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THE PROMISE & CHALLENGE OF GENE THERAPY

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THE BREAKTHROUGH ISSUE FEATURE

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If you are a CDMO serving the biologics outsourcing market, or a PE company or investor looking to define your investing strategy, you are in a competitive space – with continual announcements of new capacity being built.

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2019 | GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS
With this “Breakthrough” issue, we say goodbye to Pharma’s Almanac for 2019, simultaneously looking back at some of the trends and innovations that have driven the pharmaceutical and biopharmaceutical industry over the course of the year and forward to what the future holds.

This issue features a number of contributions focused on some of the most cutting-edge and scientifically complex topics that drove drug development and manufacturing this year. Topics include cell and gene therapy, antibody-drug conjugates (ADCs), high-potency APIs, next-generation chromatography, personalization medicine, and the increasingly complex “zoo” of multifunctional antibody and protein formats.

Consistent with the theme and our tendency to look forward in our fourth quarter installment, we also feature exciting thought leadership covering incipient science and technology that we predict will make a significant impact in 2020 and beyond. These articles stake out new therapeutically horizons in diverse next-generation fields like live biopharmaceuticals for microrome-based therapy, biofabrication and 3D organ printing, CRISPR-Cas9–based drugs and oral delivery of peptides, all subjects that we anticipate will command more real estate in future issues of Pharma’s Almanac.

Also in the context of assessing the past year’s breakthroughs and advancements, Nigel Walker’s overview article and our three-part feature assess one of 2019’s dominant topics – gene therapy – from three different perspectives: research and development, manufacturing and supply chain logistics. We analyze the gene therapy market, highlighting recent innovations and the practical challenges ahead to truly realize commercial manufacturing for the tremendous number of gene therapy products projected to be approved in the coming years.

While we maintain our primary focus on the outsourcing space and supporting industries for pharma and biopharma, our “Breakthrough” issue includes an expansion of our initiative to highlight young and innovative biotechs in each issue. Our biotech contributors discuss a range of innovations in plant cell-based protein expression, immunology and small molecule approaches to Alzheimer’s disease, ADCs, cell therapies, novel antibody development, photodynamic cancer therapy, and RNA therapies.

As always, this issue of Pharma’s Almanac additionally presents a range of content covering the primary concerns for contract development and manufacturing of pharmaceuticals and biopharmaceuticals, including adhering to delivery milestones; fast-tracking facility design, construction and equipment procurement; solving process development challenges; integrating services to reduce speed to market; scaling up to commercial manufacturing; and clinical trials logistics.

Finally, our editorial team is looking forward to 2020 for all pharmaceutical and biopharmaceutical industries for pharma and biopharma, as it marks the 25th anniversary of our parent company, That’s Nice, and you can look forward to a number of new features, initiatives and design flourishes here in the pages of Pharma’s Almanac.
Gene therapy is showing tremendous promise, with several treatments already on the market and hundreds more at all stages of development. The field had a pretty rocky start, though, and progress has been slow despite more rapid advances, concerns and questions remain. What might the future hold?

By Nigel Walker, Nice Insight

Shaky Start

The first hint that injecting DNA into human cells could affect cell function was demonstrated in 1971 in a laboratory using human fibroblast cells extracted from patients with galactosemia. The concept of delivering a gene therapy to live patients was broached shortly thereafter.1

These initial studies fueled excitement around gene therapy, and more trials were conducted. Optimism and expectations for gene therapy reached unrealistic levels and perhaps led to questionable study designs and procedures.2

When three patients died due to runaway immune responses, the U.S. FDA launched investigations into gene therapy trials.3 Issues were found with the way trials were conducted4 and with the safety of the viral vectors in use at the time.5 As a result, gene therapy development stalled in the early 2000s.

Meanwhile, new trials were conducted in the late 1980s using gene therapies based on viral vectors developed from murine retroviruses. In one trial, white blood cells from patients with advanced melanoma were modified using a retrovirus and the cells were infused back into the patients.6 Children with severe combined immunodeficiency (SCID) missing the adenosine deaminase (ADA) gene were treated with T cells modified using a retrovirus designed to deliver the missing gene and experienced improved health.7 Unfortunately, adverse events were observed for gene therapies using vectors derived from murine retroviruses; some of the patients developed forms of leukemia.8

Viral Vector Advances

Some researchers, however, remained convinced that gene therapies could be developed. The key was to overcome problems with the first-generation adenovirus and murine retrovirus vector technologies.9 This goal has been achieved through the use of adeno-associated virus (AAV) and lentiviral vectors.

AAV serotype 2, in particular, was found to be effective for transferring genes to non-dividing cells. Replication-incompetent lentiviral vectors cannot spread the virus but allow for high transduction efficiencies.10 In addition, these self-inactivating (SIN) vectors contain insulator sequences that prevent vectors from activating oncogenes from their host cells.11

More recent developments have explored leveraging recombinant AAV vectors to deliver synthetic microRNA (miRNA) for the downregulation of gene expression to treat diseases caused by undesired additional gene function rather than loss of genes or gene activity.12

The Current Landscape

Improvements in the safety of viral vectors have had a dramatic impact on the gene therapy sector. By the end of 2017, more than 2,400 gene therapy clinical trials had been conducted.13 Most were phase I studies, and the majority addressed oncology indications, followed by monogenetic diseases; some of the patients developed forms of leukemia.14

In just the last few years, six gene therapies — up from 69 in 2014, according to the Alliance for Regenerative Medicine.15

The Potential of Non-Viral Gene Transfer

Given the safety issues associated with first-generation viral vector technologies, it is not surprising that some research efforts are focused on the development of non-viral methods for delivering gene therapies. In addition to avoiding the potential for immune responses, technologies such as injection of naked DNA, electroporation, sonoporation, magnetofection and the use of oligonucleotides, lipoplexes, dendrimers or inorganic nanoparticles, may also be more amenable to large-scale production.16

Many of these approaches, however, suffer from low transfection efficiencies and require further development, although most have been used in some clinical trials. Two that have received significant attention include direct injection of DNA (or RNA) plasmids, most often into muscle, and lipofection, which involves the use of DNA plasmids surrounded by cationic liposome to facilitate delivery into cells.17

The Power of Gene Editing

The advent of gene-editing technologies has opened up whole new avenues for gene therapy development. Engineered nucleases, such as transcription activator-like effectors, CRISPR-associated nucleases (TALENs) and zinc finger nucleases (ZFNs), were the first to garner attention. The simpler and more precise CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated nucleases) system, however, appears to have the greatest potential.

Nucleases are enzymes that can insert, delete or replace DNA. TALENs and ZFNs are engineered restriction enzymes designed to bind and cut specific sites within the genome. The CRISPR gene-editing tool was developed from a natural system that affords bacteria protection against viruses. A guide RNA (gRNA) tells the Cas9 enzyme which part of the viral DNA to remove. The system has been modified to be directed editing within all types of cells, including those of plants and mammals.

Unlike traditional gene therapies, which introduce a functional copy of missing or
cost gene therapies could provide an economic advantage, in addition to eliminating the risk of suffering. The annual treatment cost for patients with SMA is $300,000–150,000, which can add up to more than $2 billion over a lifetime. Novartis has established a partnership with insurance companies that is tied to the performance of the therapy.

The cost of developing gene therapies is also significant. Given the safety issues encountered early on in the field, it is not surprising that extensive safety studies are required. Even if a viral vector has been previously used in an approved gene therapy, safety studies must still be conducted for any new development of gene therapy using that vector. The watchword is “caution.”

Many Other Hurdles to Face

Questions about pricing are not the only challenges that must be overcome if the gene therapy field is to continue its rapid advance. There are also many technical hurdles.

The persistence of gene therapy treatments must be increased to ensure that they provide the desired therapeutic effect throughout the lifetime of the patient. Further advances in nonviral delivery are needed to completely avoid the potential for immune responses. Technology that enables the development of gene therapies targeting multiple genes is needed in order to treat diseases that are driven by multiple dysfunctional or missing genes, such as Alzheimer’s disease and diabetes.

In the short term, there is a fundamental need to establish robust, reliable and readily scalable processes for the GMP manufacturing of viral vectors and to install more production capacity so that approved treatments can be made affordable. As development continues, most gene therapies have been produced in the lab using small-scale equipment that is operated manually and is not practical for larger-volume manufacturing. Equipment suppliers have made progress in developing 10-liter bioreactors and downstream processing systems amenable to vector production, but more work needs to be done.

About the Author

Nigel Walker
Managing Director, That’s Nice LLC, a Science Agency

Mr. Walker is the founder and managing director of That’s Nice LLC, a research-driven marketing agency. He has wide experience in the field of science and technology that enables the development of new technologies and products. Mr. Walker earned a Bachelor’s degree in mathematics and physics with honors from London College of Communication, University of the Arts London.

LinkedIn: www.linkedin.com/in/nigellwalker
Email: njwalker@thatscience.com
Supporting Commercialization of Live Biotherapeutic Products for MICROBIOME-BASED THERAPIES

BY MARK BAMFORTH, ARRANTA BIO

There are around 200 private and public companies developing microbiome-based therapies intended to treat a wide range of serious diseases, with large pharmaceutical companies showing increased interest by partnering with early innovators. While most of these investigational treatments are in the earliest phases of development, many have reached early clinical development, and more than a dozen are in phase II/III trials.

Commercialization of these products may be hindered, however, by the lack of sufficient manufacturing capacity. To support the advancement of this important field, Arranta Bio ("Arranta") was established as a CDMO dedicated to providing development and manufacturing services of live biotherapeutic products (LBPs) for microbiome-based diseases from early phase through commercialization.

ROLE OF THE MICROBIOME

The microbial population in the human body numbers in the trillions; estimates range from 10 to 100 trillion — well more than the number of cells that make up a person." The genes within these microbes outnumber the genes in humans too — by a factor of 150 — and are sometimes referred to as the "second genome." Comprising the "human microbiome," most commensal, symbiotic and pathogenic microorganisms are found in the nose, mouth, skin and urogenital and gastrointestinal tracts.

Established at birth, the microbiome develops as humans grow and is affected by diet, the use of antibiotics, genetics and various environmental factors. Many (~80%) of the species in the microbiome are beneficial and contribute to the healthy functioning of human bodies. As a result, when the microbiome experiences a state of imbalance, or dysbiosis, proper functioning of many systems in the body can be affected. Dysbiosis can result from the use of antibiotics, viral infections and stress, among other factors.

The Human Microbiome Project, conducted by the National Institutes of Health in the United States, characterized the microbial communities at five major body sites. Since then, there has been significant investment in research efforts to further elucidate the nature of the microbiome. Examples in the United States include the National Microbiome Initiative established in 2016 and the five-year Interagency Strategic Plan for Microbiome Research launched in 2018 by 23 U.S. government agencies.

REAL THERAPEUTIC POTENTIAL

All of this research has led to the development of evidence supporting a strong link between dysbiosis and disease. Since the initiation of the human microbiome project in 2007, the number of academic publications and active patent families around the microbiome has grown exponentially. Issues with the microbiome have been shown to contribute to the development of many different health problems, including not only the obvious, such as gastrointestinal disorders and food allergies, but everything from cardiovascular diseases to metabolic, autoimmune and neurological disorders, diabetes and cancer (Figure 1).

Gut microbiota, in particular, have been shown to be important for proper development of the immune system. Animals raised without any gut microbes have significant local and systemic defects in their immune systems. On the flip side, the presence of certain types of bacteria have been shown to lead to increased risk of various types of cancer, effects that have also been linked to influences of the microbiome on the immune system. Cancer patients with a healthy gut microbiome have also been shown to respond better to anti-PD-1 immunotherapy."
The growing body of evidence supporting the role of the microbiome in disease has led to a proliferation of start-up companies developing microbiome-based therapies. Companies such as Finch Therapeutics, Enterome Bioscience, Rebiotix, Seres Therapeutics, VSL#3, Microbiota, Axia Biotherapeutics and Kaleido Biosciences have or are attracting significant venture capital funding. Firms like Assembly Biosciences and Evelo Biosciences, on the other hand, are opting to raise money through public markets.

The major players in the microbiome space are well, largely through licensing deals and development partnerships, such as Pfizer with Second Genome, J&J with Vedanta, Genentech with Microbiotica and Teva with Enterome, Finch Therapeutics and NaBiota. Nestlé Health Science and Allergan have also very important assets to microbiome therapy developers. J&J’s Janssen division is also active in the Human Microbiome Institute. Mergers and acquisitions are also taking place, with some of the older biotechs expanding their position by combining with newer start-ups taking rapid advances, such as Ferring’s purchase of Rebiotix. Since 2015, more than $5 billion has been spent on partnership and acquisition deals in the therapeutic microbiome space.

Other companies are looking to create engineered bacteria that have improved capabilities compared with those identified in the human microbiome. In addition, bacteriophages, which are viruses that infect specific bacterial cells with genetic material, are being investigated as a way to alter the genetic code of microbiota to kill problematic bacteria or alter their behavior, such as their immune responses.

Another group is focusing on the metabolites generated by the microbiome — small molecules or biologics that have been shown to be important in the mechanistic pathways in which the microbiome is involved. Yet others are attempting to engineer bacteria that will produce specific active drug substances in the gastrointestinal tract. Vaccines are also being developed based on the idea of “molecular mimicry.”

In 2018, the most common approaches used to develop microbiome-based therapies were small molecule therapies (31%), single-strain bacteria (26%) and microbiota consortia (24%). Treatments based on genetically modified single-strain bacteria, phage cocktails and microbial ecosystems accounted for 12%, 4% and 3% of the approaches adopted for pipeline assets, respectively (Figure 2).

Significant Market Opportunity
All indications are that in the high rate of growth predicted for the microbiome-based therapy market. The market research firm MarketsandMarkets predicts that the value of the global human microbiome market, including probiotics, prebiotics, foods, medical foods, diagnostic tests and drugs, will reach $13 billion in 2027 and will expand from $364 million in 2022 at CAGR of 22.5%. Prebiotics account for the long term. By disease indication, the value of the market for products targeting infectious diseases will grow at the fastest rate.

Other estimates peg the market as expanding at CAGRs ranging from near 20% (BrandEssence Market Research estimated in 2020 of $1.28 billion to slightly more than 60% (PERSISTENT Market Research, estimated value in 2025 of $890 million).

Hurdles to Overcome
Bringing microbiome-based drugs to market is going to require a true impact on drug development and reduction will not be easy. While there are many candidates in the pipeline, with a few in late-stage clinical trials and one product to do.

More research must be conducted to fully understand the roles of the microbiome in maintaining health and dysbiosis in contributing to disease. It can be challenging to clearly establish a change in the microbiome in a cause and not a side effect. The challenge is magnified given that each person’s microbiome is unique.

In addition, drug developers must be sure to take into account the importance of factors beyond the microbiome that influence drug development. It may be that combination therapies involving microbiome-based drugs and other conventional treatments will achieve the best results.

Translating research results into commercial therapies might not be as easy, either. Reliable and cost-effective preclinical vivo models for the microbiome in the gut and other parts of the body are needed for both relevant diseases and healthy states to facilitate drug development.

Greater insight is also needed in determining how to choose the right patients for treatment. The complexity of the microbiome and its changing nature can make it not only drug development difficult; diagnosis can be equally challenging.

There are manufacturing issues as well. First, for any treatments involving live organisms, some level of standardization must be established so that regulatory authorities can have confidence in the reproducibility of manufacturing processes.

In addition, improvements are needed in the manufacturing methods used to produce small quantities of clinical trial materials. Practical solutions are needed for selecting and developing the optimized media and process conditions that will afford efficient growth of the desired bacteria to ensure the production of sufficient quantities of a given isolate for clinical trials without the need to construct large manufacturing facilities at an early stage of development. Requirements for isolated candidates in development are anaerobic microbes and must be handled in oxygen-free atmospheres throughout the manufacturing process and at the downstream processing stages. Downstream processing solutions are needed to enable cost-effective and scalable production of clinical trial products. Unlike conventional biologics, processing must be achieved without impacting the viability of the live microorganisms and they must be formulated to ensure release in the right places such as to be effectively recognize the gut or relevant area. Furthermore, patient-friendly and safe delivery solutions that are also manufacturable at scale are needed. Most clinical trial materials today are today stabilized to the bacteria and then encapsulated.

Facilities must be designed taking into consideration that some of the microbiome-based products are solid, which are hard to detect and difficult to contain. Unidirectional flow, segregation of suites to protect people and products, proper air handling and HEPA filters are some of the guidelines required for viral vector manufacturing facilities—must be applied, with added capabilities for maintaining low oxygen conditions due to drying, milling, encapsulation and packaging.

Uncertainty with respect to the regulatory approval process for novel microbiome-based drugs is another issue that ultimately must be managed. One question the U.S. FDA is raising is whether or not the bacteria should be considered a probiotic and when they should be classified as a drug. For these manufacturing and process conditions, the FDA becomes whether they can be approved following the process and requirements established for acquired drug candidates.

Guidelines for handling spore formers do exist and are applicable. In addition, the FDA has issued draft guidance and documentation in the case of specific products in particular fields such as cell and gene therapy, is willing to work with industry to provide additional guidelines for clinical trials.

Developers of microbiome-based drugs are also faced with intellectual property and patent protection challenges. For instance, existing patent law prohibits...
patenting live organisms and naturally occurring materials. Questions have also been raised about claims regarding ben-

eficial functions versus claims for spe-
cific microbes.

WHAT’S NEXT FOR MICROBIOME THERAPIES?

The number of microbiome-based ther-

apists in the clinic is astounding. One

source identified 2,400 clinical trials

up to 2018 involving candidates developed using microbiome science.2 That number was up from 1,600 in 2017,

many of which were in the early stages of development. Today, there are investment funds dedi-
cated solely to companies developing micro-

biome-based therapies, and around 200 firms are actively working on differ-

ent aspects of the microbiome.

A few products are in phase III clinical studies, more have reached phase II and even greater numbers are in early stages of development. The first products likely to receive approval will be treatments for C. diff infections. Candidates targeting diseases of the GI tract — ulcerative colitis and others — also look to have good prospects based on early clinical data.

Not too long ago, the focus in medicine had largely been on what microbes and the need for sterility, the lasting impact of the transformative “germ theory of disease.” There has been a huge shift in thinking, and in just the last 10 years, tremen-
dous advances in our understanding of the microbiome have been made. But we are just scratching the surface at this point. We are starting to peel back the outer lay-

ers of the onion and have no knowledge yet of how many layers there are in total.

Crucial clinical work needs to be done to demonstrate the safety of microbi-

ome-based therapies, establish the ex-

istence of relevant cause-and-effect rela-

tionships and clearly show how these novel treatments can address unre-

medicinal needs.

This work is being done today by com-

panies located around the world. Microbi-

ome-based therapy development has become a truly global phenomenon, and there is a high level of interest and engage-

ment in all of the possible approaches and for many disease targets. All of these efforts have the potential to lead to products that can treat and possibly prevent significant and widespread diseases and disorders, such as obesity, diabetes and Parkinson’s. As a result, there could eventually have a tremendous im-

 pact on human health.

ARRANTA TO PROVIDE EARLY PHASE TO COMMERCIAL CDMO SERVICES

With many microbiome-based candidates in early-phase, preclinical and clinical development, there is growing demand for manufacturing capacity suitable for these products, many of which comprise live bio-

therapeutic products (LBPs).

Some established biopharmaceutical contract development and manufactur-

ing organizations (CDMOs) offer limited state-of-the-art commercial manufactur-

ing facility that can handle spore formers and aneurismal organisms in early Decem-

ber 2009. One candidate site will include multiple suites with single-use fermenters up to 2000 L in capacity, as well as lyophilization and encapsulation capabilities. Both facilities are designed to be fully compliant with the FDA Code of Federal Regulations (Part 29) and the European Advanced Therapy Medicinal Products’ regulations.

Arranta has also been successful in the fundraising arena, garnering $82 million to support the launch of the business and the development of the commer-

cial capacity. We have a main institu-

tional investor (Ampersand Capital), as well as a strategic investor, Thermo Fish-

er Scientific, whom Arranta is partnering with to access processing, analyzing and material technologies that can be used to manufacture LBPs. In addition, Arranta will use its bacterial fermentation plat-

form to manufacture plasmid DNA for Therapeutic Fish’s gene therapy products.

We are led by a strong management team with many years of experience in the biopharmaceutical industry and a team of technical experts with a proven track record in both process develop-

ment and contract manufacturing from fermentation to lyophilization and en-

capsulation of live biological products. Our new COO will be joining Arranta to support the growth of this burgeoning field and enable new, effective treat-

ments to reach patients in need.

ABOUT THE AUTHOR

Mark Bamforth

Founder, President & CEO, Arranta Bio

Mark Bamforth is the founder and President of Arranta Bio, which was established in May 2019. In 2015, Mr. Bamforth founded Brammer Bio, a viral vector CDMO supporting cell and gene therapy companies, which was acquired by Thermo Fisher Scientific in April 2019. In 2010, Mr. Bamforth founded Gahat BioPharma, a CDMO supplying biopharmaceuticals. In September 2014, Gahat was sold to DPharma Holdings BV, which later became part of Thermo Fisher Scientific. He holds a bachelor’s degree in chemical engineering from Stanford University and an MBA from Harvard Business School.

