small molecule drug products are oral) due to its cost-effectiveness and patient friendliness. "Our ability to manufacture highly potent drugs and small batches, which is required for many of them, and our differentiating technologies, enable us to collaborate on projects involving innovative and hybrid drugs," he says.

He points out that Idifarma has collaborated on many projects with a focus on challenging drugs. For instance, in a recent project, Idifarma scientists increased the solubility of a BCS Class II product 8 times, helping achieve the same therapeutic effect with a lower amount of API. "Improving the bioavailability of poorly soluble APIs is one of the most common challenges in the industry," says Mr. Leal. "In another project, we reformulated an injectable drug for a severe indication as an oral dosage form, resulting in great advantages for the patients and for the sustainability of the healthcare systems."

MedPharm: Live-Agent Topical, Transdermal Formulations

MedPharm's growth over the last few years can be attributed to developers recognizing that the topical and transdermal area, while having many unmet medical needs and offering attractive returns, requires specialist knowledge that they typically do not have in house. This increased recognition has coincided with MedPharm developing sophisticated *in vitro* performance models based on fresh human tissue to ensure optimal formulation development and the de-risking of programs before important investment and/or clinical decisions are made. MedPharm has expanded its services in this area to cover applications to the eyes, nose, and lungs as well as skin and mucosal membrane epithelia. The most recent model allows clients to screen compounds targeting coronaviruses using infected cultured human nasal or lung tissue.

MedPharm works with a range of clients, including those who want to deliver topically live agents, such as bacteria or viruses/phages. The is partly fueled by the interest in the microbiome on skin and mucosal membranes. "These products have their own challenges, particularly with respect to scale up and manufacture," says Jeremy Drummond, Senior Vice President of Business Development at MedPharm. "At this point, MedPharm is supporting clients in product development and we have invested in the analytical procedures needed for these agents."

Cost-effective process development of complex cream ensures consistent quality and on-time delivery of product at a time when a quality failure or delay can have severe financial conse-

Recro Gainesville supports challenging development and manufacturing projects for oral solid dosage forms, such as those with complex modified-release requirements.

quences for a project. Recently, the MedPharm team was asked to provide multiple 25kg batches of a complex cream for a Phase 2 atopic dermatitis clinical trial by a large global pharmaceutical company. "Failure to supply or delay would increase the time to market (lost sales) and halt the start of the scheduled clinical trial (increased costs)," Dr. Drummond says.

MedPharm identified the Critical Process Parameters (CPP), such as homogenization speed and time, and cooling rates at different stages. A suitable factorial design of 12 runs using 1kg lab reactors, which model the large scale, was developed. Then, a key Critical Quality Attribute was identified to be the rheology profile of the final product. Dr. Drummond explains that this work showed that the rheology could be particularly sensitive to the homogenization time and speed, and appropriate parameters were set. An initial run at the larger scale confirmed that the selected process and parameters resulted in a product that met all specifications. This all could be achieved without delaying the project.

"Subsequently, more than 15 clinical batches were manufactured under cGMP with reproducible quality using the optimized process and used in clinical trials," he says. "Given the sensitivities to key parameters observed, this almost certainly would not have happened without the process evaluation work. Additional large-batch production would have wasted significant amounts of a high-value API and impacted the completion of the clinical trials and subsequent product launch."

Recro Gainesville: Handling Challenging OSD Formulations

All clients of Recro Gainesville have one thing in common: complex issues that need to be addressed and not a lot of time to address them. As an agile CDMO, Recro Gainesville shepherds projects through the development process and manufactures products as they progress through various clinical phases leading up to a regulatory submission.

"Clients have a certain peace of mind knowing they can start a development project with Recro and see that product all the way through to commercialization with the same company," says Myke Scoggins, PhD, Director, Product Development at Recro Gainesville. "This eliminates costly delays they would normally encounter having to conduct transfers between stages of development and then finally to a commercial manufacturer."

Recro was presented with a project that had two APIs that were incompatible with each other. In addition to incompatibilities, there was a need for an immediate-release pulse for both APIs as well as a modified-release portion for maintenance of plasma levels to achieve reduced daily dosing. Recro took the approach of formulating a multiparticulate pellet system using a rotary granulation process. Inert sugar spheres were used as a substrate onto which API was applied by powder layering. Each API was individually processed to form two separate populations of pellets. These pellets were coated with a nonfunctional (in terms of release rate) coating to provide a protective layer between the APIs to mitigate the incompatibility issue.