LinkedIn: www.linkedin.com/in/mark-bamforth-3b000140
Email: mark.bamforth@arranta.com

I bring my experience as the founder of Gahat Biopharmaceuticals, a CDMO providing biologics development and manu-

facturing services, and Brammer Bio, a viral vector CDMO supporting cell and gene therapy companies, to now lead the growth of Arranta.

As our Chief Technology Officer, Cap-

tozyme founder Aaron Cowley brings a wealth of expertise and knowledge in the field of microbiome-based therapies. Our CFO Steve Favaloro and Chief Legal Officer and General Counsell Gana Ghosh – both veterans of the life sciences industry, can bring the Arranta story on track and continue to pursue company objectives.

We are currently seeking people for positions in technical, engineering, manufacturing, quality and support op-

erations and expect by the end of 2020 to employ over 100 people in total. Arranta is a Gaelic word that means “intrepid and daring,” which reflects how we view Arranta. We are embarking on a bold mission to lead the industry in the development and manufacturing of microbiome-based therapies, and we view Arranta as a “pioneer at the frontier of these exciting therapies.”

REFERENCES


PHARMASALMANAC.COM
Clinical trials are increasingly global and include both traditional structures and newer siteless models with direct-to- and direct-from-patient delivery capabilities. Sponsor companies and trial managers need the support of clinical logistics service providers that can do more than pick up and deliver biologic samples and clinical trial materials. With its global transportation footprint and clinical packaging services, Yourway allows trials to run more smoothly, efficiently and cost-effectively.

THE YOURWAY DEPOT NETWORK
To support international clinical trials, Yourway has invested in a global depot network that currently comprises 21 locations in the U.S., Canada, Mexico, UK, Ukraine, Belarus, Russia, Colombia, Peru, Chile, Panama, Brazil, Israel, South Africa, India, China, Australia, Hong Kong and Japan.

All of these facilities are cGMP-compliant and include both ambient and cold-chain pallet and shelf locations, as well as secondary packaging capabilities. They also have designated receiving and shipping and pick-and-pack areas — the return and destruction of unused clinical trial materials can also be managed at all of our depots, and all participate in the company’s centralized web-based reporting system.

GLOBAL TRANSPORTATION SCOPE
Yourway was originally founded to rapidly deliver donor organs to transplant patients. Over the last 20 years, we have grown from this original business, constructing a platform for managing the shipment of clinical trial materials to and from anywhere in the world. With our biological, warehousing and logistical expertise and capabilities supported by our extensive network, Yourway provides same-day or next-day delivery of shipments — even for specialty materials — with no size or weight restrictions.

Our couriers pick up shipments 24 hours a day, seven days a week — with no cut-off times and no hidden or express fees. We place deliveries on the first available flight using only premium flights, regardless of when orders are received. Yourway’s temperature-controlled transport specialists enable the shipment of phase I, II, III and IV materials, finished goods and production raw materials, including those for cell and gene therapies.

Worldwide customs pre-clearance capabilities proactively expedite delivery so that Yourway can immediately clear and deliver shipments to their destinations. Yourway’s worldwide service also includes documentation support and the provision of regulatory advice regarding country-specific requirements. Our proactive management approach helps our customers avoid delays of all kinds during the shipment of critical clinical trial materials.

In addition to more traditional deliveries to investigator sites, Yourway has the capability to provide site-to-patient shipments in support of trials for personalized medicines. We can also develop customized delivery solutions if patients are traveling or moving to a new location — this makes it possible to keep all patients enrolled and receiving their medications in spite of an address change. Once a trial is complet ed, Yourway can help manage any reverse logistics requirements, including reclamation and value recovery, returns and reconciliation and storage, consolidation, destruction or disposal, when appropriate.

Through our central, web-based portal, clients can track all types of shipments and receive automated notifications. Using this system, clients are given access to all information about their shipments at any point in time throughout the course of transport.

CLINICAL PACKAGING SUPPORT
In addition to global transport capabilities, Yourway offers primary and secondary clinical packaging and storagedistribution services, providing added value to our clients. Arranging packaging, storage and shipping services within one organization allows our clients to significantly reduce their load times.

Primary packaging capabilities include bottling, blistering and over-encapsulation capabilities. Secondary services range from kitting, labeling and delabeling to binding of placebos for clinical trials — we are also happy to work with clients on additional requests. Secondary packaging activities can be performed under ambient conditions or in a cold room or freezer, as required.

Packaged materials can be stored in Yourway’s GMP warehouses. Alternatively, they can be transferred in bulk to other depots immediately upon completion of the packaging run.

Each project is supported by a team of experts that provides planning, packaging design and preparation for a comprehensive supply chain solution, including the necessary components, packaging materials, labels and other requirements. Throughout the process, customers have 24/7 access to clinical trial information through our online portal, which records the project steps, batch records, product inventory levels and product information (including locations, quantities, temperatures, etc.) in real time.

PROVIDING THE FULL GAMUT OF INTEGRATED SERVICES
With our global transportation footprint and clinical packaging services, Yourway offers the unique combination of highly responsive, personalized logistics support and the full gamut of integrated services, enabling both traditional and hybrid/virtual trials to run more smoothly, efficiently and cost-effectively.

Yourway is the only truly integrated premium courier and clinical package,...
offering – along with our comprehensive transport capabilities – primary and secondary pharmaceutical packaging services, warehousing and distribution support, including cold-chain solutions, unused product return services and assistance with logistics project management. The latter services include sourcing of comparator drugs and other supplies, establishing optimal delivery strategies across global trials, documentation support and the provision of regulatory advice regarding country-specific requirements.

Our team of pharmaceutical transport specialists is capable of supporting customer needs for the shipment of phase I, II, III and IV clinical trials materials, finished goods and raw materials. Worldwide customs pre-clearance capabilities proactively expedite delivery so that our experienced agents and associates located around the world can immediately clear and deliver shipments to their destinations. We guarantee speed of delivery with highly customized transport solutions and work with each client and every shipment on a one-to-one basis to ensure the highest level of service. Our goal is to ensure the fastest, most secure and most reliable delivery possible, anywhere in the world, with no size or weight restrictions.

**SEAMLESS OPERATIONS**

With effective project management teams and online monitoring and tracking solutions, Yourway ensures a seamless process from packaging to storage, distribution and delivery. Our customers have global access to a wealth of experts, systems and proven processes for ongoing and real-time support and the assurance of a high-quality, high-throughput supply chain. In addition, integration of our multiple services simplifies project management for Yourway's clients. Customers that outsource their clinical packaging and material warehousing, inventory management, distribution and transport with Yourway gain access to a wealth of strategic locations around the globe and advanced management technology without the issue of in-house oversight.

With all logistics needs for clinical trial materials easily obtained in one place, outsourcing to or managing relationships with multiple organizations is no longer necessary. We can source comparator drugs and other supplies, establish optimum delivery strategies across global trials and help closeout studies by returning unused materials.

**ADDING VALUE WITH BESPOKE SOLUTIONS**

Yourway does much more than provide clinical packaging and logistics services; we take a solutions management approach to customer service, working closely with our clients to provide a tailored plan for packaging, warehousing and transport that affords the maximum control of supply, speed and flexibility. In addition to biologic samples and clinical trial materials, we have familiarity with dangerous goods, controlled drugs, sample collection kits, ancillary products, medical equipment and other materials.

Customers that partner with us benefit from an array of solution-based offerings, including project management support, planning and optimization guidance, comparator sourcing, ancillary supply sourcing, forecasting, returns/reconciliation management and regulatory support, among others.

Yourway has extensive experience developing and executing strategic solutions that ensure the management and delivery of clinical trial materials within relevant time constraints to required locations, even for challenging products, such as patient-specific medicines. We maximize use of supplies and minimize waste and shipping costs while ensuring that products stay within specifications and are handled properly. Yourway is the industry’s leading service provider, capable of handling all types of pharma products and clinical materials, offering — along with our comprehensive service offering, integrated project managers who support our clients every step of the way and convenient packaging services and storage and depot assistance around the clock, customers who partner with Yourway BioPharma Services are tapping into a broader network managed by a team that will meet every challenge with a flexible solution.

**THE BENEFITS OF A FLEXIBLE PARTNER**

As a flexible, privately-owned business, Yourway works directly with our customers. We serve the pharmaceutical industry as a true one-on-one service provider. We offer our customers easy access to the top leaders of our organization, and nothing is ever off limits, day or night.

Formed in 2010, Yourway has maintained a commitment to our customers. Our attention to our customers has been unwavering over the last decade, in spite of our continuous growth, and we have grown more agile as we have expanded. Likewise, the roots on which we were founded have only become more deeply embedded into our organization. This emphasis on our company values and our organizational structure translates to increased benefits for our customers internationally. With a commitment to quality to a comprehensive service offering, integrated project managers who support our clients every step of the way and convenient packaging services and storage and depot assistance around the clock, customers who partner with Yourway BioPharma Services are tapping into a broader network managed by a team that will meet every challenge with a flexible solution.

**ABOUT THE AUTHOR**

**Gulam Jaffer**
President, Yourway

Gulam Jaffer is President of Yourway, an integrated biopharmaceutical supply chain solutions provider offering a full range of primary and secondary clinical packaging, comparator sourcing, logistics, storage and distribution services for the global pharmaceutical and biotech industries. Headquartered in Allentown, Pennsylvania, with additional strategic locations worldwide, Yourway specializes in time- and temperature-sensitive clinical drug product and biological sample shipments. Yourway is a flexible and reliable logistics partner committed to the safe, efficient and on-time delivery of client high-value, high-priority clinical materials.

Email: jaffer@yourwaytransport.com

[Image Link]
Successful and rapid analytical method development plays a key role in ensuring the development of robust processes to produce high-quality products. When standard or predefined methods fail because of buffer components or because proteins do not behave as expected, solutions can be found when the team has the knowledge and flexibility to explore the use of alternate methods.

**Case Study 1**

**Process Development and Analytical Development for a Challenging Therapeutic Molecule (Homodimer Fusion Protein)**

For a protein of interest, there were no analytical methods to measure the amount and form of the refolded protein that was expressed in Escherichia coli as an insoluble product extracted from inclusion bodies and then refolded into a noncovalent dimer. In order to develop and optimize the process to produce a sufficient quantity of material for initial toxicity studies, the process development group evaluated a number of analytical methods that could be used to assess and quantify the properly folded protein.

**The Solution**

Several standard methods were first evaluated (including size exclusion chromatography (SEC), hydrophilic interaction chromatography (HIC), sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS-PAGE)), but those methods did not provide the necessary level of resolution to separate the dimer from the other components. In this case, the poor resolution could be due to the complex refolding buffer matrix. A review of the literature on these types of products revealed that another type of high-performance liquid chromatography (HPLC) – ion-exchange chromatography (IEC) – might provide a solution. Analytical scientists developed an IEX-based analytical method to quantify the refolded molecule in the post-refold sample. The IEX assay was used to distinguish the difference charges of the correctly refolded dimer material from the improperly folded/dissociated species and other host cell proteins, monomers and fragments in the refold material. In-process quantification was performed based on using the standard curve generated from final bulk material. This rapid, robust analytical method can accurately measure the properly refolded protein versus other species, was critical to process development efforts to improve refolding efficiency, to scale up the process to pilot scale and to provide the required quantity and quality of material for toxicology studies.

**Case Study 2**

**Protein Measurement in the Presence of Detergents**

Protein quantification of the final bulk material is critical to process and analytical assay development, and is also required to perform other analytical testing, like enzyme-linked immunoassays (ELISA) and SDS-PAGE assay. For a particular protein, the inclusion of components in the buffers, such as dithiothreitol (DTT) and Tween-20 detergent, to solubilize the protein during purification process development caused the front-line traditional assays to fail. The A280 method did not work due to the presence of oxidized DTT, which absorbs at the 280 nm wavelength. A bicinchoninic acid (BCA) assay failed due to DTT interference, and a Bradford assay failed due to Tween interference. The Pierce 660 kit-based assay was tolerant to DTT and Tween; however, the assay runs at acidic pH, which possibly caused precipitation of the product. Developing a protocol as a means to tolerate DTT was required.

**The Solution**

A size-exclusion column (SEC) method was explored and eventually developed that can quantify protein concentration in the presence of the interfering detergents without precipitating the protein. The SEC method is easy and robust, and the method is isocratic compared with other HPLC-based methods requiring use of a gradient of buffer. The protein concentration is determined on the basis of a bovine serum albumin (BSA) standard curve with application of the corrected extinction coefficient value. Even with the SEC-based method, Tween caused significant assay interference at high concentrations; therefore, the Tween concentration needed to be tracked. SEC could not be used to determine Tween concentration, likely due to Tween adsorption to the SEC material, so a colorimetric assay was developed to track and control Tween 20 detergent through the purification process.

**Summary**

Analytical tools are the key to understanding and optimizing any process, and having the experience and means to explore alternative methods allows the analytical scientist to rapidly meet the demands of any project. Where appropriate, established methods based on existing standard operating procedures (SOPs) and protocols are relied upon. When those established methods fail, custom solutions are developed to meet the needs of the product and project. The ability to use alternative methods to solve problems is the key to developing novel protein molecules. These two case studies demonstrate the value brought to the process when scientists with extensive training are given the freedom to apply their knowledge and identify new approaches to the challenges we face. Each challenge builds on the existing foundation and improves the traditional methods to increase efficiency, productivity and quality.

**About the Author**

Shaonly Saha, Ph.D.
Analytical Development Scientist-MS&T Analytical
Grifols Recombinant Protein CDMO Services

Shaonly Saha is an Analytical Method Development Scientist for biopharmaceutical molecules in the Manufacturing Science and Technology group at Grifols. She has 5 years of industry experience in analytical sciences. Shaonly holds a Ph.D. in life sciences (cancer biology) and has postdoctoral research experience from Stanford University Medical Center.

Email: cdmo@grifols.com

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**Solving Process Challenges Requires Flexibility to Explore Alternative Analytical Methods**

**Process and Analytical Development**

Grifols Recombinant Protein CDMO Services

Grifols is a global biopharmaceutical company that has led the way in developing life-saving treatments for over 90 years. From therapeutic proteins to medical devices, Grifols’ innovative solutions improve the quality of life and healthcare standards around the world. In this series, Grifols’ experts share their insights on the latest trends in the pharmaceutical sector, focusing on the essential role of analytical development in ensuring the reliability and efficiency of their products. Each case study is carefully crafted to offer practical solutions for challenges faced in the industry, emphasizing the importance of flexibility and innovation in analytical methods to meet the needs of customers and patients alike. Whether it’s grappling with the complexities of developing a new therapeutic molecule or optimizing existing processes, Grifols is at the forefront of pushing the boundaries of analytical science to drive progress in healthcare.

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Analytical tools are the key to understanding and optimizing any process, and having the experience and means to explore alternative methods allows the analytical scientist to rapidly meet the demands of any project. Where appropriate, established methods based on existing standard operating procedures (SOPs) and protocols are relied upon. When those established methods fail, custom solutions are developed to meet the needs of the product and project. The ability to use alternative methods to solve problems is the key to developing novel protein molecules. These two case studies demonstrate the value brought to the process when scientists with extensive training are given the freedom to apply their knowledge and identify new approaches to the challenges we face. Each challenge builds on the existing foundation and improves the traditional methods to increase efficiency, productivity and quality.

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Shaonly Saha, Ph.D.
Analytical Development Scientist-MS&T Analytical
Grifols Recombinant Protein CDMO Services

Shaonly Saha is an Analytical Method Development Scientist for biopharmaceutical molecules in the Manufacturing Science and Technology group at Grifols. She has 5 years of industry experience in analytical sciences. Shaonly holds a Ph.D. in life sciences (cancer biology) and has postdoctoral research experience from Stanford University Medical Center.

Email: cdmo@grifols.com
ADHERING TO DELIVERY MILESTONES

Investors expect pharmaceutical companies to meet commercialization timelines, and failure to do so can have significant financial consequences. Contract development and manufacturing organizations (CDMOs) that have a track record of adhering to project timelines and delivering product on time and in full, regardless of the project’s complexity, have a competitive advantage.

FOUNDATION OF COLLABORATION
CDMOs cannot provide effective support to clients unless they establish the right collaborative relationships with them. Collaboration must be integrated into the culture of the CDMO and permeate all of the interactions. On the other hand, real-time communication helps alleviate customer anxiety and ensures that the best decisions are made.

This high level of collaboration must be established at the start of the project, with both parties fully sharing all information needed to achieve the best possible outcome. Successful process development, implementation, and achievement of all milestones. The project team should be all-inclusive and include experts from both the CDMO and the customer.

A face-to-face kickoff meeting is important to help establish connections and build a strong relationship between the CDMO and customer teams. It also provides the opportunity to establish direct lines of communication between the program manager and different groups involved in the program. Establishing a strong relationship and foundation of trust leads to greater success in managing the program as it moves forward. Collaboration also ensures that everyone contributes to the decision-making process, leading to the best possible outcomes.

UNDERSTANDING CUSTOMER NEEDS

The kickoff meeting also provides an opportunity for the CDMO to advance, which project and customer teams to get to know one another. Project cannot be completed successfully unless the CDMO truly understands the short- and long-term goals of the customer. Only with the understanding of the customer’s primary concerns and essential factors for success can the CDMO establish the deliverables and determine what is needed to achieve these goals.

It is essential to be as flexible as possible so that important customer milestones can be achieved without issue, and so that robust, commercial-ready processes and methods can be established. It is also critical that, by the end of the kickoff meeting, all team members—from both the CDMO and customer—are very clear on what the deliverables are within the scope of the project and the timeline for those deliverables.

MULTIPLE LINES OF COMMUNICATION

True collaboration requires frequent communication. One key to success is providing a clear, consistent, and comprehensive timeline that lists all milestones. The timeline should be established at the kickoff meeting, and all team members should provide input. This helps ensure that everyone is on the same page and that any changes to the timeline are documented.

Communication should occur on an agreed regular basis, generally weekly during the early stages of the project. Cutting-edge teams maintain open lines of communication with all team members involved. During conference calls, it is critical that everyone on the team verbally expresses their thoughts and ideas. In addition, the CDMO is responsible for ensuring that milestones are achieved on time, not only by making sure that the internal CDMO team is prepared but also helping to guide product development and commercialization. The CDMO should always ensure that milestones are achieved on time to maintain trust.

Communicating with the customer during the project can be challenging. Some key considerations include:

- Regular face-to-face meetings. It is critical to make sure that the CDMO and customer/guests have adequate time to communicate.
- Regular meetings, including regular face-to-face meetings. It is critical to make sure that the CDMO and customer/guests have adequate time to communicate.
- Regular phone calls to keep the project stakeholders informed.
- Regular updates to the project team.
- Regular updates to the project team.

The deadlines are not fixed, and communication is important to the success of the project.

PLANNING FOR CHANGE

Unfortunately, no project will progress exactly according to the initial plan laid out at the kickoff meeting. Effective CDMOs are mindful of the unexpected changes and work to determine and plan for potential changes. Asking the right questions to ensure that the customer always has input is important to help make connections and ensure that the CDMO is meeting the customer’s needs.

The problem should be laid out, and the team should identify the key milestones and issues. It is essential to plan for unexpected issues to minimize the impact on the project timeline. The project team should be proactive in identifying potential problems and creating contingency plans.

The results of a clinical trial may determine whether a project goes down path A or path B. If an FDA meeting is scheduled, changes to the milestones and timeline could follow. A candidate may receive an accelerated approval designation, which gives the CDMO the opportunity to fast-track the project on track. Experience and flexibility are crucial under these circumstances.

ABOUT THE AUTHORS

Julie Risdon

Business Director Pharma Solutions, Albemarle Fine Chemistry Services

Julie Risdon has been with Albemarle since July 2018 and currently leads the custom pharma business within the Albemarle Fine Chemistry Services division. She has over 17 years of experience in pharmaceutical andcustom manufacturing, including increasing leadership positions at Pfizer. Julie received her BS in chemical engineering from Ohio University.

Email julie.risdon@albemarle.com

LinkedIn www.linkedin.com/in/julierisdon-25025258

Megan Duffy

Program Manager, Albemarle Fine Chemistry Services

Megan Duffy has been with Albemarle since February 2019 and currently leads custom programs at the South Haven, Michigan facility as a Program Manager in the custom pharma business within the Albemarle Fine Chemistry Services division. She has both process development engineering and program management experience in pharmaceutical and custom manufacturing. Megan received her BS in chemical engineering from Penn State University.

Email Megan.Duffy@albemarle.com

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COMMERCIAL MANUFACTURING

ADVANCING COMMERCIAL MANUFACTURING
FROM ORPHAN DRUGS TO BLOCKBUSTERS

BY TYLER EWALD, UPM PHARMACEUTICALS

The key to success for pharmaceutical contract development and manufacturing organizations (CDMOs) is to understand the needs of the market and evolve the business to ensure that it can always meet customer needs as they change and grow. UPM Pharmaceuticals is dedicated to optimizing manufacturing processes for both small- and large-volume projects to ensure the best production of high-quality drug products.

TAKING PROJECTS TO THE COMMERCIAL STAGE
To ensure that we grow with our customers as they graduate their products from early- to late-stage clinical trials and through to commercialization, UPM has taken a series of proactive steps. We have enhanced our services for clients involved in later-stage development projects, such as scale-up and the production of registration batches. We have also advanced the manufacture of commercial products as a second supplier.

By combining our early- and late-stage R&D groups into one unit, we are more fully leveraging the talents of our highly skilled and experienced staff. Overall, an updated, clearer review process for incoming project requests allows us to give each project the level of attention required.

All of our clients, whether their projects require one or 100 batches per year, benefit from these upgrades. UPM works hard to accommodate all projects, carefully selecting those that fit our equipment train, manufacturing expertise and available capacity.

For all projects that are accepted, whether blockbuster or orphan drugs, we apply lessons learned about improving efficiency and productivity to provide reliable, high-quality services at the most cost-effective prices possible. Greater efficiency also increases reliability and predictability and boosts our available capacity. Customers with projects of all sizes benefit directly from these improvements, as well.

MAXIMIZING EFFICIENCIES AT SCALE
Large-scale commercial projects provide the greatest opportunities for increasing efficiency and productivity. Running multiple batches on a frequent basis allows for greater process optimization. Operators repeating the same process many times are able to identify opportunities to improve the yield, reduce the run time, reduce error rates, and optimize other parameters, all of which lead to increased efficiencies and better productivity. In addition, ongoing improvement efforts lead to greater reliability and tighter quality assurance. Operators are also able to do cross-training and increase their knowledge and experience, which is then applied to future projects.

STREAMLINING ORPHAN DRUG PRODUCTION
Orphan drug projects, on the other hand, may require batches to be completed only a handful of times per year, or less. Our staff takes great pride in the work they are doing in this space and the knowledge that they are having a significant positive impact for patients suffering from rare diseases, especially in cases where we can help provide the first real treatments for an unmet medical need. They are committed to improving these processes as much as possible in order to reduce not only the cost to produce these critical therapies, but the time to get them to market and in the hands of patients. Even though the batch sizes may be smaller and the number of batches fewer, the products are produced using the same equipment trains employed for high-volume projects. Many efficiencies identified for large-volume projects are product-independent and can be applied to any product produced using the same manufacturing line. Every process and product has nuances, so we learn new things that can be applied to future projects every time we run a batch, regardless of the batch size.

TECH TRANSFER EXPERTISE
UPM has an experienced group of scientists and engineers working on technology transfer, with backgrounds in formulation, manufacturing equipment, process development, scale-up and validation. Our heads of formulation and manufacturing, for instance, have over 40 and 30 years of experience in the industry, respectively. Members of our staff, in general, have 5–25 years of experience in formulation development and technology transfer and
We have worked on successful applications of peptide therapies, to modified peptide chemistries and delivery technologies, sizes through commercial manufacturing. We have technical flexibility, capacity flexibility, and pride in each project in which they are involved. With these experienced and committed teams and our internal consulting approach, UPM is capable of rapidly investigating and effectively troubleshooting issues that do arise, enabling us to keep projects on track and to consistently meet timelines.

Full-service COMO

UPM’s Bristol, Tennessee plant includes a Solids Formulation R&D Facility, modern manufacturing suites and a state-of-the-art, fully service analytical laboratory to support the production of solid and semi-solid products from 100 g to approximately 1 ton annually. The analytical lab provides method development for raw material release, API and drug product characterization, stability testing, in-process testing and product release. Two high-speed packaging lines with serialization capabilities enable basic packaging for many products. A secondary packaging line is available for production of sample kits, product displays and other items that require manual manipulation. UPM also has a separate 250,000 ft² warehouse and provides warehousing and distribution services. Offering final product manufacturing, packaging, warehousing and distribution capabilities in one facility helps clients streamline their supply chains and reduce time to market.

Throughout our history, we have been approached about orphan drug projects that require only one or two small batches per year, as well as commercial transfer projects requiring hundreds of millions of doses annually. We have requests for products that are ANDAs, NDAs, INDs, 505(b)(2)s, new formulation development and scale-up projects. UPM has the capability, capacity, expertise and experience to succeed in all of these categories and scales of work.

UPM IS CAPABLE OF RAPIDLY INVESTIGATING AND EFFECTIVELY TROUBLESHOOTING ISSUES THAT DO ARISE, ENABLING US TO KEEP PROJECTS ON TRACK AND TO CONSISTENTLY MEET TIMELINES.

Flexibility is essential for developing effective, safe and robust formulation and manufacturing process solutions for the challenging drug candidates moving through the pharmaceutical pipeline today. UPM’s experienced group of technical services scientists – with extensive backgrounds in scale-up, technology transfer, product development and validation – can support client projects of all sizes through commercial manufacturing. In addition, UPM has established expertise in a number of different complex chemistries and delivery technologies; from highly potent compounds to many different types of pharmacologicals and oral peptide therapies, to modified-release technologies and dosage forms. We have worked on successful applications for particle coating, sustained-release matrix tablets, tablets with modified-release coatings and complex combination products.

We also have the flexibility to produce both generic and branded products, which enables us to more fully utilize our process and scale-up knowledge and maximize effective and efficient use of our manufacturing capabilities for increased cost-effectiveness and output. At present, we have the capability to produce 700 million capsules annually, 3.5 billion tablet units per year, with 50% of this capacity spoken for by 2021.

Finally, although we take a structured approach to project management that includes assigning each client project to an interdepartmental team headed by a project manager with daily scheduling meetings, unexpected challenges cannot be completely avoided. When they do arise during process development and commercialization, UPM has built-in operational flexibility to address unexpected manufacturing issues, as well as changing client and market needs.

Quality as a Core Value

As a global contract development and manufacturing organization (CDMO), Almac Pharma Services recognizes that quality determines the extent of our success. We prioritize our company-wide quality systems and ensure that they exceed global regulatory standards. Quality is a core value for Almac and is embedded in our organization. It flows down to our business operations through our quality mission statement, which is translated into departmental objectives that are supported by individual objectives assigned to specific staff throughout the business.

Leveraging Internal Metrics

On a more detailed level, our commitment to quality is reflected in internal targets for the Almac Pharma Services business to have three internal targets provide a measurement of our level of compliance and are used to identify areas for continuous improvement. They are challenging targets that we aim to improve on each year and thus enable Almac to stay one step ahead of regulatory expectations.

Importance of Regulatory Intelligence

While many countries around the world (approximately 60-70% of the markets supplied by Almac) accept EU and U.S. regulatory inspection results as sufficient, many countries do not. Some perform “desk-based” inspections in which documents are exchanged with the regulatory agency, but others conduct site inspections. As result, Almac must be prepared to host inspectors from many different countries with their own sets of regulations and different inspection styles and hot-button topics. Intelligence gathering, done in-house, through consultants and in partnership with our clients, is essential to ensuring compliance on a global scale.

Focused Inspection Planning

Regardless of whether an inspection is conducted by an authority from an emerging market or more established authorities, it is scheduled at an unannounced, good preparedness embedded in a quality culture is the key to success. It is important to always have an element of inspection readiness within the business. Good planning involves the preparation of a strong internal team trained on how to host the inspectors and another team ready to manage the inspection. Each team rapidly responds to any critical or major findings, while the FDA inspections closed without any 483s being issued. This is an important lesson for the Almac Pharma Services business to have three regulatory authority inspections within such a short period of time, and it is a great credit to the skilled and experienced teams involved across all locations that they resulted in a positive outcome.

Successful completion of these inspections at our multiple global facilities reflects our ongoing commitment to quality and teamwork across the entire organization.

The inspections of the UK sites were planned, and Almac was aware of them with a few months’ notice. The FDA’s inspection of the U.S. site was unexpected, however. The MHRA inspections of the company were also planned and resolved any issues that are raised. This approach has helped Almac achieve its desired outcome for inspections: no critical issues or 483s.

Three Successful Tandem/Overlapping Inspections

Indeed, that was the recent result of not one but three inspections conducted by the U.S. Food and Drug Administration (FDA) and the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) in late August and early September 2019. Three global regulatory GMP inspections were successfully completed within two weeks at our Charnwood, UK facility, our Craigavon, Northern Ireland facility and our Audubon, Pennsylvania facility. The UK facility provides GMP development and manufacturing of solid oral clinical trial material and the manufacture of commercial products. The global HQ site in Northern Ireland provides GMP and non-GMP pharmaceutical development, commercial-scale manufacturing and packaging of solid oral dosage material, secondary packaging, labelling, serialization and distribution of drug products globally. Our U.S. facility in Audubon provides a range of specialized commercial packaging services, including complex kit assembly for medical devices, combination products and biologic packs.
## CORPORATE SOCIAL RESPONSIBILITY

### GIVING STRUCTURE TO A LONG-TERM CSR STRATEGY

**BY VINCENT MINVIELLE, SERVER**

Since its founding, Servier has adopted a patient-centric focus and has been committed to producing high-quality drugs while simultaneously providing a positive work environment for its employees. Four years ago, the company decided — in light of new challenges facing the pharmaceutical industry — that its corporate social responsibility (CSR) efforts would benefit from more structure. The new CSR strategy is already benefiting Servier’s many stakeholders.

### HISTORY OF CORPORATE SOCIAL RESPONSIBILITY

**CSR at Servier** is a question of conviction, rooted in our culture. Since its creation, the Servier Group has embraced social and environmental responsibility and the importance of pursuing a sustainable economic model. While not previously formalized, CSR is embedded in Servier’s culture, and we practice this responsibility in our relationships with our stakeholders.

Our four main company values are Carrying, Growing by Sharing, Committing to Success and Daring to Innovate. These values align directly with major components of effective CSR initiatives, which address the concerns of people inside and outside the company and the surrounding ecosystem and require commitment and innovation to be successful.

### ESTABLISHING A CSR STRUCTURE

Approximately four years ago, management at Servier determined that the company would greatly benefit if a clear CSR structure and strategy were developed that provide visibility to the value of the many CSR initiatives taking place across the global organization.

A new CSR department was established in 2016 with a mission to propose a strategy and an organization. Today, the department includes a team of seven full-time SMEs. It monitors the progress of action plans, the achievement of goals and predefined extra-financial indicators and contributes to the rollout of CSR initiatives at all of our sites, in all departments and to all employees.

The CSR department works with several bodies, including the Executive Committee, which validates the CSR strategy; the Group CSR Committees, which participates in defining CSR guidelines; and the CSR Operations Committee, which proposes CSR actions based on feedback and competitive intelligence and participates in the implementation of the CSR action plan. The CSR network comprises representatives at each site who contribute to local deployment by including the CSR strategy in site activities and are responsible for extra-financial reporting and communication regarding CSR activities.

### DEFINING A CSR STRATEGY

In 2016, the newly created CSR department conducted a key stakes assessment (a materiality analysis) following ISO 26000 guidelines and using an inclusive and participatory approach. Through interviews with internal and external stakeholders who were asked to describe their expectations for social, environmental and economic activities at Servier, four main CSR commitments and 17 priority stakes were identified to address primary goals.

This work is the basis of our CSR roadmap, which is continuously enriched through constant involvement by key actors with the aim of capitalizing on existing best practices and action plans devised jointly with each department involved in new projects.

Each of the four main CSR commitments is focused on one stakeholder group:

- Servier is a company committed to healthcare (patients);
- Servier cares about people (employees);
- Servier is focused on business practices (business partners);
- Servier aims for a positive footprint (community and environment).

Many of the 17 stakes we identified have become important to the company since its founding. Others are related to new challenges facing Servier and the pharmaceutical industry as a whole, such as climate change.

### TAKING A CSR INVENTORY

Once our CSR strategy was developed, we implemented a step-by-step rollout across the company and communicated our intentions to all of our stakeholders. This information is being used by each department to determine what steps need to be taken to integrate the CSR strategy into their overall business strategies and plans at all levels.

At the same time, Servier began taking an inventory of CSR initiatives, programs and activities underway within each division and at each site within the Group. Many achievements are realized each year at all Servier sites. It is important to inventory these different areas and identify best practices that can be shared across the entire Group.

### IMPARTING VISIBILITY AND VALUE

In August 2019, we published our first Corporate Social Responsibility Report. Because of its legal structure, Servier has no legal obligation to communicate the progress we have achieved along our CSR journey. However, we believe strongly that a commitment to publish an annual report helps to hold the company accountable. In addition, the annual CSR Report provides a mechanism for communicating our CSR successes.

### CONTRIBUTING TO PERFORMANCE

Our CSR policy helps consolidate links with our stakeholders, gives value to the initiatives to which we contribute, and adds to our overall CSR strategy. Our CSR report provides stakeholders with an overview of our CSR efforts.

### FIVE KEY CSR PROJECTS

To better communicate our CSR efforts, Servier selected five CSR key projects we consider to be important on a global basis and that demonstrate the value created by our CSR efforts.

With our Ecodesign by Servier project, our ambition is to include the principles of ecodesign in the development of future drugs, throughout the value chain from R&D to disposal, notably via the choice of raw materials, manufacturing processes and packaging. This global initiative was launched in 2019 by a multidisciplinary project team that is defining the methodology via a pilot project and a Group Ecodesign reference system. During the second phase, the methodology will be progressively applied to all new drugs in development. Benefits are anticipated for patients and in terms of industrial, logistic and environmental performance.

The #ServierDiversity project is an ambitious policy designed to create an even more inclusive work environment that already exists at the company, as well as to promote diversity and equal opportunities to the roll out of CSR initiatives and to fight against discrimination throughout career paths. This project comprises inclusion of diversity principles in our corporate Code of Conduct (in line with our Ethical Charter), training on non-discrimination and follow-up indicators. This policy is in line with our value “Caring” and will benefit everyone, collectively and individually, through its impact on employee engagement and performance, corporate attractiveness and talent retention.

Since its creation, the Servier Group has embraced social and environmental responsibility and the importance of pursuing a sustainable economic model.
The Servier Climate Commitment project involves the development of a low-carbon strategy in line with the Paris COP 21 agreement (Δ<2°C by 2030), with a focus on reducing our direct and indirect impact in terms of greenhouse gases, the supply of carbon-free energy and carbon offsets. We use the internationally recognized SBTi (Science Based Targets initiative) methodology. Two precise objectives and timetables are currently being defined, but numerous actions are already underway, such as the regeneration of solvents, flow chemistry or catalysis at our chemical sites, transition from air travel to shipping for our logistic flows and reduction of energy consumption at our industrial sites and at the head office. Overall, the Group is aiming for carbon neutrality.

NEW RESEARCH INSTITUTE HIGHLIGHTS MANY ASPECTS OF CSR STRATEGY

The Servier 1st Class Partner project involves formalization and implementation of partnership policies that support our partnership model based on mutual respect of economic, ethical and responsible engagement combined with open and transparent communications. CSR criteria are also being gradually incorporated into our purchasing process. Each department is sharing best practices to integrate CSR, and all of us are dedicated to enhance our value creation.

Servier is constructing the new Servier Paris-Saclay Research Institute to house Servier’s research activities located in France by 2022. The nearly €330 million investment underscores Servier’s ongoing commitment to the discovery of innovative therapeutic solutions for patients.

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ABOUT THE AUTHOR

Vincent Minvielle
Corporate Social Responsibility Director, Servier

Vincent Minvielle holds a MSc degree in human resources and management from the DISERNA school in Nice - Sophia Antipolis (France). After two years in Japan and a first experience in LVMH, he joined the Servier Group in 1996. He started as Deputy and then HR Director for the research centers in France. From 2007, he was successively appointed HR Director of Servier in Vietnam (5 years), in Brazil (4 years) and in China (2 years). In October 2016, he was appointed Group CSR Director at French headquarters.

LinkedIn linkedin.com/in/vincentminvielle
Email vincent.minvielle@servier.com

PHARMASALMANAC.COM
PCI Pharma Services has invested heavily in expanding capabilities to meet the growing need for parenteral packaging services to support a range of products from niche, personalized medicines to large-volume treatments.
Our San Diego site has been expanded to operate on either a stand-alone or integrated packaging suites are purpose-built to allow of specialty cold-chain products. The new Operational in September 2019 at the Rockford, Illinois facility and invested in additional infrastructure for the storage and packaging of controlled substances, including unit-dose packaging, for clinical and commercial products at our Philadelphia and Rockford locations. Finally, PCI has created and expanded senior positions in Strategic Marketing, Program Management, Clinical Services and Global Clinical Quality to help us and our clients prepare for the future. These changes in leadership, in addition to our investments in global infrastructure and innovation, ensure support of our continued growth, an enhanced focus on delivering the best customer experience and solidification of our well-recognized position within the industry.

The Philadelphia site is just one component of our ongoing investment in our business, we have a dedicated team of experts to ensure that PCI is able to meet the evolving needs of both existing and potential new customers. The expansion increases our syringe labeling and assembly capacity by approximately 25%, adding top-load cartoning and in-line serialization, as well as furthering our expansion on site cold-chain storage.

PCI has also expanded on the state-of-the-art containing manufacturing facility for the development and manufacturing of high-potency molecules, with increased potential packaging capacity alongside additional liquid filling capacity at our Tredegar, Virginia facility and in additional infrastructure for the storage and packaging of controlled substances, including unit-dose packaging, for clinical and commercial products at our Philadelphia and Rockford locations. PCI has created and expanded senior positions in Strategic Marketing, Program Management, Clinical Services and Global Clinical Quality to help us and our clients prepare for the future. These changes in leadership, in addition to our investments in global infrastructure and innovation, ensure support of our continued growth, an enhanced focus on delivering the best customer experience and solidification of our well-recognized position within the industry.

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PCIs is a global market leader in serialization. We have actively provided serialized commercialization for both domestic and global markets for many years, enabling a robust understanding of the detailed industry requirements. This industry experience was developed through our partnership with leading serialization technology provider Antares, the platform for many of our global serialization services. We have implemented a sophisticated network of technologies to provide serialized product for our global clients. Partnering with clients as they develop and implement their global secure supply chain strategies, PCs dedicated team works to understand requirements providing flexible solutions based on the product package, packaging configuration and ultimate market destination. This includes integrated serialization technologies for highly automated packaging and configurable offline serialization technology capable of providing serialization for almost any product format.

In addition, we support differing regulatory requirements in countries around the world, including in-line product aggregation, providing the confidence of structured relationships in various countries, including in-line product aggregation, providing the confidence of structured relationships in various countries.
Ensuring that patients receive novel medicines is a key driver for working to reduce the time it takes to design and build a new biopharmaceutical facility. Despite the complexity of biopharma projects, CRB’s integrated ONEsolution delivery enables fast-track design and construction, reducing project timelines by four to six months.

SEAMLESS EFFORT IN LESS TIME
When fast-tracking complex projects, design and construction proceed in parallel. With the traditional design-bid-build approach, going from project initiation to completion typically takes approximately 20–30 months. Fast-track projects are generally executed in 16–24 months because the entire process is streamlined.

In a fast-track project, early packages are issued in order to start construction prior to the completion of the full design. For instance, the design package for the foundation and all underground components of the facility are completed first so that work on those aspects can commence while the more complex production process and interior design can be completed. While construction proceeds on the first design package, the architectural package for everything above the floor is developed, taking the needs and concerns of numerous stakeholders into account. When the next package is sent out to bid and construction proceeds, the design team readies the next package, including details regarding the location of power sources, gases and other utilities, the transportation of raw materials – and many other factors – which are established in a final design package that is approved and then sent out for bid. By performing design and construction activities concurrently during the project, timelines can be reduced by as much as 40%.

DESIGN AND CONSTRUCTION STAFFING
Too often in the design and construction industry, firms are given unreasonable demands in an effort to achieve lean operations. Pressures are applied to keep design and construction staffing to a minimum. Because the labor cost of a design and construction management team makes up a very small portion of the overall project costs but has a great effect on the overall success or failure of the project, this is no place to skimp. CRB understands how important it is to have the right number and types of professionals on site at all times. With too few people, long hours are required, mistakes can be made and quality can decline. Equally as important, safety can become an issue. When people are overworked and the project is understaffed, injuries can occur.

APPROPRIATE OUTLOOK NEEDED
For the fast-track approach to be effective in design-build projects, clients must know what they want and have the willingness to share their experience and be involved in the project. They also need to be sufficiently flexible to allow for the development of facility designs in stages.

FOUNDATION OF TRUST
The fast-track approach is appropriate for forward-thinking companies that have established trust with their design-build partner, either through previous relationships or on the basis of recommendations and the company’s reputation and track record of success. Clients must trust that their design and construction partner is honest and forthright when it comes to the dollars and cents of the project. A good design-build partner will always be transparent. Clients must also trust that the firm has the ability to do what it claims it can achieve for fast-track to be successful. In addition to facilitating fast-track processes, this type of trusting relationship invariably leads to the construction of facilities that best meet client needs because relationships are established across the board—from the owner to the architect, the engineers and the construction workers.

INCREASED NEED FOR COLLABORATION
Indeed, fast-track projects cannot succeed without extensive collaboration between the design and construction teams within the engineering procurement and construction (EPC) firm and between the EPC firm and the client. However, the traditional design-bid-build process often creates adversarial relationships among the main players on a project. For example, in the traditional method, the architect provides complete construction documents, but when contractors later find errors or omissions in the design, they ask the owner to pay for these additional costs, which may put them at odds with the designer. Both the contractors and architect want to maximize their profitability while the owner wants to limit spending; the system inherently sets these parties at odds.

The fast-track approach, however, can only effectively be implemented by an integrated design, engineering and construction firm. With a truly integrated EPC, the architects, engineers and construction teams are accustomed to working together day after day. This familiarity breeds better, faster and more consistent outcomes. All of the players are part of the same organization and work to support each other in order to achieve the best outcomes for the client without the added cost of rework and redesign.