Dr. Scoggins explains that at this point in the process, Recro had manufactured two immediate-release sets of pellets. "We then took parts of each population of immediate release pellets and further processed them with a modified-release coating," he says. "We now had four individual sets of pellets, an immediate release for each API, and a modified release for each API. Using our encapsulators, we then filled pellets in specific ratios to obtain the correct strength. Formulation, process development, and desired dissolution profiles were successful for this product." ◆

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Technology & Services Showcase

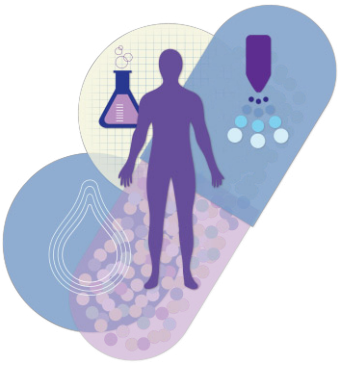
Formulation Development

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

Small Molecule CDMO

Cambrex is the leading small molecule company for drug substance, drug product, and analytical services across the entire drug lifecycle. With over 35 years' experience and more than 2,100 experts servicing global clients from sites in North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and dosage form development and manufacturing. Cambrex offers an end-to-end partnership for the research, development, and manufacture of small molecule therapeutics along with a range of specialist drug substance technologies and capabilities, including biocatalysis, continuous flow, controlled substances, solid-state science, material characterization, and highly potent APIs. The team has expertise with conventional dosage forms, including oral solids, semi-solids, and liquids, as well as with manufacturing specialized dosage forms, such as modified-release, fixed-dose combination, pediatric, bi-layer tablets, stick packs, topicals, controlled substances, and sterile and non-sterile ointments. For more information, visit Cambrex at **www.cambrex.com.**

Modified-Release Technologies



Catalent, with its broad toolkit of drug formulation and delivery technologies, offers a number of solutions for drug developers looking for modified-release dosage forms. These include the use of enteric coatings on traditional softgels, or the use of its OptiShell® gelatin-free softgel capsule technology, which is ideally suited for the encapsulation of higher melting-point fill formulations. The Zydis® platform offers industry-leading orally disintegrating tablet (ODT) formulation for fast-dissolving dose forms, and through the expanded Zydis Ultra technology, drug loadings can be up to four times higher, broadening the range of drug molecules that are now applicable to ODTs. Catalent is highly experienced in offering solutions to clients for controlled-release dosage forms, such as bi-layer tablets, drug-layered spheres, as well as tablets within capsules. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Differentiated Injectable Delivery

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change*. By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com.**

Technology & Services Showcase

Super Refined™ Excipients

CRODA

Croda manufactures a complete range of high purity excipients and delivery aids, offering superior quality for the global pharmaceutical market. These excipients are ideal for multiple dosage forms, including topical, parenteral, oral, and ophthalmic formulations as well as advanced delivery systems. Croda's Super Refined™ excipients go through a proprietary process to remove the polar and oxidative impurities that can cause performance and stability issues. These excipients are ideal for use when working with sensitive drug actives, helping to maximize the stability and overall performance of the drug product. Excipients in the Super Refined range include PEGs, polysorbates, oils, and triglycerides, propylene glycol, castor oil, and a range of topical penetration enhancers, such as oleic acid and dimethyl isosorbide. For more information, contact Croda at (732) 417-0800 or visit **www.crodahealthcare.com.**

Enteric Coatings

New platinum standard for enteric coatings: Evonik has created an advanced combination polymer solution for enteric coatings to reduce processing complexity, lower preparation times and save costs. EUDRAGIT® FL 30 D-55 combines the respective benefits of two existing polymers with well-accepted monographs including EUDRAGIT® L 30 D-55: the gold standard for enteric coatings since 1955. Being highly flexible, plasticizer-free and able to be sprayed with a smooth, fast and no-stick process, it is ideal for microparticulates and other dosage forms that require excellent adhesion. As a single product, preparation times can be reduced by up to 70%. With only a thin film able to provide reliable enteric protection, it creates options for higher drug loadings. For more information, contact Evonik at **healthcare@evonik.com.**