CULTURAL ALIGNMENT
To provide the best possible outcome for a given project, it is important for the owner and EPC to have similar company cultures. If both firms share the ideals of “people first” or “technical excellence,” the opportunity for a cohesive team is greater. In addition, the owner and the design-build firm must be in alignment with the project’s subcontractors. CRB, for
BY PERFORMING DESIGN AND CONSTRUCTION ACTIVITIES CONCURRENTLY DURING THE PROJECT, TIMELINES CAN BE REDUCED BY AS MUCH AS 40%.

instance, has a responsive, collaboration-focused culture and specifically selects business partners with a similar culture. All fast-track projects are challenging by nature, perhaps the most challenging for biopharmaceutical facilities given their complexity, the number of stakeholders involved and the extensive regulatory requirements, but, with the right team, a good plan and an established collaborative relationship, we have been able to reduce project timelines from 20 months to one year, which enables our clients to get their novel therapies to patients much faster.

Our ONEsolution™ process is a genuinely integrated approach. Unlike large construction firms that hire architects and engineers and assign them discrete tasks, CRB is a full-service firm. We can provide support at any stage of a project – from operations improvement to predesign and pre-construction through procurement and construction. Our integrated teams of architects, designers and engineers work with one another daily. These cohesive teams have expertise in supporting clients from the conception of an idea for a facility to the initiation of operations.

CRB specializes in listening to clients and determining their specific fast-track designs. We begin this process by considering the purpose of the facility and determining its basic steps that can be taken to sufficiently improve operations, eliminating the need for a new facility entirely.

CRB’S ONEsolution™
CRB specializes in listening to clients and determining their specific fast-track designs. We begin this process by considering the purpose of the facility and designing it around our client’s budget. With our fast-track approach and transparent, collaborative relationships, we have been able to reduce project timelines from 20 months to one year, which enables our clients to get their novel therapies to patients much faster.

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OPERATIONS IMPROVEMENT
CRB’s operations improvement team has the experience, knowledge and ability to assess the current operations at a facility and determine what needs to be done to make it run more efficiently in terms of productivity, energy consumption and personnel movements. This information is used to inform the design of the new facility. However, in some cases, the team identifies basic steps that can be taken to sufficiently improve operations, eliminating the need for a new facility entirely.

SMALL COMPANY SERVICE
The operations team is just one example of how CRB, despite being a worldwide organization with nearly 1,200 employees, can perform like a small company when appropriate. Projects are led out of local offices with teams of people accustomed to working together. Team size and composition vary depending on the size and type of facility.

Larger projects are managed by a project director in charge of design who is supported by design and construction project managers. These three individuals serve as contact points for the customer. Mechanical, electrical and process leads and engineers of various types may work on the design team. Construction managers, superintendents, engineers, estimators and safety staff are typically part of the construction team.

Smaller projects, on the other hand, may have as few as three people. The team is tailored to the project to ensure the leanest solution that can provide the best possible results for both the client and CRB.

KEEPING OUR PURPOSE IN MIND
At CRB, we feel lucky to be involved in the pharmaceutical industry and to have the opportunity to be in a position to help people by bringing facilities that manufacture lifesaving medicines to fruition.

Many of our recent projects are intended for the production of next-generation therapies, including cell and gene therapies and other biologic drugs. One recent example was a facility in Pearland, Texas that remains the largest dedicated cell and gene therapy manufacturing facility in the world. These facilities are highly complex, and completing their design and construction in a fast-track manner is not easy. Unless properly managed, there is a potential to get bogged down by day-to-day responsibilities because we are constantly working to ensure that everything is done right.

To avoid this common issue, we make a point of taking a step back to remember why we are pursuing the fast-track approach. The reason we are in such a rush to build the facility and make it operational as quickly as possible is that these manufacturing plants produce treatments that in many cases can cure diseases that previously could not be treated in any way — especially for pediatric patients. When working long hours to move fast-track projects along, thinking about those patients gives us a real sense of purpose and makes our efforts that much more worthwhile.

ABOUT THE AUTHOR

Tim Tench
Senior Project Manager, CRB

Tim has over 18 years of experience in all types of construction projects, with a focus on commercial and industrial facilities. His experience includes all aspects of construction operations and life cycle project management, concept development, pre-construction, estimating, design review, constructability review, scope variance control, scope development, equipment procurement, cost control, scheduling, startup, commission, validation and final turnover.

LinkedIn www.linkedin.com/in/tim-tench-2364592
Email tim.tench@crbusa.com

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38 PHARMA’S ALMANAC GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS | 04-2019
The pharmaceutical industry is increasingly focused on the development of next-generation drug products that allow the targeted delivery of active ingredients with multiple functionalities, increasing both efficacy and safety. Bi- and multispecific antibodies are prime examples of new drug substances with the potential to offer higher potency combined with new mechanisms of action while also reducing the cost and time for drug development.

MARKET GROWTH REFLECTS INCREASING INTEREST
Currently, two U.S. FDA-approved bispecific antibody (BsAb) products are on the market: Removab (catumaxomab) from Fresenius Biotech and Trion Pharma for the treatment of patients with malignant ascites and Blincyto (blinatumomab for injection) from Amgen for the treatment of relapsed/refractory acute lymphoblastic leukemia. There are more than 85 BsAbs in clinical development today, and this number is expected to increase. Researchers from academia and industry, including big pharma and small, specialty biotech firms, are advancing new bi/multispecific modalities, and this is happening at a much faster rate than standard mAbs. Overall, the pipeline of new molecular formats is predicted to grow at up to three times the rate of standard mAbs through to 2025, with the majority of BsAbs targeting cancer indications. By 2025, the value of the global market for BsAbs will surpass $8 billion as new molecules are introduced to the market and commercial products gain approvals for additional indications.

MANY BENEFITS OF BI/MULTISPECIFIC MODALITIES
The interest in bispecific antibodies is driven by their potential to be both more precisely targeted and more potent than conventional mAbs. BsAbs are designed to bind to two separate antigens or different epitopes of the same antigen. The close proximity of the binding/interaction sites can lead to the formation of new protein complexes and trigger new cellular contacts. In many cases, the enhancements are greater than if two individual drugs were administered as a combination therapy. BsAbs may also provide access to new therapeutic targets or combinations of targets not possible with mAbs.

With two or more sites for interacting with the target cell, more targeted binding can be achieved and additional immune responses can be activated via the redirection of cytotoxic immune effector cells, such as T cells and natural killer (NK) cells, leading to significantly greater targeted cytotoxic effects. Alternatively, BsAbs can act as inhibitors of two proteins within a single disease pathway or from different signaling cascades simultaneously. The involvement of multiple binding sites and different pathways may also reduce the potential for development of resistance.

Multispecific antibodies designed as T cell engagers may also offer advantages over autologous chimeric antigen receptor (CAR) T cell therapies, as they would be available off the shelf but not carry the potential for immunogenic responses associated with allogeneic cell therapies.

AS OF MID-2019, MORE THAN 20 COMMERCIALIZED TECHNOLOGY PLATFORMS WERE AVAILABLE FOR BSAB DEVELOPMENT AND PRODUCTION.

ZOO OF MOLECULES
Advances in protein engineering have led to the development of many different bi/multispecific modalities: a zoo of molecules made through the combination of different numbers and formats of heavy and light chains. BsAbs are generally categorized on the basis of whether they contain a Fragment crystallizable (Fc) region, and the pharmacokinetics, half-life, Fc receptor-mediated function (if applicable) and biological activity can vary significantly depending on the structural details.
Some bi/multispecific Abs are designed to improve the effector function or extend the half-lives so that they are comparable to conventional mAbs. These are interesting as second-generation products but do not provide access to new biological targets. A second group with additional binding sites for higher specificity might enable the realization of new therapeutic concepts. These Abs are based on antibody fragments or other protein scaffolds that can be linked together, and a fourth group includes conjugates of antibodies with other molecules, such as antibody-drug conjugates. BiAbs can also be generated by fusing different antibody-producing lines, such as scFv or Fab, to other protein domains, enabling further functionalization. Most candidates in the clinic today are either BITEs, DARTs, homodimeric “knob-in-holes” technology, which enforces heterodimer formation by introducing a “bulky knob-like structure” on one arm and a “hole-like structure on the other.”

VARIous MANUFACTURING APPROACHES

As of mid-2019, more than 20 commercialized technology platforms were available for BsAb antibody production. Platforms under development by companies such as Amunix, Invenra, Glycotope, Xencor, Novartis, Daiichi Sankyo and Roche are intended to streamline bi/multispecific antibody development, increase patient safety and enhance efficacy. As more complex proteins make it through approval and the number of biotherapeutics advanced to clinical and preclinical stages, the landscape of next-generation antibodies and biologics is evolving. The advent of advanced molecular biology and flexible manufacturing systems will be essential to making them a commercial reality.

REFERENCES


4. Lonza. “Lonza’s XS™ Pichia Expression System: Biologics, proteins, including BsAbs, the pXC Multidomain vector allows assembly of either a double, triple, or quadruple subtype in a single vector using type I restriction enzymes, Site-specific conjugation (SSC) vectors are also available to simplify production of conjugation-competent antibodies.”

5. Recently, we also added the proven transposon-based technology piggyBac™ to this toolbox. PiggyBac preferentially targets large gene cassettes to stable regions of the genome, providing high transfection efficiency. Lonza is also evaluating additional synthetic promoters that will enable fine-tuning of expression of different components in a single construct with the molecule. By modulating expression of the components, the increase in the proportion of correctly paired chains will help overcome some of the purification and analytical issues outlined below.

For certain new-molecular formats or components, microbial systems may provide a faster and more cost-effective solution. Lonza’s X™ Plchica Expression Systems allow rapid commercial screening and straightforward fermentation regimes that yield high titers (up to 30 g/L) in short time. Due to gene optimization and synthesis, primary and secondary screening and the production of milligram quantities of the target BsAbs are achieved in just 10-12 weeks.

For all downstream processes, the use of platform solutions is more challenging and product-related impurities must be achieved based on the specific characteristics of the BsAbs. Alternative resins (rather than protein A) are often needed for some BsAbs due to absence of the Fc region. Resin screening is therefore typically required, and much more time and effort is spent on characterizing the right resins for purification of these BsAbs. As many of the candidate BsAbs move through the clinic, challenges with scale-up of manufacturing processes are a growing concern. Many of the current technologies used in the laboratory are not applicable in the clinic, and significant development efforts are underway to identify practical commercial-scale solutions.

Finally, alternative solutions for BiAbs may be necessary due to their higher potency, such as micro delivery systems.

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Finally, alternative solutions for BiAbs may be necessary due to their higher potency, such as micro delivery systems.

Given the multiple heavy and light chains, simple gel analyses are insufficient for mapping the essential effector function. The higher potency of BsAbs also demands the development of analytical methods with much higher sensitivities.

While methods must be tailored, high-throughput analytical capabilities and access to rapid analytical tools are also essential. The goal is to establish platform solutions for aspects of analytical work that can be applied across different bi/multispecific antibody modalities.

SUMMARY

At Lonza, we are building capabilities to meet the manufacturing needs of next-generation protein therapeutics, including bi-specific antibodies. Through our work with companies in preclinical development, we see that around two-thirds of the early pipeline consists of non-standard antibodies. Supporting these therapies with rapid and scalable manufacturing for drug substance and drug product will be vital in offering better outcomes for patients.

In addition, many of the companies developing these new molecular formats are small, even virtual biotechs with a strategy of commercializing their molecule. Many have little interest in building in-house manufacturing capacity and are looking for partners who can not only provide the right technical solutions but can also de-risk their path to market and ensure they are set up to scale when needed.

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ANALYTICAL ISSUES

Product-related impurities, such as aggregates and variants, are generally present at a higher concentration than in a monoclonal antibody (mAb) product. These impurities can have very similar physicochemical characteristics to the product itself, such as hydrophobicity and net surface charge. To remove these impurities, extra chromatography steps are often required, but, given the similarities between the molecules, the resolution for these chromatography steps is generally lower than in a mAb process. High yields may need to be sacrificed to achieve the target purity, and optimization of these steps can be more difficult than in a mAb process. It is also critical to be able to identify these product-related impurities and clearly understand which molecules are present in the supernatant to develop effective purification processes.

As more complex protein molecules make it through approval and the number of biotherapeutics advanced to clinical and preclinical stages, the landscape of next-generation antibodies and biologics is evolving. The advent of advanced molecular biology and flexible manufacturing systems will be essential to making them a commercial reality.
 BIOPRINTED ORGANS ARE HIGHLY COMPLEX STRUCTURES WITH SPECIFIC VASCULATURE FOR BLOOD AND OXYGEN FLOW COMPRISING MULTIPLE CELL TYPES THAT COMMUNICATE WITH ONE ANOTHER.

**BIOPRINTING METHODS**

Bioprinted organs are highly complex structures with specific vasculature for blood and oxygen flow comprising multiple cell types that communicate with one another. Developing 3D printing methods that enable manipulation of the biological materials without damage or degradation and result in functioning organs remains a significant challenge.

The choice of printing method is generally dictated by the bioink formulation, the desired printing speed and the structural design. The three main methods of bio-printing include extrusion-based, inkjet-based and laser-assisted bioprinting. In extrusion-based bioprinting, structural and cellular layers are printed in alternating fashion. With this technique, however, there is no special control of cellular deposition, and shear stress can impact cell viability. Inkjet and laser-guided bioprinting provide greater spatial control, but the heat generated in these processes can damage the cells, leading to reduced cell viability. Laser printing is rapid but requires inks with low viscosity, while laser-assisted printers can tolerate highly viscous inks.

Other methods include stereolithography, which provides high resolution but is a slow process and can impact cell viability. Fused deposition modeling produces porous structures but is a high-heat process not suitable for cellular formulations. Selective laser sintering is useful for making complex structures, but also involves heat and is not suitable for cell-based biinks.

Several research groups have been focused on developing improved methods for organ and tissue bioprinting.

A new process developed by scientists at Vienna University of Technology that relies on two-photon polymerization allows for the creation of very fine structures with high precision at a speed of greater than one meter per second and is compatible with cellular materials. The SWIFT (sacrificial writing into functional tissue) technique created by researchers from Harvard's Wyss Institute for Biologically Inspired Engineering and John A. Paulson School of Engineering and Applied Sciences (SEAS) enables 3D printing of vascular channels into living matrices composed of stem cell–derived organ building blocks (OBs), yielding viable, organ-specific tissues in high cellular density and function.

The suspended layer additive manufacturing (SLAM) technique developed at the University of Birmingham uses low viscosity biopolymers in a self-healing fluid gel matrix to generate soft materials in very fine detail, while the new open-source technology referred to as stereolithography apparatus for tissue engineering (SLATE) from Rice's Brown School of Engineering allows for the printing of complex vascular networks that mimic the body's natural passageways for blood, air, lymph and other vital fluids.

Meanwhile, the freeform reversible embedding of suspended hydrogels (FRESH) extrusion-based bioprinting technology from scientists at Carnegie Mellon University allows fabrication of collagen scaffolds capable of replicating the structure and function of tissues and organs.

Scientists at the Friedrich-Alexander-
In August 2019, iBio entered into a Master Services Agreement ("MSA") with Lung Biotechnology BPC to scale up production of Collagen bioinks in tobacco plants from CellPlant Ltd. As part of the technology transfer process, iBio will develop and commercialize downstream purification process for mCollagen.

BIOKINS
Biosinks for 3D bioprinting can contain a variety of different ingredients. Some may be based only on proteins of polymers intended to form the scaffold for the tissue or organ (cells are added later). Others may contain the cells and components that aid growth and maturation (scaffold-free approach). You could include a combination of structural and cellular materials (cell-scaffold-based approach). Regardless, all biomaterials in a bioink must be sterile and have appropriate mechanical, thermal and other physical properties, plus be biocompatible and retain their bioactivity after printing.27

The structural framework can be produced using structural biosinks containing synthetic polymers, including polyethylene-polyglycol (PEG), gelatin, methacrylate (GelMA) and Pluronic® or natural proteins, such as collagen, gelatin, hyaluronic acid, silk, alginate, agarose, fibrin, fibronec- tin, elastin, laminin and other decellularized extracellular matrix (ECM)-based materials. Other acellular materials can also be used to provide structural support and sites for cell attachment and to impart porosity. Examples include chitosan, polycellulose and polylactic acid (PLA), and polycaprolactone (PCL), among others.27

Cell-encapsulating hydrogels allow the creation of living tissue structures with precise control over the attachment and spatial distribution of the cells and other biomolecules in the scaffold.25,26 Natural biopolymers are preferable for 3D bioprinting of organs and tissues because they can communicate with cells and readily undergo reorganization of the ECM as needed.28 Sacrificial bioinks are deposited and then removed to create channels that enable the formation of vascular networks. They are often water soluble or degrade to enable the formation of vascular networks.29

Functional bioinks contain compounds that help direct the formation of the tissue or organ. They often contain extracellular matrix factors and compounds that enable cell differentiation. Tissues that are implant- ed before they are fully developed often require external support, which is provided through the use of supportive bioinks that generate protective lattices produced from polymeric materials, such as polyactic-co-glycolic acid (PLGA).27

Much research to date has focused on collagen, but there is growing recognition that optimized combinations of different proteins will be needed to mimic the multifaceted ECM. Future bioinks may enable 4D bioprinting—or the print- ing of biomaterials that respond to external stimuli in some way, such as changing their shape, structure or function.28

SIGNIFICANT MARKET OPPORTUNITY

Given the rapid progress and high level of funding taking place in the bioprinting field, market research firm 10TechRx predicts that the value of the global market for 3D bioprinting—including hardware, software, ingredients and services—will reach $1.0 billion by 2028.29 Notably, this value only includes bioprinting that involves the deposition of materials in a spatially controlled manner in the absence of any pre-existing scaffold.

Initial revenues will be generated by applications in product development and testing for cosmetics, consumer goods and drugs, while, in the longer term, regenerative medicine, cell-based bio- sensors and food production will become important. Regenerative medicine has the potential to be the largest application for 3D bioprinting in the future.28

FACILITATING R&D AND COMMERCIALIZATION WITH PLANT-BASED EXPRESSION TECHNOLOGY

Production of recombinant proteins for the formulation of bioinks used in the 3D printing of tissues and organs is an important strategic growth area for iBio. The iBio-plant-based Expression® (iBioPE)™ Expression System is ideally suited to the produc- tion of bioinks, maturegans and other biologics for use in 3D bioprinting. Green systems are generally economical and in-depth- matically defined in media specifically designed, climatically controlled indoor grow rooms. Following a short growth period, the plants are exposed to a mild vacuum with leaves submerged in a solution of agrobacteria containing the engineered recombinant virus. The plants absorb the agrobacteria through their stoma to equilibrate pressure when the vacuum is released. With this method, gram quantities of target protein in the plant leaves per kilogram of fresh plant material can be released. With this method, gram quantities of target protein in the plant leaves per kilogram of fresh plant material can be released. Within approximately 8 weeks.

iBio's plant-based production platform offers a better safety profile than animal systems, and the automated hydropon- ics system presents reduced variability compared with soil-grown plant-made formulations. In addition, the platform facilitates customization of gly- cosylation, allowing better glycosylation controls compared with bacteria (which do not glycosylate proteins), yeast and hyperglycosylates and Chinese hamster ovary or myeloma mammalian lines (which fail to precisely mimic human glycosyl- ation patterns). Due to the cost-effectiveness of our plant-based platform combined with higher yields, inherent scalability and tighter process control, the FastPharming® System has great potential for facilitating the rapid development of new varieties of bioprinted tissues and organs. Simplifi- cation of protein production allows rapid manufacture of biologics for R&D work. Processes can then be readily scaled to GMP quantities for clinical testing and commercial production without the scale-up issues that plague other, bioseer- requiring production methods.28

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here is unprecedented pressure on the biopharmaceutical industry to improve the performance of monoclonal antibody (mAb) development and manufacturing processes. There are several factors essential to addressing this challenge, including flexibility, in which product change-over time is reduced; quality, as defined by increased robustness and reliability; speed, in which production and product release are accelerated; and cost reductions in manufacturing and capital expenditure.

Improving mAbs development and manufacturing processes

Improvements in processes and productivity can enable smaller and simpler facilities and lower costs, leading to several advantages, including the ability to:

- Improve competitiveness and long-term sustainability.
- Enable business models for new biologics and novel therapies.
- Supply developing countries with affordable biologics, and
- Reach emerging markets profitably.

A key strategy for delivering higher productivity and enabling more flexible manufacturing processes is the adoption of single-use technologies. We have witnessed major improvements in upstream processes with single-use bioreactors and perfusion strategies that can deliver significantly higher titers. In parallel, single-use approaches are being incorporated into downstream processes, including clarification, tangential flow filtration, virus filtration and final fill. Owing to a lack of more productive and efficient alternatives, the use of low-throughput chromatography processes requiring large and expensive units has continued, however, preventing implementation of a fully single-use downstream flow path.

Resin-based columns are often oversized to match new achievements in upstream productivity, and this translates into a large footprint requiring a large amount of maintenance, quality assurance and quality control labor. Such high capital and high operating-expense facilities require amortization to fully utilize resin media’s lifetime to achieve any kind of cost efficiency. While costs can be reduced via economies of scale for large-volume products, this is not the direction in which industry is heading. Moreover, amortization is a luxury that usually is not realized during clinical production; media lifetime is rarely fully utilized due to a limited quantity requirement and the high failure rate in clinical development.

An important initiative that is gaining momentum is the use of membranes for high-productivity chromatographic purification processes that match upstream efficiency without the need for oversizing. Capital expenditures can be reduced due to the possibility of downsizing the chromatography unit operation, which derives from lower costs for media and supporting systems and hardware. Elimination of column packing, unpacking, cleaning and storage between batches, as well as associated labor and validation requirements, further reduces the operational expenses. In parallel, the single-use, plug-and-play nature of membrane chromatography in downstream operations using this approach can increase flexibility, resulting in more rapid changeovers, which can increase production and support creation of a multi-product facility.

Advancements in membrane chromatography

In contrast to resin chromatography, where the mass transfer is dominated by diffusion and requires long residence time to achieve decent binding capacity, membrane chromatography relies on an intensified high-productivity, truly single-use purification platform. The high-binding, short residence times of single-use membrane chromatography presented in this article are enabled by the combination of a non-woven reinforcing mesh skeleton and porous hydrogel containing functional groups (FIGURE 1). The skeleton provides mechanical strength and durability, while the hydrogel creates large chromatography surface area that contains a high density of functional groups with interconnected pores allowing for convective flow channels to achieve high flow rates. The high density of binding exhibit modest binding capacity due to a limitation of binding site density. Advances in membrane science that have focused on resolving this fundamental trade-off have resulted in affinity and ion-exchange membranes with a combination of high dynam-
sites, together with a macroporous structure, enables high binding capacity for not only proteins, but also large molecules, such as virus and DNA, at seconds resident time.

This innovative membrane chromatography design offers a rapid binding mechanism that can be exploited to achieve very short residence times — on the order of seconds — without compromising binding capacity, which together enable very high productivity purification processes. Below, we describe the use and benefits of a fully single-use membrane chromatography approach for intensified capture followed by intermediate and polishing purification for host cell protein (HCP), aggregate removal, and viral clearance.

PROTEIN A MEMBRANE FOR INTENSIFIED CAPTURE

A novel Protein A affinity chromatography membrane has been developed for rapid multi-cycling bind and elutes the capture membrane has been developed for rapid membrane chromatography is a platformable tool.

The combination of cation and anion exchange technology enables a new paradigm for mAb manufacturing, offering key benefits to address productivity and cost challenges:

- Cytotoxicity attributes are comparable to reference resin processes
- Improved productivity enables smaller columns and facilities
- Novel Protein A membrane enables fully single-use manufacturing
- Potential affinity membranes for other applications enables process intensification
- Fully single-use processes enable flexible, low-cost facilities and promote better facility utilization

Note: Content originally published in European Biopharmaceutical Review.


cation exchange (CEX) membrane for high-productivity aggregate and HCP clearance

The use of CEX membrane in flow-through mode delivers efficient aggregate and HCP removal at a 12.5x higher mAb load capacity compared with beads. This high productivity intermediate purification reduces process time and buffer consumption and allows:

- Right-sized purification media
- Reduced equipment footprint, and
- True single-use operation.

Anion exchange (AEX) membrane for effective impurity and viral clearance at unmatched load capacity

The high ligand density on our advanced AEX membrane provides a more robust impurity removal and viral clearance and a >60x higher mAb load capacity than beads to further reduce media volume requirement (Figure 4). The impurity clearance performance (HCP and viral clearance) is independent of the load up to 20 kg/L, enabling downsizing of the unit operation. Good viral clearance is achieved over a range of buffer and pH conditions, which provide a wide design space for operation. Performance is maintained at high conductivity (0 mS/cm) even in phosphate buffer, which reduces feed dilution or buffer exchange requirement for a simplified process with reduced cost factors.

Gary Skarja, Ph.D.
Head of Membrane Chromatography R&D, MilliporeSigma

Gary Skarja has 20 years of experience leading dynamic research and development teams in a variety of life sciences sectors, including biopharma, medical device and cell and gene therapy. He holds over 20 patents related to novel polymers, devices and processes for life science applications. Gary has bachelor’s and master’s degrees in chemical engineering from McMaster University and a Ph.D. in Chemical Engineering from the University of Toronto.
Gene Therapy R&D Accelerates

Since the first discoveries suggesting that gene therapy might be possible, the field has experienced significant advances and setbacks. Research efforts have expanded greatly in recent years following the development of safer viral vectors and the advent of gene-editing technologies. The possibilities seem endless, and many companies are exploring them.

Successful gene therapies address significant unmet medical needs, have clear mechanisms of action and can readily reach the target organ. Several gene therapies, including cell therapies that have been genetically modified, have met these criteria and reached the market.

As of October 2018, Pharma Intelligence had identified 11 gene therapies that had been approved in China, South Korea, Russia, Singapore, Taiwan, and the United States. However, not all are currently on the market. The first was approved in 2015 in China, but most have been approved in the EU and United States within the last three years. Some have been withdrawn due to limited sales. Since then, Novartis’ Zolgensma (onasemnogene abeparvovec-xioi) for spinal muscular atrophy was approved in the United States, and bluebird bio’s Zyntre
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Several Approved Products

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Numerous Growth Drivers

The successes achieved with these approved gene and gene-modified cell therapies and the potential for these products to cure – rather than just treat – serious conditions has driven significant investment in the sector, venture capital and large and mid-sized pharma companies are actively funding startups and more established firms focused on developing novel gene therapies, as well as investing in their own programs. During just the first half of 2019, gene and gene-modified cell therapy companies raised $4.3 billion. Regulatory agencies have also established approval pathways and provided guidance on regenerative medicines, including gene and gene-modified cell thera
pies. The European Medicines Agency created a regulatory framework for advanced therapy medicinal products (ATMPs) in 2007, while the U.S. Food and Drug Administration implemented the acceler
cated regenerative medicine advanced therapy (RMAT) designation in 2016.

As a result, the value of the global market for genetic modification therapies is growing at a record pace. Various market research firms estimate a CAGR for the sector of 20–50%, with most estimates in the 30–40% range,1,4 with the global value projected to surpass $5 billion by 2026.6

Strong Clinical Pipeline

The rich clinical pipeline of gene-modified cell therapies is also driving rapid growth in the sector. According to the Alliance for Regenerative Medicine, 386 gene therapy and 410 gene-modified cell therapy clinical trials were underway at the end of the first half of 2019, accounting for nearly 79% of all regenerative medicine trials.6 The bulk (85%) of the studies were phase II trials, followed by phase I (39%) and phase III (6%). Many of the therapies in phase III development could be commercialized by the end of 20207 and as many as three quarters of products in early clinical development could reach the market by the late 2020s.8

Along with the rapid rise in numbers of clinical trials has been an increase in the number of gene and cell therapy-related journal articles, patents and substances registered by the Chemical Abstracts Service EAS. CAS reports that, of the 8500 substances registered in the last 30 years, most were added in the last 10 years, with 600 added in the first six months of 2018.7 As a result, the value of the global market for genetic modification therapies is growing at a record pace. Various market research firms estimate a CAGR for the sector of 20–50%, with most estimates in the 30–40% range,1,4 with the global value projected to surpass $5 billion by 2026.6

In Vivo and Ex Vivo

Gene and gene-modified cell therapies differ in the method used to modify the target cells. Gene therapies are in vivo treatments in which the targeted genes or genetic modifications are administered directly into cells that are inside the body. Gene-modified cell therapies are ex vivo treatments in which cells, either from the patient (autologous) or a healthy donor (allogeneic or patient-specific), are modified and then administered to the patient. According to Pharma Intelligence, approximately 55% of pipeline candidates are in vivo or gene therapies, and most of the ex vivo investigative therapies are autologous.2 Chimeric antigen receptor (CAR) T cell therapy is the most widely investigated ex vivo approach, with lead
ing biomarkers including CD19, CD20, HER2 and CD30, among others.9 Other cell types of interest for ex vivo therapies include natural killer (NK) cells, human stem cells (HSCs) and Listeria-based, tumour-infiltrating lymphocytes (TILs).3 Some gene therapies regulate the
expression of genes through the delivery of RNA. The predominant technologies include RNA interference (RNAi), which halts production of disease-causing proteins; antisense interference, which inhibits or enhances translation of mRNA into target proteins; microRNA modification (miRNA), which also inhibits or enhances translation of mRNA into proteins; and messenger RNA (mRNA), which generates therapeutic proteins. RNA therapies can also be in vivo or ex vivo.

**Viral Vector Delivery Dominates**

Regardless of the type of therapy, the genetic material must be delivered into cells using some type of delivery system. The choices fall into one of two categories: viral or nonviral.

The first generation of gene therapies were developed using viral vectors, and this method dominates today (nearly 70% of candidates). Among viral vectors, adeno-associated viruses (AAV) and lentiviruses (LV) are most widely used owing to their reduced immunogenicity and long-term expression capacity and megamolecules.1 As potential vector technologies for gene delivery include retroviruses and gamma retrovirus-modified herpes simplex virus, adenoassociated virus, vaccinia virus and baculovirus.

Significant attention is being paid to the development of nonviral delivery technologies that eliminate the safety concerns associated with viral vectors. Examples include injection of naked DNA, electroporation, sonoporation, magnetofection and the use of oligonucleotides, lipoplexes, dendrimers or inorganic nanoparticles, which may also be amenable to large-scale production.2 Most of these approaches exhibit lower transcription efficiencies, but progress is being achieved.

**Gene Editing Advances**

Gene editing, which relies on the use of engineered nucleases to modify DNA sequences, provides yet another approach to gene therapy development. In this case, the dysfunctional gene is manipulated, removed, rather than adding a functional gene and leaving the impaired genetic material in the cell. Advancements in gene editing technologies have made it possible to more precisely repair errors in the genetic code and have led to acceptance of this technology for the development of new medicines. The CRISPRCas9 clusters regularly interspaced short palindromic repeats (CRISPR-associated nuclelease 9) system received the most attention, because it enables the efficient and precise insertion, deletion, modification or replacement of specific genes.3 Other technologies in use include transcription activator-like effector nucleases (TALENs), zinc finger nucleases (ZFNs), and megamolecules.4

There are significant concerns regarding the use of genetic editing in the development of new drugs, particularly with respect to off-targeting. Only in the last couple of years have candidates entered into clinical trials, and most target severe genetic diseases that are typically rarer, for which the benefits would dramatically outweigh the risks. Some of these gene therapies are designed to stop production of a protein (gene knock-out), replace or repair a dysfunctional protein (gene correction) or start production of a new protein (gene insertion).5

Continued development of gene-editing technologies that have improved targeting and greater specificity is ongoing, as is work to develop tools that are capable of editing multiple genes simultaneously, which would open the door for gene therapies that treat polycystic diseases such as Alzheimer’s disease and diabetes.6

**Focus on Oncology and Rare Diseases**

Of the 1,069 clinical trials underway for regenerative medicines, 60% address oncology indications, while 6% and 5% are for cardiovascular and metabolic and genetic disorders.

**Phileads of Gene Therapy Developers**

The companies developing gene therapies include both small biotechs and larger biopharmaceutical firms, with nearly 400 companies focused on the development of stage candidates, according to a report from Transparency Market Intelligence: Informa White Paper. Nov. 2018. Web.

Many Manufacturing Considerations

There are numerous factors that must be considered when establishing a manufacturing strategy for gene and gene-modified cell therapies. First, the disease target, the dose for each patient, the size of the patient population and the expected market penetration will dictate the quantity of product that must be produced. Whether the product is an allogenic or autologous therapy is a key consideration.7 Ex vivo therapies require transfection and cell expansion via cell culture, while in vivo therapies only require vector manufacturing. Production processes for autologous therapies must be scaled out, while those for allogenic treatments can be scaled up. The choice of viral or nonviral delivery and the specific vector type (i.e., lentivirus, recombinant adeno-associated virus, plasmid DNA) have direct impacts on the optimal upstream and downstream production platforms – many of which are emerging or still under development – control strategies and analytical requirements.8 The possible regulatory pathways must also be considered, particularly whether an expedited approval process will be sought, which will affect manufacturing timelines. Equally important is the decision regarding where manufacturing will take place – in house or at a contract development and manufacturing organization (CDMO).9 Either way, access to both capacity in appropriately designed facilities leveraging appropriate technologies must be established.10

**Complex Processes**

The manufacturing processes for gene and gene-modified cell therapies are complex. The Spark Therapeutics biology license application for Luxturna was nearly 60,000 pages long, with most of the information related to manufacturing, not clinical data.11 Indeed, U.S. FDA commissioner Scott Gottlieb has noted that approximately 80% of the standard review time for gene therapies is spent on manufacturing and quality issues.12

Those therapies that utilize viral vectors – the majority – require manufacturing the viral vectors, which can be challenging, because viruses often kill the cells used to produce them and are much larger than recombinant proteins and antibodies.13 Transient expression of the components essential to produce a virus also limits fills.14 Manufacturing of viral vectors includes production of plasmids encoding helper virus functions and the therapeutic gene and cell lines used to manufacture the vector and other materials, followed by transfection or the generation of mammalian or insect producer cell lines followed by infection; harvesting, purification, characterization, formulation and fill/finish.15 Ex vivo products require additional cell culture to expand the target cells that must then be genetically modified, purified, formulated and freeze dried.

Production of gene therapies that rely on nonviral vectors for gene delivery is similarly complex.

References


In most cases, upstream processes are highly product-specific. Analytical methods must also be tailored to the specific viral vector and gene of interest. Thus, the manufacture of gene and mod- ified cell therapies is not readily amenable to a platform approach. Downstream processes, however, tend to be similar to those used for conventional biologics, including chromatography, buffer exchange, and viral clearance.

Need for Practical Production Technologies

Rapid introduction of gene therapies to the market requires the development of scalable processes that are robust, reproducible and ensure high-quality product at a reasonable cost. Manufacturing issues – particularly scale-up challenges – for gene therapies are a significant concern for the FDA. Some vendors are looking to develop automated, end-to-end integrated, scalable platforms leveraging single-use technologies and continuous bioprocessing. Cell line designs for more product suspension cell culture are needed for use with these platform technologies. There is also a focus on developing standardized yet flexible viral vector components that can be readily produced on a large scale. These approaches leverage new closed bioreactor technologies that enable cost-effective production at up to 2000-L scales. New process control technologies designed for viral vector production systems are also leading to more consistent processes and higher-quality products.

Better solutions are also needed to increase both primary and secondary virus titer to reduce the need for downstream purification. Examples include improved or alternative methods for clarification and particle capture that do not damage viral vectors and offer enhanced productivity. Platform purification processes for common viral vectors would be highly beneficial as well.

Managing raw materials is also a challenge, particularly for autologous ex vivo therapies that require modification and growth of patient cells. For all gene therapies, ensuring that all biologic raw materials are free of adventitious agents and that single-use components do not impact production processes is essential. Appropriate risk-management strategies are needed to ensure that raw materials are fit for purpose and of the appropriate quality.

Analytical method development can also be challenging, owing to the complexity of viral vectors and gene-modified cell therapies. As such, a multifaceted approach using multiple orthogonal methods is essential to accurately and confidently understand the physicochemical properties and quality of viral vector products.

Application of digital droplet polymerase chain reaction (ddPCR) offers significant advantages over standard quantitative PCR methods, allowing for absolute, rather than relative, quantification of the target DNA molecules present in a sample, an ability that is important for numerous analytical assays necessary for viral vector production and characterization.

Formulae approaches that allow for the manufacture of viral vector products that are stable at room and elevated temperature would eliminate the need for cold-chain distribution, enabling simplification of the supply chain. Low-shear filling protocols would provide products with reduced effects on viral vector structure and potency.

Ongoing Investment and M&A

The demand for CDMO services in the gene and cell therapy space is driving significant investment and M&A activity. Some of the biggest moves have involved the acquisition of CDMOs with expertise in viral vectors and gene and cell therapy manufacturing, including Brammer Bio by Thermo Fisher Scientific ($1.7 billion in March 2019), and Paragon Bioservices, Inc. by Catalent ($1.2 billion in 2019). Paragon opened a new 200,000-ft2 4GTM gene therapy manufacturing facility in Maryland in April 2019.

Other recent investments by contract manufacturers include construction of a facility in Pearland, Texas by Lonza that doubled its production capacity for viral gene and virally modified cell therapy cell lines which it acquired in 2019. It is the largest dedicated cell and gene ther- apy manufacturing facility. Novasep also constructed a $30 million viral vector fa- cility at its Benefit, Belgium site. Also in Europe, Finnish company Biovian opened a new QA/QC site in 2018, Ansanmco is investing in a new large facility for the production of ATMPs, as well as R&D activities, and MatrTherCell S.A. signed a lease agreement in March 2019 for a 5,700-m2 facility in Belgium that will be operational in 2021.

Wuxi opened its Center for Clinical and Commercial Manufacturing in Boston, Massachus- etts in late 2018, and Brammer Bio has been investing in its facilities since its founding in 2013. Else (Catalent Biologics) is building a 100,000-ft2 4CDMO facility in Cambridge, Massachusetts. LakePharma Inc. and Oxford Biomedica Plc have also invested in viral vectors in 2019.

Importance of Outsourcing

The manufacturing complexity associated with viral gene and and cell-based therapies and mod- ified cell therapies has limited the number of companies with installed capacity and capabilities. Most emerging biotech/bio- pharma companies developing these prod- ucts lack the resources and expertise to achieve efficient, scalable manufacturing and thus rely on CDMOs.

Even larger pharmaceutical companies leading in this space face manufacturing challenges. Some have elected to build in-house capacity and expertise, such as AlexesNovartis, BioMarin Pharmaceuti- cal, Spark Therapeutics, Colgene/Juno and Pfizer4-7. Others, including Genところで Kline, have chosen to outsource. Novartis in 2018 is acquiring a $30 million viral vector fa- cility at its Benefit, Belgium site. Also in Europe, Finnish company Biovian opened a new QA/OC site in 2018, Ansanmco is investing in a new large facility for the production of ATMPs, as well as R&D activities, and MatrTherCell S.A. signed a lease agreement in March 2019 for a 5,700-m2 facility in Belgium that will be operational in 2021.

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There is a crucial need for high levels of synchronicity among various stakeholders and processes to ensure delivery of biological materials.

References

Gene therapy is a promising approach to altering the genetic composition of cells as a way to correct disease-causing mutations or to introduce proteins or RNA molecules that have potential therapeutic benefits. On a high level, gene therapy seeks to deliver nucleic acids to target cells to change their function in a favorable manner. While gene therapy is the introduction, removal or change in the content of a person’s genetic code with the goal of treating or curing a disease, cell therapy, while closely related, is the transfer of intact, live cells into a patient to help losens or cure a disease.¹

The importance of these breakthrough medical approaches cannot be understated, and, as of September of 2019, the U.S. Food and Drug Administration (FDA) has approved a total of 17 gene and cellular therapy products¹ aimed at treating a wide array of medical conditions, with that number expected to grow rapidly in the coming years. Although global research and clinical trials that utilize genetic and cellular therapeutic approaches abound, of paramount importance is seamlessly mitigating challenges associated with the supply chain of these biological materials. Maintaining the integrity and transparency of these autologous and allogeneic cells throughout extraction, storage, transportation, delivery and administration of surgical procedures can present a myriad of logistical challenges, requiring close and cooperative collaboration among industry, academic, regulatory, clinical and patient communities.

### A Holistic Approach to Transport and Delivery

Before delving into the challenges associated with the gene and cell therapy supply chain, early considerations need to be evaluated and tested to determine the best methodology for cell delivery. A primary consideration is whether to deliver cells fresh or frozen, which often is determined by necessity rather than an understanding of how preservation impacts cell function.¹ While freezing cells is common practice for research purposes, clinical administration of gene and cell therapy requires a more specified and calculated approach to understanding the impact of preservation methods for their specific product, both in the short and long term, to better predict whether the cells will perform differently when fresh or frozen. This understanding is crucial early in the clinical research process to reduce bottlenecks that can delay approval and go-to-market viability. Another challenge is quality control — ensuring that there are sufficient surrogate markers of quality and/or function that are quick and easy to test.² Compared with pharmaceutical products that are easily controlled, variability abounds in autologous therapies, specifically as it pertains to variables that exist within patients and donors, making it difficult to achieve consistency in processing. Methods need to be continually tested and improved to ensure the highest levels of quality control.

### Preparation, Packaging and Shipping

Medical technology companies are developing a range of packaging products that aim to preserve cells and maintain their integrity throughout transport and delivery. Cells are most often shipped under cryopreservation, a process that involves deep freezing cells with dimethyl sulfoxide (DMSO), which acts as an antifreeze.³ The DMSO inhibits the formation of ice crystals, which can cause cells to expand and become damaged. However, DMSO is toxic to cells and must be thoroughly washed out to prevent contamination. Once frozen, cryopreserved cells have traditionally been stored using either liquid nitrogen for aircraft travel or dry ice for ground transportation, which fail under passive (static) or semi-active packaging models. High-tech solutions are becoming more common, such as active (dynamic) packaging, which requires an external power source to maintain a constant temperature.⁴ In semi-active solutions, a static cold source, such as a phase-change material (PCM), is placed in an isolated compartment, and heat exchange between the biological material and the cold source is regulated using a system that operates without a power source.³ Passive packaging comprises eutectic plates of a PCM within an insulating material.⁵ All three of these approaches ultimately aim to provide an appropriate environment for cells to maintain their viability throughout transport.