Formulation Support, Lipid-Based Technologies

GATTEFOSSÉ

With application and R&D Centers in the United States, France, India, and China, the **Gattefossé** group is providing formulation support for oral, topical, transdermal, and other routes of administration. Equipped with state-of-the-art analytical and processing instruments, we are able to support your development efforts and stay at the forefront of research both in basic and applied sciences pertaining to lipids and related drug delivery technologies. Our support covers all stages of development, from solubility screening and preclinical to late-stage formulation and "proof-of-concept" studies. Moreover, we provide extensive regulatory support, sharing toxicological and safety data, and analytical/characterization methods. For more information, visit Gattefossé at **www.gattefosse.com.**

Functional Chemicals

MITSUBISHI GAS CHEMICAL

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

Technology & Services
SHOWCASE

ANALYTICAL TESTING

Pace Analytical Life Sciences is a network of full-service contract CMC development and GMP analytical testing laboratories. CMC development, chemistry, and microbiology central lab testing services are provided to the Pharmaceutical, Biopharmaceutical, Medical Device, and Combination Product manufacturing industries. Our investment in state-of-the-art facilities and highly trained personnel emphasizes our commitment to delivering positive customer experiences across all channels of our business. We are well-equipped to handle almost any project regardless of scope or complexity. Pace Analytical operates FDA-registered laboratory testing facilities in Oakdale, MN, San German, Puerto Rico, Woburn, MA, and Somerset, NJ. Pace Analytical Services is the largest, American-owned environmental testing company in the US. For more information, visit Pace Analytical Life Sciences at **www.pacelifesciences.com.**

SPECIALIZED PRODUCTS & SERVICES

Pfanstiehl is a leading cGMP manufacturer of parenteral grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low-endotoxin (HPLE) carbohydrates such as trehalose, sucrose, mannitol, galactose, and mannose utilized as injectable excipients for the stabilization of proteins, mAbs, and vaccines. These HPLEs are also used as supplements for industrial cell culture, cell therapy, and cryopreservation media. Pfanstiehl also works closely with some of world's largest multinational pharmaceutical and biopharmaceutical firms, as well as with virtual pharmaceutical companies, to synthesize proprietary and commercial compounds in quantities ranging from grams to MT quantities. Manufacturing and development occur at Pfanstiehl's a 13-building campus located near Chicago, IL. For more information, visit us at **www.pfanstiehl.com.**

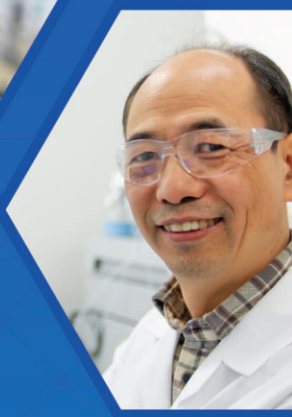
FIXED-DOSE COMBINATIONS

Many diseases are treated with a combination of drugs that must be taken in set combinations in pre-defined quantities. It is here that oral solid fixed-dose combinations can be of huge benefit to both manufacturers and patients. By combining a number of drug substances into one dose, it is possible to achieve numerous patient benefits as well as ensure the right amount of drug is being administered at the right time. At Recipharm, we have the expertise and equipment needed to develop, scale-up, and manufacture oral fixed-dose combination products efficiently and reduce project complexity. In particular, we have specialist expertise in pellet and mini-tablet technology that can overcome many of the challenges of developing and manufacturing fixed-dose combinations. For more information, visit Recipharm at **www.recipharm.com.**

AGILE CDMO

Singota Solutions is focused on getting your product to patients faster by being an agile, accountable, and transparent CDMO. Our clients can reach their preclinical and clinical milestones more quickly with our shorter lead times and industry expertise. Singota's formulation development, analytical testing, finishing, and supply chain services all support our robotic aseptic filing operation. This completely gloveless, highly repeatable, and precisely controlled process is beneficial for filling your high-value drug product into vials, syringes, or cartridges. Whether a virtual company or large pharma, our team at Singota is here to collaborate with you and customize our services to meet your needs and hit your milestones. Contact us at 812.961.1700 to schedule a visit. For more information, contact Signota Solutions at (812) 961-1700 or visit **www.singota.com.**

Pace Analytical®
LIFE SCIENCES



Delivering Science Better

Pace Analytical® Life Sciences provides premier product development services, with world-class expertise, robust quality systems, and advanced technology tools. We operate three full-service laboratories to provide a full range of services to global clientele.