### Other Logistical Concerns Affecting Delivery and Use

There is a crucial need for a high level of synchronicity among stakeholders and processes to ensure successful delivery of biological materials. Real-time monitoring and tracking of packages are necessary to ensure that they are handled properly, maintained at precise temperatures and successfully delivered to the correct destination at the right time. Providing transparent visibility during the shipping process is also crucial for maintaining a chain of custody and identity to establish accountability among all parties involved in the process. Other factors, including comprehensive understanding of local, national and international transport regulations, as well as the use of quality management systems, aid to increase the probability that cells are delivered on time and in usable condition.⁶

Upon arrival at their destination, cells need to be thawed and then require time to acclimate and grow. Once fully thawed, an entirely different set of challenges emerges. Cells typically must be used within one to two hours, requiring surgeons, nurses and patients to coordinate very tight windows to execute the administration of treatment. Any delays in transportation can complicate or even terminate the viability of the cells, increasing costs required to restart the supply chain cycle. Another concern stems from the behavior of the cells post-thawing, as they may differ genetically and behaviorally as a result of the cryopreservation and shipping process.⁴

### Decentralization and Scalability

As more gene and cell therapy products gain U.S. FDA approval and their clinical administration becomes more common, manufacturers will have to decide how best navigate challenges that arise from production from a centralized location. Due to the transportation sensitivities and limited shelf life of the cells themselves, the fastest route from laboratory to patient is most desirable. There are cases where it may be concluded that there are no viable routes to guarantee delivery of materials within an acceptable time frame. While this issue can theoretically be overcome by collecting patient samples sooner or requiring manufacturers to offer more flexible in accepting or dispatching material to make it possible to align with available transportation schedules, a decentralized approach for collection and delivery may prove more sustainable as the industry grows and expands. Another possible solution is having patients travel to within closer proximity to manufacturing sites, but this approach is not as scalable or sustainable as decentralization, which should prove to become more feasible as the field continues to grow. Although the field is essentially still in its infancy, gene and cell therapy products offer hope to potentially billions of people around the globe. If the range of curable conditions through gene and cell therapy continues to increase, thereby creating higher patient demand, researchers, manufacturer, medical technology companies and medical practitioners will undoubtedly continue to collaborate to increase efficiency, consistency and quality control in the supply chain process.

### References


PHARMA'S ALMANAC. GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS | 04 2019

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There’s a quiet revolution taking place in medical research, and it only depends upon combining familiar, existing technologies in just the right way.

THE EVOLUTION OF PERSONALIZED MEDICINE

Personalized medicine is an emerging branch of health care that treats the individual patient as a high-resolution source of data. By collecting a wide spectrum of information on the individual – their lifestyle, heritage, medical history, genetic information, and beyond – professionals working in this field can compare it to a set of parameters on similar individuals who faced similar medical problems. The thinking goes: what worked well for those patients will likely work for this one.

Personalized medicine represents a paradigm shift from the “one size fits all” approach that’s all too common in health care today, granting patients quicker access to medical treatments that yield them more favorable results. We live at a time rife with talk of driverless cars, space exploration, and technologically enabled convenience. Personalized medicine harnesses the best of this technology to move beyond entertaining ourselves with virtual reality headsets. It restores our health when we are sick.

Here are the four main technology trends driving personalized medicine today:

IMPROVED MEDICAL TECHNOLOGY MAKES IT EASIER TO SPOT GENETIC MUTATIONS

We’ve come a long way in genetic medicine. The scope was highly limited five or six years ago, but technology inevitably improves over time. For consumers, this usually means smaller phones and faster computers. For medical professionals, it means newer and better tools for saving lives.

The stuff of science fiction is becoming real, and this is especially exciting for medical applications. Nowadays, it’s not especially complicated to give a fruit or an exact copy of a patient’s cancer tumor, then run drug screenings on the fly to observe the results. We work on the fly will work on the human patient, and when you do this at scale – we’ve used up to 400,000 fruit flies at once – you get compelling results far more quickly than an individual oncologist consulting a research journal.

Medical technology might not improve as affordably as its counterparts on the consumer tech side, but it still improves nonetheless. The genetic medicine methodologies that enable personalized medicine were highly complex not all that long ago, but the times have thankfully changed – what was once highly complicated is now an everyday thing in a medical lab.

BIG DATA TECHNOLOGY LETS US CAPTURE AND MANAGE VAST STORES OF INFORMATION

A popular buzzword from the business sector, big data refers to a set of parameters techniques for extracting, analyzing, and interacting with datasets far too large for people to handle. Imagine an Excel spreadsheet so big and packed with data that it crashes your personal computer; that’s why companies use specialized tools to manage it.

In the manufacturing industry, for example, big data methodologies reduce production line failures and optimize supply chain management for near-zero downtime. In the media world, they’re instrumental in targeting content and advertising to people in the right place at the right time, maximizing the appeal of a certain article or promotion.

In medicine, big data is about taking advantage of all the research and treatments that have come before you own consultation. Doctors and researchers get to lean on previous results to tweak their experiment (or patient treatment) based on historic information.

ARTIFICIAL INTELLIGENCE TECHNOLOGY WILL HELP US MAKE SENSE OF ALL THAT DATA

If big data is the open ocean, then AI is ourclass yacht for navigating it. AI is proliferating rapidly across consumer and enterprise technologies, and it’s only going to continue to improve. From the voice-activated virtual assistant that lives in your smartphone today to the driverless car systems of the near future, all of it depends on artificially intelligent software to add new ease and convenience.

Humans tend to falter miraculously short when it comes to organize mathematical or scientific data into a clean pattern. But this is exactly the arena in which AIs excels. As the figurative beating heart of AI is raw mathematics, this makes it next-class tool for science-based medical research. Not only do most major pharmaceutical companies boast an AI research arm, but that research is leading the way to new medicines.

PERSONALIZED MEDICINE REPRESENTS A PARADIGM SHIFT FROM THE “ONE SIZE FITS ALL” APPROACH THAT’S ALL TOO COMMON IN HEALTH CARE TODAY, GRANTING PATIENTS QUICKER ACCESS TO MEDICAL TREATMENTS THAT YIELD THEM MORE FAVORABLE RESULTS.

Consider the fact that a research team in Australia is on its way to releasing the first medical treatment designed top-to-bottom by an AI system. It’s a flu vaccine, and preliminary animal testing shows it to be highly effective.

PERSONALIZATION TECHNOLOGIES ARE ALL THE RAGE LATELY

People tend to like a product or service a little bit more when they know that product or service has been tailored to them specifically. That’s why businesses have started leaning on technology to add new layers of personalization to what they do.

Your Facebook newsfeed, for example, is driven by an algorithm that serves up content based on the friends it thinks you want to interact with and the content it thinks you want to consume. This personalized approach to social media significantly drives engagement on the site.

Netflix is another standout example for its world-famous recommendation algorithm. Netflix offers this service by mining a record of all the content it distributes on a user-by-user basis, so it uses that data to suggest what a user might want to watch next. The company even awarded a $1 million “Netflix Prize,” awarding the money to whichever team could increase the accuracy of its recommendation engine by 10% or more.

In the medical realm, personalization means that a treatment is conceived from the ground-up for the individual patient. It’s bespoke medicine that accounts for more individualized details and medical history than any textbook could.

It’s important to emphasize that personalized medicine is real and practical today. It’s already proven to be an effective mechanism for beating diseases that had previously stumped medical teams. As technology and medical research continue to advance they always do, there’s no telling how simultaneously accessible and powerful personalized medicine can become.

ABOUT THE AUTHOR

Laura Towart
Founder/Chief Executive Officer, My Personal Therapeutics

Laura is the founder and CEO of My Personal Therapeutics, a London-based digital health company offering the most advanced personalized cancer therapies. Laura is also the founder and former CEO of Celmatix, a leader in diagnostics and predictive analytics for female infertility and women’s health. Laura is a graduate of the Weill Cornell Graduate School of Medical Sciences and Memorial Sloan Kettering Cancer Center’s Doctoral program and received a Certificate in Bioinformatics.

LinkedIn www.linkedin.com/in/laura-towart-1446332/
Email laura@mypersonaltherapeutics.com

REFERENCE

SHOULD YOU CHOOSE A COMMERCIAL HPAPI MANUFACTURER FOR YOUR CLINICAL PROGRAM?

BY GEORGE HLASS AND DAVID BASTIE, FAREVA

Switching from an early-phase CDMO to a commercial-scale manufacturer for your highly potent active pharmaceutical ingredient (HPAPI) projects can be costly and lead to project delays. Partnering from the outset with a CDMO capable of supporting HPAPI projects from concept to launch can accelerate development timelines and reduce overall costs.

EXPANDING HPAPI MARKET LEADS TO LIMITED OUTSOURCING CAPACITY

The percentage of drug candidates in the pharmaceutical pipeline based on highly potent active pharmaceutical ingredients (HPAPIs) is rising steadily, owing to the rapid growth of the oncology segment and a growing tendency toward a more conservative estimate of the potency of new chemical entities.

Overall, cancer drugs as a class account for the greatest share of the global pharmaceutical market, and this segment is growing rapidly. Cancer treatment garnered nearly $150 billion in 2018, an increase of nearly 13% over the year before— the fifth straight year of double-digit growth.1 In 2018, a record number (15) of anti-cancer drugs was launched, and 849 molecules were in late-stage development, an increase of 63% since 2013.2 By 2023, the global oncology therapeutics market is predicted to reach a value of $200–230 billion, according to IQVIA.3

HPAPIs are classified at an Occupational Exposure Limit (OEL) starting at <10 μg/m³, and can often require controls of OEL of <1 μg/m³ or even <100 ng/m³. The purpose and specialty of an HPAPI facility is the control of exposure with regard to the plant workers and exposure of other products manufactured in the same facility. Both of these factors are of ultimate consideration for the sponsor, who is responsible for the safety of their product.

Many cancer drugs are being classified as highly potent, cytotoxic compounds. The growth in the oncology segment is, therefore, driving demand for HPAPIs. Market estimates project the value of the global HPAPI market to be expanding at a CAGR of 8.5% to exceed $28 billion by 2024.3

ACCELERATED APPROVALS COMPLICATE THE PICTURE

At the same time that oncology and highly potent drugs have been expanding their share of the pharmaceutical market, the percentage of drug candidates receiving designations allowing for accelerated development pathways has also increased.

In the United States, these designations include Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review. Under these programs, which are intended to get therapies to patients with unmet needs more quickly, drugs can receive marketing authorization after successful completion of phase II studies. Larger studies must be conducted to confirm the results once the drugs are commercially available, rather than performing larger, longer and more expensive phase III studies prior to approval. The development times for accelerated approval pathways can be reduced by many months to several years. In 2018, 73% of new drug approvals issued by the US, Food and Drug Administration received one of these designations— up from 38% in 2008.4 Over the last five years, more than 60% of newly approved drugs in the United States have received expedited approvals. Cancer drugs tend to receive more expedited approvals than drugs for other indications.

TWO APPROACHES TO DEVELOPMENT

Pharmaceutical companies looking to outsource early-phase projects involving highly potent drug substances have two...
Since many HPAPIs are oncology candidates with accelerated approval designations, they often reach the marketplace stage more rapidly than conventional drugs. Working with a CDMO that can take a project from early phases to commercial launch becomes even more important for these projects when considering the compressed timelines associated with positive clinical trial results.

**WORKING WITH A CDMO THAT CAN TAKE A PROJECT FROM EARLY PHASES TO COMMERCIAL LAUNCH BECOMES EVEN MORE IMPORTANT FOR THESE PROJECTS WHEN CONSIDERING THE COMPRESSED TIMELINES ASSOCIATED WITH POSITIVE CLINICAL TRIAL RESULTS.**

When working with an integrated CDMO also facilitates the consolidation of complex pharmaceutical supply chains. Large pharmaceutical companies currently work with many different suppliers, requiring extensive management resources. Consolidation of their supplier networks through the establishment of strategic partnerships with fewer, integrated CDMOs helps reduce the time and costs associated with project management. Small and emerging pharmaceutical companies likewise benefit from their CDMO partnerships to a few integrated suppliers that can support their projects from concept to commercialization.

**FAREVA: INTEGRATED SOLUTIONS**

Fareva has been involved in the production of HPAPIs for more than 10 years in its Fareva — Exellia facility located in Germany. Recognizing the growing demand for CDMO HPAPI capabilities and capacity, we invested in the construction of a new, state-of-the-art building specifically designed for high-containment development and manufacturing activities at large scale.

We are an integrated CDMO offering support of HPAPI projects from the earliest phases through commercialization. We follow projects as they progress through all phases of clinical development and on to commercial manufacturing. With a process development lab, pilot plant and commercial suite all in one location, there is no need to transfer processes to another CDMO or to another Fareva site. Products can be produced as both non-GMP and GMP material depending on what is required. The laboratory and pilot plant in Fareva — Exellia are similar to the equipment used at commercial scale for effective scale-down modeling and rapid regulatory approval.

In addition, the same analytical instruments and methods are used at one site, in contrast to a tech transfer scenario where the project is transferred to the large-scale commercial CDMO, which takes time and money, and can cause significant issues for candidates with accelerated development timelines. And, as a dedicated HPAPI CDMO, we have the ability to produce the full range of quantities that might be needed throughout all phases of a project. We can quickly ramp up and down, as needed, due to overlapping capabilities, if needed. This is an added benefit when considering contingencies planning. In addition, each site has complementary syntheses and final processing capabilities. We evaluate these capabilities when a project involves numerous synthetic steps with a wide variety of functional groups and the need for highly specialized processing technology, such as microcrystallization.

**STRAATEGIC ADVANTAGES**

One of the key differentiators for Fareva as an integrated CDMO offering HPAPI development and manufacturing services is our family ownership. As a family run business, we have no outside shareholders or private equity firms involved in the company. In this result, we can operate more strategically, consider both the long and short term decisions and make investments that enable us to adapt and grow with our customers.

The recent investment in the new HPAPI building at the Fareva — La Vallée site is a perfect example. Fareva has been involved in HPAPI production for over a decade. A few years ago, it became apparent that capacity constraints existed in the highly potent manufacturing space, with most established CDMOs at or above capacity. We responded quickly to the market needs, establishing new capacity. The new building at Fareva — La Vallée was designed based on our experience at our Fareva — Excella facility and with the need for expansion in mind; the existing capacity at Fareva — La Vallée can be rapidly expanded as part of a pre-conceived expansion to meet growing customer requirements, if needed.

**REFERENCES**


**ABOUT THE AUTHORS**

George Hlass
Senior Director of Business Development for Active Pharmaceutical Ingredients, Fareva

George Hlass is the Senior Director of Business Development for Active Pharmaceutical Ingredients (API) at Fareva. He has 10 years of experience in the pharmaceutical and biotech industries and has been the head of business development in North America for Fareva's drug substance business for the past eight years. Previously, he worked for 10 years at two other chemistry-focused contract development and manufacturing organizations (CDMOs) that offered services in discovery, development and commercial manufacturing of small molecule APIs. He began his career in biotechnology, with three years of experience in the field of gene therapy.

LinkedIn: www.linkedin.com/in/geor gehlass/
Email: ghlass.usa@fareva.com

David Bastie
Commercial Project Coordinator, Fareva – La Vallée

David Bastie is the Commercial Project Coordinator at Fareva – La Vallée. He received his degree in chemical engineering from the French National Engineering School of Chemistry Clermont Ferrand. He has 22 years of experience in the pharmaceutical safety & industrial production, project management, and project costing. He has been with Fareva for four years and was previously with Merck for 18 years.

Email: DBastie.lavallee@fareva.com
Antibody–drug conjugates are highly complex, and their manufacture involves multiple and disparate technologies. Most biopharmaceutical companies, therefore, rely on contract service providers. Working with different suppliers for each part of the process can potentially add risks, time and cost to an ADC production program. The PROVEO™ Alliance overcomes these difficulties by offering streamlined support from antibody production through conjugation and fill-finish to labeling and packaging.

**POSITIVE ADC OUTCOMES DRIVING MARKET GROWTH**
Antibody-drug conjugates (ADCs) are next-generation antibody therapies that provide targeted delivery of cytotoxic anti-cancer agents to cancer cells. They comprise an antibody and a cytotoxic payload that are conjugated via a linker. By avoiding systemic delivery and attacking the cancer cells directly, ADCs offer increased efficacy with reduced side effects. As technology has advanced, second- and third-generation ADCs have become safer and even more precisely targeted.

There are currently six marketed ADCs and approximately 250 ADC candidates under development. Of those, nearly 40% are undergoing clinical studies, with over half targeting solid tumors. ADCs account for approximately 20% of the clinical pipeline of antibodies for cancer. With 11 additional drugs in late-stage clinical development, double-digit approvals are expected in the next few years.1

Significant R&D effort is focused on expanding the types of conjugated payloads, targeted indications and treatment protocols, particularly their use in combination therapies.2 In addition, 40 trials are underway involving ADC/checkpoint inhibitor combination therapies for the treatment of various cancers. ADCs are also being developed with payloads other than small molecules, such as proteins, enzymes and Fab fragments, the latter of which generates bispecific antibodies.

The value of the global market for ADCs is estimated to be expanding at a compound annual growth rate of 20% and expected to reach $15 billion by 2030.3 Notably, more than $5 billion has been invested in this ADC sector, and partnership activity has increased at an annual rate of 30%.4

**COMPLEX PRODUCTS AND MANUFACTURING PROCESSES**
Monoclonal antibodies used in ADCs should be designed for manufacturability at scale.5 They need to be robust, stable biomolecules that can withstand the further processing conditions involved in ADC production and contain the appropriate sites for conjugation to the cytotoxic payload via the desired linker chemistry. The drug (payload)-antibody ratio (DAR) and sites of conjugation must be carefully controlled and verified, as they directly impact the potency and efficacy of the ADC. Undesired payload binding and other modifications of the antibody can potentially lead to reduced stability (i.e., aggregation), reduced efficacy and immunogenicity and other adverse patient reactions. ADC purification often requires unique equipment and capabilities.

ADC drug substance manufacturing needs to balance bioburden-controlled activities while ensuring protection of operators and the environment from exposure to the highly potent payloads. Achieving these two goals requires conflicting control of air flows and air pressure in the facility. Extensive use of isolators in combination with unique facility designs is required to protect the product components, operators and the environment. As such, facilities for the production of ADCs require high capital investment and extensive operator training.6 Manufacturers must have capabilities in cell culture and synthetic chemistry and a deep understanding of conjugation chemistry, which must be highly controlled to ensure proper site selectivity and prevention of aggregation.7 Fill-finish capabilities, including lyophilization, are also necessary. Furthermore, because ADCs are highly complex, structurally heterogeneous and often contain not just a single product, but many product-related species, analytical expertise that bridges biology and chemistry is absolutely essential to ADC characterization and control.8

**RELIANCE ON CONTRACT MANUFACTURERS**
The complexity of ADC development and manufacturing has led many biopharmaceutical companies to turn to contract manufacturers.
Combining the strengths and expertise of the three companies and their ADC capabilities, PROVEO delivers stream-lined support from antibody production through conjugation and fill-finish to labeling and packaging, all directed to the client. The service is designed to provide significant efficiency gains in the ADC manufacturing process. By offering the services of specialists or specialized companies that are globally qualified and able to provide product development and manufacturing support, creating value through integrated project and supply chain management.

PROVEO is a solution provided by AGC Biologics, Cerbios and Oncotec Pharma Production GmBH to simplify the complexity of ADC outsourcing. All three companies are well-established, global suppliers that work together to reduce the time, cost and resources required for ADC manufacturing, giving customers multiple development and manufacturing options.

PROVEO supports the entire ADC supply chain: the development of a microbial or mammalian cell line, as well as production and purification processes to deliver the purified binding protein for the ADC; development of appropriate manufacturing processes for the payload, linker and bioconjugation step with cGMP production of the ADC drug substance; and sterile filling and labeling of the drug substance.

“Safe” early transfer steps were identified and supported by a transfer framework that enables fast development of optimized ADC processes and products. Across all sites, we use harmonized basic analytical methods and share the analytical methods specific to each phase of the project. As a result, we are able to compare results and reduce or avoid the need for method transfer. In addition, harmonization of quality assurance across the entire supply chain is achieved through a shared quality management system, making it possible to guarantee a high level of QA standards throughout the entire manufacturing process from monoclonal antibody (mAb) to packaged ADC product.

PROVEO also employs a fully integrated project management system across the supply chain with a single project manager that works with project managers at each site. This approach allows for seamless transitions across the network and enables complete integration of development and manufacturing efforts. As a result, we can provide risk-free timeline delivery. By offering a direct transition from DNA to fill-finish from 30 months for the traditional supply chain with four separate providers to 20 months.

ANTIBODY MANUFACTURING EXPERTISE
AGC Biologics is one of the largest global producers of antibodies, marketed and commercial and commercial development of therapeutic proteins, with a 15+ year track record of technical success in development and cGMP manufacturing. A leader in the implementation of innovative technologies and solutions that accelerate time to market, AGC has an agile, entrepreneurial culture and a commitment to cultivating strong partnerships that enable client success. AGC Biologics also has experience successfully transferring processes and technologies between sites to facilitate scale-up or market expansion.

Monoclonal antibodies are produced at AGC’s FDA- and EMA-approved sites in Copenhagen, Denmark and Seattle, Washington using the CHEPF proprietary expression technology platform with four commercial products in the market, as well as other ongoing manufacturing processes. Mammalian capacities range from 10,000 L in single-use and stainless-steel equipment, and mAb manufacturing capacity of 1.5 Gg per year. The fill-filling machine is robotic, and filling is achieved using peristaltic pumps with a line speed of 400 vials/hour. The system can handle products formulated in solvents. There is also the possibility to fill ADCs into disposable bags.

PAYLOAD AND CONJUGATION EXPERTISE
Cerbios has over 40 years of experience in the development of processes for the production of APIs and 25 years of experience in handling highly potent compounds, with production over 60 countries. Harmonization of quality assurance across the entire supply chain is achieved through a shared quality management system, making it possible to guarantee a high level of QA standards throughout the entire manufacturing process from DNA to fill-finish from 30 months for the traditional supply chain with four separate providers to 20 months.

FILL-FINISH EXPERTISE
Oncotec has been manufacturing sterile products for oncological indications since 1999, providing contract manufacturing services for highly potent substances to more than 20 companies. The plant in Dessau, Germany has been successfully inspected by numerous regulatory authorities, including the FDA, ANVISA, PDA, FDA Saint-Arabia and the Turkish, Libyan and Russian MoHs.

The final formulation, sterile filling, packaging and labeling of final ADC drug products takes place at Oncotec. Both small- and large-scale aseptic filling lines were GMP-qualified and other filling capabilities are available for the production of highly potent ADCs. Vial sizes from 2 to 20 mL are supported. The freeze-dryer line has a capacity of 800 Gg per year. The filling machine is robotic, and filling is achieved using peristaltic pumps with a line speed of 5000 vials/hour. The system can handle products formulated in solvents. There is also the possibility to fill ADCs into disposable bags.

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TO OUR KNOWLEDGE, PROVEO PROVIDES THE ONLY CDMO OUTSOURCING SOLUTION THAT INCLUDES ALL THE STEPS INVOLVED IN ADC MANUFACTURING, FROM DNA TO FILL-FINISH.

This level of ADC outsourcing will increase, at least 70% of ADC manufacturing is outsourced, and this level will increase, owing to the fact that many third-generation ADCs include antibody-hybrid and small molecule conjugates, and these expensive products are not of a volume of units that clients are able to make themselves and, therefore, they outsource. Working with an integrated ADC CDMO, PROVEO enables the development and manufacturing organization to fully focus on the core scientific research and development, while leveraging the global service backed by years of experience and the implementation of innovative technologies between sites to facilitate scale-up or market expansion.

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WHAT IS BLOCKCHAIN TECHNOLOGY?
Blockchain technology has its origins in the field of cryptocurrency and was originally used to establish Bitcoin, the first viable digital currency. A distributed ledger technology (DLT), blockchain enables proof of ownership and the transfer of ownership from one entity to another without using a bank. Today, it is used for many different applications in many industries because it offers a unique combination of features not possible with other digital technologies.

Those features include the creation of permanent, immutable, signed and time-stamped records of ownership of assets of various types, identities, transactions and contractual commitments that can be shared among all members of a business ecosystem in near real time. The records are stored on dozens to thousands of computers around the world. Authorizations can be assigned to specific types of information by specific members. Most importantly, blockchains are “essentially unhackable” for anyone without authorized access. That is because once a record has been added to the “chain,” the data cannot be altered or deleted, because new blocks can only be added to the end of the chain.

Given that blockchain technology allows the secure creation and sharing of time-stamped records among numerous parties in real time, it isn’t surprising that it might be of interest for improving the pharmaceutical supply chain. Pharmaceutical companies aren’t stopping there, though. Blockchain technology is being explored for drug discovery, clinical trials and much more.

In addition to this high level of security, blockchain technology enables supply chain transparency. Everyone in the supply chain can access the same data as soon as it is created. The sources of data and records are also more clearly identified and can be readily traced, significantly decreasing the time it takes to identify problems in the supply chain and increasing the ability to manage quality and inventory flows. Business transactions can also be accelerated when blockchain technology is combined with “smart contracts” and the Internet of Things (IoT). For international transactions, the time it takes to transfer ownership of goods can be reduced from 10 days to 10 minutes.

There are many potential uses for blockchain technology in the pharmaceutical industry, including facilitating patient, physician, payer and pharma company access to medical records; prescription sharing, enhancement of the supply chain, tracking and reporting of clinical trial data, provider credentialing, quality-of-care tracking, drug pricing strategy tracking and adverse event tracking and evaluation. The primary use for blockchain in the pharma industry, according to KPMG analyst Arun Ghosh, is to serve as a “ledger...
Blockchain technology also has the potential to help prevent diversion, counterfeiting and tampering, because drug products can be tracked from the time they are manufactured until the time they reach patients. Any attempts to change records will be visible to all parties immediately.\(^4\)

As importantly, recalls are much simpler.\(^4\) The product can be readily traced back to the manufacturer and distributed with a production batch, allowing identification of other potentially problematic products and where they have been shipped.

A NOTE ABOUT BLOCKCHAIN AND SERIALIZATION
Blockchain technology will play a pivotal role in the industry’s ability to comply with various serialization regulations around the world, including the 2013 U.S. Drug Supply Chain Security Act (DSCSA) and the EU’s Falsified Medicines Directive (FMD). Serialization will provide the unique identification of every drug product at the level of individual units, as well as aggregated package data. Information on the product, its manufacturer (location, date, batch number, etc.), logistics route, and so on, must be shared with all supply chain partners involved in the delivery of the drug to the patient. The challenge is to make it possible to trace products back through the supply chain to their point of origin.

The transparency and security of blockchain technology is ideal for pharmaceutical companies, and who have difficulty due to complications of their diseases to participate. The hope is that one day blockchain technology will be in place with master health records for protecting patient privacy and ensuring the protection of trade secrets, and the demonstration of the security and privacy features of blockchain solutions.

Building the infrastructure to support data sharing and transaction tracking across the pharmaceutical manufacturing supply chain and the wider healthcare system is one of the major limiting factors for implementation of blockchain technology in the pharmaceutical industry — and other sectors.

MANUFACTURING IMPACTS?
Blockchain technology could also facilitate the advancement of next-generation, personalized therapies. The logistics involved in the production of autologous cell therapies is highly complex and requires an assurance of chain of identity – the sample taken from a patient, once converted into the cell therapy, must be returned to that patient. Blockchain technology can support the manufacture of this type of personalized product.

It may also enable 3D printing of personalized drugs in a physician’s office or hospital. There is already one such drug approved by the FDA: Sigraniv\(^1\) for the treatment of epilepsy as approved in 2015. To make this approach to drug manufacturing more practical and accessible to patients who are needed for managing manufacturing and patient data, AI and ML can be used to automate and speed up the identification of the ideal dosage and formulation for a given patient and inputted into a 3D printer for production of a personalized medication.

DOES BLOCKCHAIN TECHNOLOGY SOLVE THE PROBLEMS?
Blockchain technology can potentially solve the problems associated with supply chain and the wider healthcare system, but there are limitations. For intellectual property protection, blockchain technology is also beneficial for tracking the delivery of the drug to the patient. The logistics route, and so on, must be shared with all supply chain partners involved in the delivery of the drug to the patient. The challenge is to make it possible to trace products back through the supply chain to their point of origin.

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MANAGING PATIENT DATA
The hope is that one day blockchain technology will realize the management of patient data across providers, including different insurers and even research organizations. A single unique identifier could be used to securely track a patient (using audit trails) across the entire healthcare system while maintaining patient privacy. The system could be shared and allow for the management of patient data across providers — with patient consent — sharing data with research partners for drug development, etc.

The hope is that one day blockchain technology will

provide the most efficient way to manage and organize patient data. They also ensure that data can be shared securely and in real-time with all involved parties, maintaining patient privacy and ensuring that raw research data files are not tampered with.\(^3\)

The immutable nature of records kept using blockchain technology can also provide assurance that initial clinical trial designs and protocols have been adhered to. The potential for the technology to assure privacy and accuracy of clinical trial data is of particular importance.\(^6\) People are more likely to participate in clinical studies if their data will be protected and if they are sure it will be used properly. Issues with conformed consent could also be addressed through the unqualified time-stamping of consent forms.\(^\text{7}\)

Blockchain technology could also be used to develop public registries for the rapid disclosure of clinical trial results. In addition, access by all stakeholders in a clinical trial to a central repository of data in real time should help reduce trial timelines.\(^8\)

DTs can also enable the implementation of virtual trials, in which a centralized trial center and patients receive their medications and have samples picked up at home.\(^9\) Trials can make it possible for patients in remote locations, or who have difficulty due to complications of their diseases to participate. The hope is that one day blockchain technology will be in place with master health records for protecting patient privacy and ensuring the protection of trade secrets, and the demonstration of the security and privacy features of blockchain solutions.

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All of the major application software companies and start-ups are focused on developing solutions that can leverage blockchain technology. In addition to being a tool to track claims throughout their life cycle and do so for large volumes of patients — up to millions, or even more.

On a smaller scale, some insurance companies, providers and a lab services leader have joined the Synaptic Health Alliance. This is a collaboration of companies and provider directories — a requirement of the Centers for Medicare and Medicaid (CMS) to test the technology. The hope is that one day blockchain technology will be in place with master health records for protecting patient privacy and ensuring the protection of trade secrets, and the demonstration of the security and privacy features of blockchain solutions.

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Blockchain technology could also facilitate the advancement of next-generation, personalized therapies. The logistics involved in the production of autologous cell therapies is highly complex and requires an assurance of chain of identity – the sample taken from a patient, once converted into the cell therapy, must be returned to that patient. Blockchain technology can support the manufacture of this type of personalized product.

It may also enable 3D printing of personalized drugs in a physician’s office or hospital. There is already one such drug approved by the FDA: Sigraniv\(^1\) for the treatment of epilepsy as approved in 2015. To make this approach to drug manufacturing more practical and accessible to patients who are needed for managing manufacturing and patient data, AI and ML can be used to automate and speed up the identification of the ideal dosage and formulation for a given patient and inputted into a 3D printer for production of a personalized medication.

DOES BLOCKCHAIN TECHNOLOGY SOLVE THE PROBLEMS?
Blockchain technology can potentially solve the problems associated with supply chain and the wider healthcare system, but there are limitations.

For intellectual property protection, blockchain technology is also beneficial for tracking the delivery of the drug to the patient. The logistics route, and so on, must be shared with all supply chain partners involved in the delivery of the drug to the patient. The challenge is to make it possible to trace products back through the supply chain to their point of origin.

The transparency and security of blockchain technology is ideal for pharmaceutical companies, and who have difficulty due to complications of their diseases to participate. The hope is that one day blockchain technology will be in place with master health records for protecting patient privacy and ensuring the protection of trade secrets, and the demonstration of the security and privacy features of blockchain solutions.

Building the infrastructure to support data sharing and transaction tracking across the pharmaceutical manufacturing supply chain and the wider healthcare system is one of the major limiting factors for implementation of blockchain technology in the pharmaceutical industry — and other sectors.

MANAGING PATIENT DATA
The hope is that one day blockchain technology will realize the management of patient data across providers, including different insurers and even research organizations. A single unique identifier could be used to securely track a patient (using audit trails) across the entire healthcare system while maintaining patient privacy. The system could be shared and allow for the management of patient data across providers — with patient consent — sharing data with research partners for drug development, etc.

The hope is that one day blockchain technology will facilitate the management of patient data across providers, including different insurers and even research organizations.
With blockchain technology, the entire supply chain can be managed with one piece of software that is shared among authorized stakeholders.

There are, in the meantime, a number of smaller efforts underway to test the potential for blockchain technology to benefit the pharmaceutical industry. In one example,6 pharmaceutical companies have collaborated with SAP in developing the SAP-Pharma Blockchain Network. The objective of this network is for tracking drug shipments, which was launched in 2017 and has undergone multiple iterations since.2 In early 2019, SAP announced the availability of SAP Innovation Collaboration Hub for Life Sciences, a blockchain solution designed to help customers comply with the U.S. Drug Supply Chain Security Act (DSCSA).

Novartis is using blockchain technology and artificial intelligence to monitor patient medications and track temperature with real-time visibility for all participants in the supply chain.7 Merck recently garnered a blockchain grant on its own supply chain technology for preventing counterfeit drugs by increasing supply chain security. In a combined effort, Pfizer, Amgen and Sanofi are investigating the use of blockchain technology to safely store patient health data to speed clinical trial and lower drug development costs. Blockchain startup Elixirax offers a way to securely store and manage clinical trial patient data that also allows patients to control how researchers may interact with their medical data.8 Boehringer Ingelheim (Canada) has partnered with IBM to test the ability of the latter’s blockchain platform to “improve trust, transparency, patient safety and provider empowerment in clinical trials” by improving the management of clinical trial processes and records.9

Recently, IBM announced that it is working with KPMG, Merck and Walmart to develop a pharmaceutical blockchain platform that can track drugs as they move through the global supply chain.10 There are several other FDA DSCSA projects utilizing blockchain technology. One of the most prominent is MediLedger, which has over 20 members, including Pfizer, Amgen and Adidas. The goal is to leverage blockchain capabilities to create an interoperable system in which multiple parties, including manufacturers, wholesale distributors, retailers, hospitals and pharmacists can register, verify and transfer pharmaceutical products with absolute trust in their authenticity and provenance.11

RISKY PROPOSITION?

The benefits of implementing blockchain solutions to improve supply chain security, facilitate clinical trials and increase the efficiency of patient data management are clear. Of course, with the adoption of any new technology comes some level of risk. While blockchain technology is attractive because it assures security, the risk of data breaches or system failures cannot be fully eliminated or ignored. This is also an issue that has yet to be resolved.10

The upfront cost and time to implement new blockchain solutions is not insignificant. In addition, companies in the pharmaceutical industry is conservative by nature, and there is a hesitancy to make major changes to existing data and IT infrastructure, despite the potential benefits.12 When it comes to patient data, companies may be slow to adopt blockchain technology simply because of concerns around meeting regulatory requirements regarding the protection of patient privacy.13

About the Author

Cynthia A. Challener, Ph.D.
Scientific Content Director, Nice Insight

Dr. Challener is an established industry editor and technical writing expert in the areas of chemistry and pharmaceuticals. She writes for various corporations and associations, as well as marketing agencies and research organizations, including Nice’s and Nice Insight.

LinkedIn www.linkedin.com/in/cynthiachallener Email cynthia@thatinsider.com

REFERENCES

very three seconds, there is a new case of dementia around the world. There are 50 million people living with Alzheimer’s Disease (AD) worldwide, including 5.8 million Americans; these numbers coincide with a 14% increase in deaths from AD between 2000 and 2017. The number of cases is expected to increase to over 152 million worldwide by the year 2050, with associated costs exceeding $2 trillion by 2030. With AD affecting so many families around the globe, AC Immune is aggressively working toward treatment and a cure for AD and other neurodegenerative diseases.

Early Discovery

AD is typically diagnosed by neurologists and psychiatrists through a series of cognitive functioning tests once symptoms are already clinically present. Diagnosis usually occurs at a stage when treatments have little impact. AC Immune has already demonstrated to solve the challenge of drug discovery 

The active immunization approach is based on the ability of peptide antigens attached to liposomes to elicit the body’s own immune system to produce antibodies against self-proteins.

The rational, chemical design of Morphomer enables us to generate small molecules, or Morphomers, which bind very specifically to misfolded proteins, break up neurotoxic aggregates and inhibit their aggregation and seeding.

Treated Misfolded Proteins: SupraAntigen® and Morphomer®

One challenge in developing therapeutics and diagnostics for neurodegenerative diseases is that, although misfolded proteins are pathogenic, they are still recognized as “self-proteins,” so the body does not easily make antibodies against them. Another challenge is that the difference between a normal protein and a pathological protein is only related to a conformational change in protein structure, making drug specificity difficult to achieve. Two AC Immune proprietary technology platforms, SupraAntigen®, and Morphomer®, generate a robust pipeline of antibodies, vaccines and small molecules, which selectively bind to the misfolded proteins that are responsible for a broad range of neurodegenerative diseases.

Our biological platform SupraAntigen was developed to solve the challenge of immunogenicity of self-proteins. This technology generates conformation-specific antibodies and is used to create products for active immunization (vaccines) and passive immunization (antibodies). The active immunization approach is based on the ability of peptide antigens attached to liposomes to elicit the body’s own immune system to produce antibodies against self-proteins.

Passive immunization involves selecting antibodies for their ability to break up aggregated forms of misfolded proteins and changing the equilibrium from the insoluble to soluble forms, which are depleted by the antibodies.

Innovating the Approach to Neurological Disease Treatment

AC Immune is developing treatments that reduce excessive neurological activity that has recently been shown to be associated with Alzheimer’s disease (AD) and other disease processes.

Developing Medications with a New Target

Until recently, most companies developing AD therapies were targeting pathways leading to the formation of the amyloid plaques that accumulate in the brains of AD patients as the disease progresses. Most of these approaches have failed. In 2008, we founded AgeneBio to focus on a novel therapeutic target. After research I had conducted on the role of the protein tau, we entered into a partnership with Eli Lilly and Company to develop a new class of investigational oral small molecule tau Morpher inhibitor that will be studied in neurodegenerative diseases that are characterized by the presence of pathological tau aggregates under our collaboration with Eli Lilly and Company. A phase Ib clinical trial to evaluate ACI-35.030 – a clinically advanced anti-phospho-Tau design to reduce tau pathology in Alzheimer’s disease – demonstrated to drive the spread of tau pathology in AD causing frank neurodegeneration, and the therapeutic space has shifted to tau pathology as a therapeutic target. Several other companies are following this lead with a focus on tau pathology and are currently in early stages of developing drugs that target the protein tau.

AgeneBio aims to reduce the overactivity of neurons in the brain to prevent the progression of AD. AD has a very protracted clinical course. The earliest prodromal phase, which involves the emergence of pathology before a clinical diagnosis, lasts approximately 10 years. We are targeting patients in this transitional stage from normal aging to early dementia.

New Molecules Under Development

We are also excited to be pursuing a second program focused on the development of a new class of small-molecule drugs that have the potential to treat MCI due to AD, autism, schizophrenia and even a broader range of neurological and psychiatric conditions.

GABA, α5 receptors were initially a major target for Pfizer, Merck and Roche, but these companies were looking to block inhibition at these sites to produce greater excitation within the neural circuits where these receptors are highly localized. At the time, we had not yet discovered the contribution of overactivity in a range of neurological and psychiatric disorders. Not surprisingly, Pfizer found that their GABA, α5 inhibitors raised to a concerning level in elderly patients in clinical studies. AgeneBio’s GABA, α5 Positive Alloste ric Modulator (PAM) program is the science developed for AGB-101. We are developing GABA, α5 PAMs with high selectivity and potency to treat neural imbalance in excitatory and inhibitory function. A lead candidate is now advancing to an IND and clinical phases.

In addition to evaluating the effectiveness of AGB-101 to treat MCI due to AD and to prevent or delay progression to Alzheimer’s dementia, this trial will help AgeneBio test the hypothesis that overactivity drives disease progression. We are recruiting patients who are experiencing changes in their episodic memory beyond what would be expected at their ages, which is an indication of the transitional phase between normal aging and the diagnosis of clinical dementia. Notably, only patients with early signs of memory loss and the presence of amyloid plaques in the brain – as determined by positron emission tomography (PET) imaging – qualify for the therapeutic trial.

Planning for Success

Looking to the future, we expect to have readouts of definitive data from our AGB-101 phase III study in approximately two and a half years. In the meantime, commercial partnerships are under discussion to enable us to reach patients around the world as we are anxiously awaiting an effective treatment for AD. At the 12th annual Clinical Trials on Alzheimer’s Disease (CTAD) on December 4-7, we presented an update on the status of the phase III clinical trial and new scientific information on AGB-101. While the phase III study proceeds, we will be investigating other potential indications that could benefit from treatments targeted to liposome sites to produce greater excitation within the neural circuits where these receptors are highly localized. At the time, we had not yet discovered the contribution of overactivity in a range of neurological and psychiatric disorders. Not surprisingly, Pfizer found that their GABA, α5 inhibitors raised to a concerning level in elderly patients in clinical studies. AgeneBio’s GABA, α5 Positive Allosteric Modulator (PAM) program is the science developed for AGB-101. We are developing GABA, α5 PAMs with high selectivity and potency to treat neural imbalance in excitatory and inhibitory function. A lead candidate is now advancing to an IND and clinical phase I.

Reference

Increasing the Potency of Antibody–Drug Conjugates

Novel linker technology enables the rapid development and manufacture of highly stable antibody-drug conjugates (ADCs) with improved safety and efficacy.

Targeted Nature Drives Interest in ADCs
ADCs are powerful biopharmaceuticals that deliver highly potent drugs very specifically to the desired target tissue. Comprising highly potent, small molecule cytotoxics conjugated to antibodies using various linker technologies, ADCs enable the highly selective delivery of the payload to the diseased tissue. After binding of the antibody to the targeted cells, the linker chemistry is designed to release the payload. As a result, the impact of the treatment on healthy cells is minimized, leading to reduced side effects compared with conventional chemotherapies.

The global ADC market was valued at $1.57 billion in 2017 and is projected to grow at a CAGR of 25.9% through 2025.

Issues with Conventional Linker Technology
ADCs to be effective, the payload must remain linked to the antibody until binding has occurred to the site of action. Otherwise, if the payload is released too early, it will have to be manufactured multiple times. With many conventional linker technologies, premature loss of the drug occurs in the body owing to the unstable nature of the bond. Early payload release leads to toxicities in healthy tissue (causing side effects) and reduced overall safety and efficacy.