Our services support your product development and commercial manufacturing:

- Small molecules
- Biologics
- Oligonucleotides
- Characterization of Novel Compounds
- Formulation Development
- Product Development
- Commercial Product Support
- GMP Laboratory Testing

See how Pace can be the best solution for your projects.

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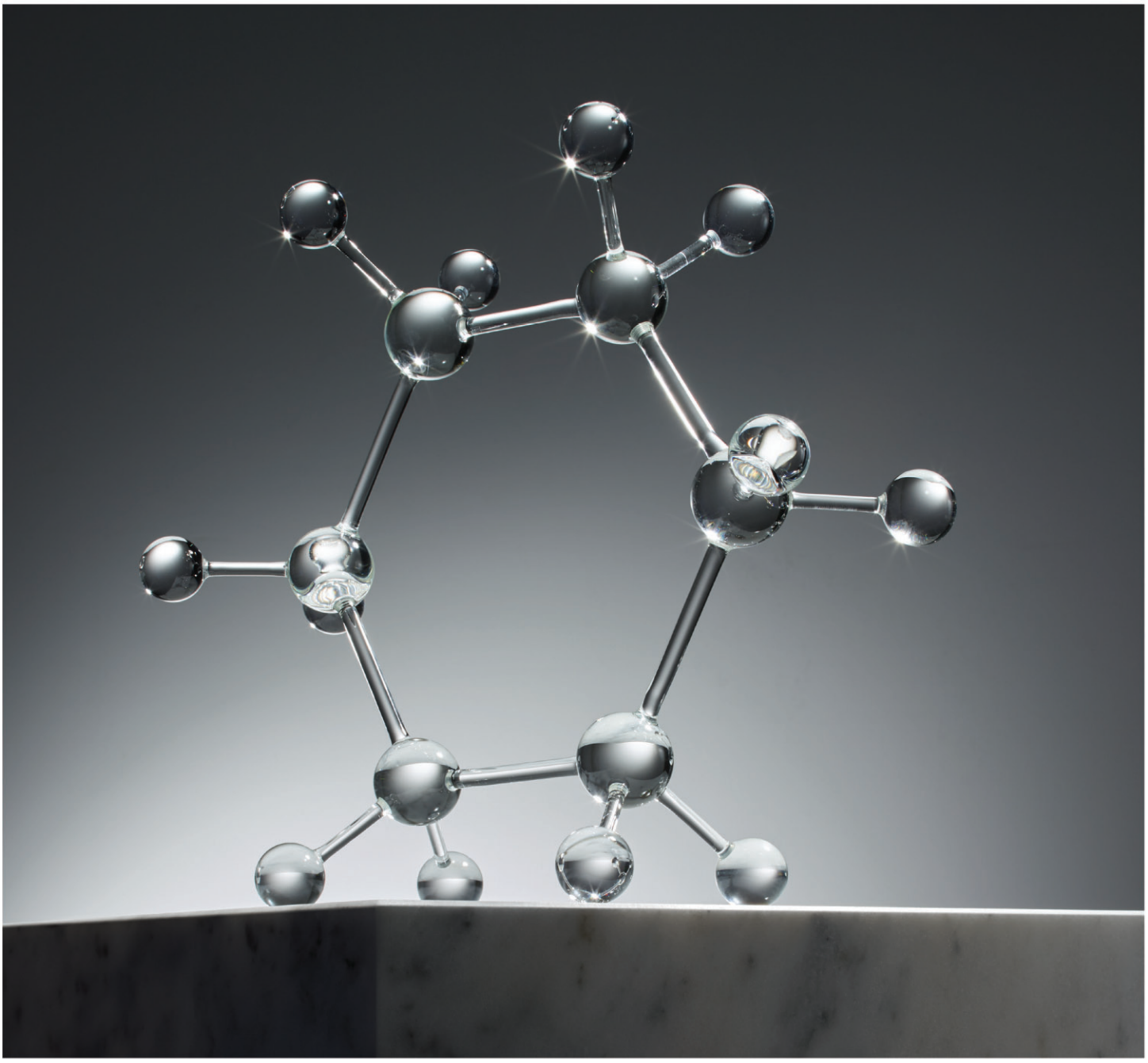

DRUG DEVELOPMENT IS SCIENCE. CRAFTING SUCCESSFUL TREATMENTS IS ART.

Successful treatments with better outcomes for patients are built on science, superior formulation technologies and the art of drug design.

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