Many site-specific payload-conjugation technologies face development and manufacturing challenges, because they require time-consuming and costly antibody and/or cell line engineering, use linkers with limited solubility for hydrophobic payloads, which can lead to aggregation and fast blood clearance, and/or deploy unstable chemistries for payload linkage.

Novel Linker Technology
Founded in January 2019, Araris Biotech AG is a spin-off company from the Paul Scherrer Institute (PSI) and ETH Zurich pioneering a novel site-specific ADC-linker technology. Our peptidic linker platform enables the attachment of any payload to native, ‘off-the-shelf’ antibodies without the need for prior antibody engineering.

Most importantly, ADCs developed with the Araris linker technology have exhibited high efficacy and reduced toxicities of toxicity.

Eliminating the requirement for antibody engineering reduces the time and cost required for ADC development. In addition, the novel linker technology is hydrophilic and offers excellent solubility, even when conjugated to highly hydrophobic payloads.

Furthermore, due to the peptidic nature of the linker, it is easy to incorporate reactive (functional) chemical groups that enable the attachment of many types of payloads (e.g., toxins, dyes, metal chelators) to different antibodies using a wide range of chemistries (e.g., azide, thiol, hydrazide, and combinations). In fact, more than one type of payload can be conjugated to the same antibody. Regardless of the chemistry, however, ADCs with a clear drug-to-antibody-ratio (DAR) of two or four are always obtained. Another benefit of the Araris linker technology is its highly efficient, high-throughput screening, which allows for the rapid identification of the optimum antibody-payload pair. As a result, with our linker platform, payload attachment can generally be achieved in less than two days.

Most importantly, ADCs developed with the Araris linker technology have exhibited high efficacy and low levels of toxicity. In experiments conducted to date, antibody-payload combinations with the identical attachment sites but using the Araris linker technology have exhibited higher efficacy in vitro and in vivo than ADCs prepared using conventional methods. This higher performance can be attributed to the greater stability of the linkage and its attractive biophysical properties.

Two-Pronged Business Plan
Araris Biotech has several business goals. Initially, we are focused on providing a high-quality technical platform to develop ADCs access to our novel linker technology, ideally through licensing arrangements. In the medium term, we also intend to develop our own ADC drugs for the treatment of cancer and other indications. This work is at the preliminary stage of development. We are conducting an ongoing project to evaluating potential targets in oncology and other disease areas.

With the building of the platform, we recently completed a seed financing round and are in active discussions with existing and potential investors regarding a tranched Series A round. The money raised will be used to explore the full potential of our linker technology and to develop our own pipeline of ADCs.

Reference

CD34+ Cell Therapy in Clinical Trials
CD34 Biociences is harnessing the ability of natural occurring, preprogrammed CD34+ cells to build blood vessels and treat various forms of cardiovascular disease.

Targeting the Microvasculature
Heart attack, chronic heart failure, critical limb ischemia and stroke are all caused by an acute or chronic deficit in the supply of oxygenated blood. The conventional treatment approach is to use or bypass large vessels to restore the supply of oxygenated blood. This approach, however, ignores the largest part of the vascular system – the microvasculature that delivers oxygen to all the tissues of the body.

One of the body’s natural responses to acute or chronic deficit in the supply of oxygenated blood is the recruitment of CD34+ cells – naturally occurring, preprogrammed endothelial progenitor cells that have the ability to grow in the bone marrow. In response to ischemia (i.e., a lack of oxygen in a tissue), CD34+ cells are recruited to those tissues, where they are capable of growing new microvascular structures, the cells restore the tissue, and undergoing the adverse consequences caused by chronic ischemia.

$100,000 to treat a patient with a critical limb ischemia (CLI) who has suffered severe tissue loss. Based on data from our概念 clinical trial for coronary microvascular disease (CMD), we are exploring the therapeutic potential of our CD34+ cell therapy platform. CLBS12 is designed to stimulate the growth of microvasculature and address conditions caused by critical limb ischemia (CLI). No medical therapy has ever been shown to be effective in this condition. We are currently evaluating indications for the use of CLBS12 to heal non-healing ulcers and severe pain caused by a lack of blood supply in the legs.

CLBS2 is designed to induce new microvascular structures and address conditions caused by critical limb ischemia (CLI). No medical therapy has ever been shown to be effective in this condition. We are currently evaluating indications for the use of CLBS2 to heal non-healing ulcers and severe pain caused by a lack of blood supply in the legs.

CLBS14 is currently in late-stage development in Japan. The full readout of data is expected in 2020. CLBS14 is designed to induce new microvascular structures and address conditions caused by critical limb ischemia (CLI). No medical therapy has ever been shown to be effective in this condition. We are currently evaluating indications for the use of CLBS14 to heal non-healing ulcers and severe pain caused by a lack of blood supply in the legs.

CLBS14 is designed to induce new microvascular structures and address conditions caused by critical limb ischemia (CLI). No medical therapy has ever been shown to be effective in this condition. We are currently evaluating indications for the use of CLBS14 to heal non-healing ulcers and severe pain caused by a lack of blood supply in the legs.

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CLBS14 is designed to induce new microvascular structures and address conditions caused by critical limb ischemia (CLI). No medical therapy has ever been shown to be effective in this condition. We are currently evaluating indications for the use of CLBS14 to heal non-healing ulcers and severe pain caused by a lack of blood supply in the legs.

All patients with cardiovascular diseases could potentially benefit from treatment with CD34+ cell therapies.

CD34+ Cell Therapy is being studied in the ongoing E5I2aP-CM-DC phase II US, proof-of-concept clinical trial for coronary microvascular dysfunction (CMD). We have completed phase IIa clinical trial, which is investigating the performance of CD34+ cell therapy in patients who have refractory chest pain but no blockage of their coronary arteries and thus suffer from chest pain due exclusively to microvascular insufficiency. Preliminary data reveal a significant improvement in coronary flow reserve (CFR) and reduction in chest pain in treated patients.

Huge Potential to Treat Heart Disease
One of the most exciting aspects of CD34+ cell therapies is that they are the first therapy to directly regenerate the damaged microvasculature. Anyone that suffers from a form of CVD most likely has microvascular disease as well. Even though patients may have only a low level of angina, there is a high probability that they have occurred to the microvasculature. As a result, all patients with CVDs could potentially benefit from treatment with CD34+ cell therapies.
Leveraging Natural Killer Cells as CAR-T Therapies

Covyl is developing CAR-T therapies that have the potential to address both hematological and solid tumors.

Differentiated CAR-T Receptor
Covyl’s technology allows for the construction of a unique epitope that elicits many antibodies and small molecules. Chimeric antigen receptor (CAR-T) cell therapies take a different approach by leveraging the immune system and its innate biochemical pathways.

Personalized Therapies CYAD-01
Covyl’s lead candidate, CYAD-01, is a CAR-T cell therapy incorporating the NGK22 CAR-T receptor, which has been shown in preclinical studies to bind to ligands expressed by blood vessels that feed tumors and inhibitory cells that help tumors evade the immune system. CYAD-01 targets and kills the tumor while impacting the microenvironment and potentially inducing an adaptive immune response owing to the creation of long-term cell memory against targeted tumors.

CYAD-02 is a next-generation NK-actuated CAR-T candidate that incorporates short hairpin RNA (shRNA) technology to target the NGK22 ligands MICA and MICB, silencing their gene expression via RNA interference (RNAi) on the CAR-T candidate. With our technology, the single shRNA module expresses both ligands, which translates to increases in vitro proliferation, in vivo engraftment and antitumor activity in early testing. The ability to target and incorporate a selective PEK inhibitor.

Our current lead allologic candidate CYAD-001 is a non-gen-edited, healthy donor-derived CAR-T that can express the NGK22 CAR of CYAD-01 and TIM. The expression of TIM reduces the risk of anti-CAR-T antibodies.

Covyl has identified antibody–target pairs that are noncanonical. We express them with fusion partners using our shRNA technology to target the candidate of interest.

Focused on a Sophisticated Part of the Immune System
Highly tumor-educated B cells isolated from patients’ peripheral blood by using Immunome’s proprietary hybridoma technologies. By interrogating 8 B cell responses at unprecedented breadth, depth and speed, we are able to identify novel and unique antibody–target pairs against various cancer-related antigens.

We have identified antibody–target pairs that are unique and can underwrite an efficacy hypothesis. Once confirmed, the antibody against the target is advanced into preclinical development.

Leveraging Human Immune Responses
Most drug discovery today follows a similar path: study of disease biology in animal models, selection of a target based on a proposed mechanism of action and development of a potential means of engaging the target. Immunome has taken the opposite approach, leveraging technologies developed at MIT’s Whitehead Institute and Thomas Jefferson University.

Our technology both captures and interrogates patient immune responses to uncover novel antigens, and antibodies associated with them, that can have significant therapeutic potential. We are currently developing first-in-class cancer therapies based on the insight derived from evaluable B cell responses in patients.

Four Preclinical Candidates
We are currently evaluating four antibody–target pairs in preclinical development. Each of these candidates has unique mechanisms of action and can be tailored to patient-specific disease biology.

Expanding into ADCs
Many of the antibodies we identify have high specificity and selectivity and may be uniquely suited to combine with other targeting technologies, such as cancer drugs linked to pseudocapases that deliver the therapeutic payload directly to cancer cells.
Ocugen offers a robust and diversified ophthalmology portfolio that includes novel gene therapies, biologics and small molecules targeting a range of high-need retinal and ocular surface diseases.

**Rare and Underserved Ophthalmic Disorders**

Ocugen is targeting inherited retinal diseases (IRDs), age-related macular degeneration (AMD) and ocular GVHD (oGVHD). The FDA has approved therapies for the treatment of wet AMD, diabetic retinopathy (DR) and diabetic macular edema (DME), but many patients do not respond to existing treatments. There are no FDA-approved treatments available for dry AMD.

**GVHD affects approximately 60% of allogeneic bone marrow transplant patients and can lead to significant vision loss in transplantable ocular diseases.** While ocular GVHD can affect patients with ocular graft versus host disease (GVHD), it is most common in patients with ocular transplantation. This includes patients with ophthalmic GVHD (OcGUHN), which can occur after a bone marrow transplant or an organ transplant.

Ocugen is developing OCU300, an investigational steroid-free, preservative-free ocular solution. Phase III clinical trials have been initiated for OCU300 in the treatment of ocular GVHD and multiple IRDs.

**Leveraging Proprietary Nanoemulsion Technology**

Ocugen’s lead candidate OCU300 is an investigational steroid-free, preservative-free ocular solution for the treatment of OCU300. The FDA has approved two IRDs to date. CanSinoBIO will provide all CMC development and clinical supplies for the treatment of OCU400, with their own capital and resources. Ocugen plans to focus its capital on pre-clinical to toxicology studies for different disease targets within its gene therapy platform and OCU400’s potential for the treatment of wet AMD will be granted Orphan Drug Designation by the FDA.

**CanSinoBIO** will provide all CMC development and clinical supplies for the treatment of OCU400, with their own capital and resources. Ocugen plans to focus its capital on pre-clinical to toxicology studies for different disease targets within its gene therapy platform.

**OPHTHALMOLOGY**

**Developing a Potential Cure for Bladder Cancer**

Current bladder cancer treatments are not curative. A novel photodynamic therapy (PDT) platform being developed by Theralase could be the new gold standard.

**Limited Options for Bladder Cancer Patients**

Bladder cancer is the fifth most common cancer globally. Approximately 75–85% of patients with bladder cancer present with non-muscle invasive bladder cancer (NMIBC).

Adjuvant intravesical instillations with bacillus Calmette-Guerin (BCG) is the recommended treatment option for patients with intermediate- and high-risk NMIBC. Despite adequate BCG treatment, a large proportion of patients experience a recurrence. Although radical cystectomy is the gold standard for BCG-unresponsive NMIBC, some patients are not suitable candidates for surgery. Theralase’s PDC, a ruthenium-based candidate, provides a clear path to advance development and manufacturing processes that reach the clinic.

**A Novel Fusion Protein**

The drug is instilled in the bladder, which is treated with light activation using Theralase’s proprietary TLC-3200 medical laser. The drug is completely removed from the bladder within 72 hours. The drug-drug interactions or side effects. Photodynamicinetic studies have shown that the drug is completely removed from the bladder within 72 hours and from plasma within 72 hours.

**Exciting Early Results**

In 2018, Theralase completed a phase Ib trial with TLD-1433 in NMIBC. Six patients were involved in the study, with three receiving the therapeutic dose. In one of these patients, it was later determined that the cancer had metastasized once the patient should no longer receive therapy. The other two exhibited a complete response to treatment with no disease recurrence after 18 months. Theralase has begun a phase II clinical study for TLD-1433 in patients with NMIBC presenting with carcinoma in situ (CIS). We have submitted the US FDA and intend to have 20 sites enrolling 100–125 patients who will receive a maintenance treatment after six months and be followed for 360 days.

**Hopes for Rapid Commercialization**

The FDA has confirmed that the phase II study meets the requirements established in the February 2018 FDA guidance for accelerated approval for Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment. If we can achieve similar results to those shown in the phase I study (67% CR) for approximately 20–25 patients, our TLD-1433 anti-cancer therapy (ACT) platform may be suitable for accelerated approval and marketing authorization without the need for a phase III trial.

**Beyond Bladder Cancer**

We plan to extend the broader applicability of PDT and are conducting preclinical work on Theralase’s intravesical and exophoral cancers, including evaluation of potential ruthenium complexes and delivery methods.

**New Photostimulable Anticancer Agent in Development**

**Photodynamic Therapy**

**New Photostimulable Anticancer Agent in Development**

**Photodynamic compounds (PDCs) or drugs are cytotoxic when exposed to light at specific wavelengths and power levels.** Theralase’s PDCs are unique and can be activated by a wide range of laser wavelengths depending on their intrinsic properties of the bladder. This can be highly toxic to bladder cancer cells and released into the cells. This can be highly toxic to bladder cancer cells and released into the cells.

**Breaking a Beacon of Hope**

We are currently focusing on rare and orphan diseases in order to pursue accelerated pathways to commercialization. Once our initial candidates have reached the market, we will be able to shift our focus to diseases affecting large patient populations.

**Reference**

Innovative Therapies for Rare Eye Diseases

Ocugen offers a robust and diversified ophthalmology portfolio that includes novel gene therapies, biologics and small molecules targeting a range of high-need retinal and ocular surface diseases.

Rare and Underserved Ophthalmic Diseases

Ocugen is targeting inherited retinal diseases (IRDs), age-related macular degeneration (AMD) and ocular GVHD (oGVHD). The FDA has approved Theralease for the treatment of wet AMD, diabetic retinopathy (DR) and diabetic macular edema (DME), but many patients do not respond to existing treatments. There are no FDA-approved treatments available for dry AMD.

gGVHD affects approximately 60% of allogeneic bone marrow transplant patients and can lead to significant vision loss and unmanageable ocular surface damage, but lacks an FDA-approved therapy. There are no approved drugs in the marketplace today for ophthalmic diseases like gGVHD and multiple IRDs.

Leveraging Proprietary Nanomodeling Technology

Ocugen’s lead candidate OCU300 is an investigational steroid-free, preservative-free and drug-delivery technology. Ocugen is developing a novel gene therapy platform using a proprietary non-viral vector that delivers a therapeutic gene into the eye. The vector is designed to target the disease site and achieve retinal delivery of the therapeutic gene, resulting in improved vision.

Degeneration, and Rhodopsin mutation- associated retinitis pigmentosa. OCU410 achieves retinal delivery of the RDS gene, which regulates other genes associated with AMD and plays an important role in lipid metabolism and reduction of inflammation.

Given the wide applicability of our gene therapy platform and OCU410’s potential utility for many IRDs, we anticipate that we will be able to conduct parallel studies for different disease targets without investing further in manufacturing, licensing preclinical studies, and selecting the development of additional ophthalmic therapies with reduced cost.

Deve loping a Potential Cure for Bladder Cancer

C urrent bladder cancer treatments are not curative. A novel photodynamic therapy (PDT) platform being developed by Theralase could be the new gold standard.

Limited Options for Bladder Cancer Patients

Bladder cancer is the ninth most common cancer globally. Approximately 75-85% of patients with bladder cancer present with non-muscle invasive bladder cancer (NMIBC). Adjuvant intravesical instillations with bacillus Calmette-Guérin (BCG) is the recommended treatment option for patients with intermediate- and high-risk NMIBC. Despite adequate BCG treatment, a large proportion of patients experience a recurrence.

Adjuvant intravesical instillations with bacillus Calmette-Guérin (BCG) is the recommended treatment option for patients with intermediate- and high-risk NMIBC. Despite adequate BCG treatment, a large proportion of patients experience a recurrence. Although radical cystectomy is the gold standard for BCG-unresponsive NMIBC, some patients are not suitable for this option. BCG also has known side effects that impact patient acceptance and there has been worldwide supply shortage since 2012.

Despite bladder cancer being the fifth most common cancer in the United States, there has been virtually no advances in its treatment. Currently, intravesical therapies are limited by the intrinsic properties of the bladder. This is changing in the face of our improved understanding of the mechanisms of PDT and the pharmacodynamics of intravesical advanced photodynamic drug instillation and the development of novel intravesical light delivery and dosimetry technology.

New Photostimulative Anticancer Agent in Development

Photoactive compounds (PDCs) or drugs are cytotoxic when exposed to light at specific wavelengths and power levels. Theralase’s PDCs are unique and can be activated by a wide range of laser wavelengths regardless of the oxygenation level present in tumor tissue for PDT treatment, an advantage when dealing with cancers that have poor oxygenation.

Theralase has been working with research partners to develop our patented lead PDC, a ruthenium-based candidate (TLD-1433) for the treatment of NMIBC, and the associated patent-pending and proprietary TLD-3200 medical laser system.

TLD-1433 is designed to bind to transferrin, a protein involved in iron homeostasis. Because cancer cells have many more transferrin receptors than normal cells, much more TLD-1433 is bound to cancer cells. In preclinical studies, it has been shown to be highly toxic to bladder cancer cells, producing a complete kill rate at very low concentrations.

One-Day Treatment

Unlike BCG treatment and regimens for other bladder cancer therapies involving multiple sessions over several weeks, PDT with TLD-1433 takes place over just 45 minutes to 2 hours on one day. The drug is instilled into the bladder. One hour later, the patient is in the operating room under local anesthesia. The bladder is rinsed, instilled with sterile water and treated using laser light.

Because the drug is instilled in the bladder, there are no concerns regarding drug-drug interactions or side effects. Pharmacokinetic studies have shown that the drug is completely removed from the urine within hours and from plasma within 72 hours.

Exciting Early Results

In 2018, Theralase completed a phase Ib trial with TLD-1433 in NMIBC. Six patients were involved in the study, with three receiving the therapeutic dose. In one of these patients, it was later determined that the cancer had metastasized after treatment, and an additional dose has been enrolled. The other two exhibited a complete response to treatment with no disease recurrence after 18 months.

Theralase has taken phase II clinical study for TLD-1433 in patients with NMIBC presenting with carcinoma in situ (CIS). We have an accelerated 505(b)(2) regulatory pathway. We plan to explore the broader applicability of our technology and the role for accelerated approval.

Hopes for Rapid Commercialization

The FDA has confirmed that the phase II study meets the requirements of the accelerated approval pathway. We plan to seek accelerated approval and marketing authorization without the need for a phase III trial.

Beyond Bladder Cancer

We plan to explore the broader applicability of PDT and are conducting preclinical work in several other solid and hematopoietic cancers, including evaluation of potential ruthenium complexes and delivery methods.

Reference

the main goal of the pharmaceutical industry is to get drugs into the hands of the patients who need them as quickly as possible. Especially for new drugs, or for those that address conditions where there is an unmet need, a fast-track program can mean the difference between life and death. Whenever a timeline is speed up, relevant equipment must be procured, while surplus machinery must be removed. Because of cost pressures of the market and heightened production demands, partnering with a used equipment supplier like Federal Equipment Company creates an advantage when faced with tight timelines.

THE TIME AND COST OF DRUG DEVELOPMENT
Whether a project is being rushed internally or has been given accelerated approval by the U.S. Food and Drug Administration (FDA), taking a drug to market quickly is one of the most challenging tasks that any contract drug manufacturing organization (CDMO) can face. Starting with research and continuing all the way through approval, drug development is both time and cost intensive. On average, it costs $2.6 billion to develop a successful drug. Only a select few drugs in development end up being approved; the clinical success rate of a drug is estimated to be approximately 12%. Beyond being extremely costly, bringing a drug to market is a notoriously slow process. It takes 10 years on average to complete the development of a new medicine.

To get help drugs onto the market faster, the FDA has determined three types of drug designations — Fast Track, Breakthrough Therapy and Priority Review — based on the unmet need for treatments for the underlying conditions. Drugs receiving one or more of these designations means that the review process is streamlined and abbreviated, providing a significant benefit to the pharma company and the targeted patient population but also a potential manufacturing challenge, particularly for CDMOs competing for that business.

PROCURING EQUIPMENT ON A CONSTRAINED TIMELINE
Fast-tracked projects can increase the pressure on what can already be intense purchasing situations, where even small differences in turnaround can have significant consequences in achieving delivery milestones. Secondary equipment suppliers like Federal Equipment Company can often help reduce this pressure better than original equipment manufacturers (OEMs) by having inventory in stock, ready for inspection and immediate shipping and installation.

The average lead time for new equipment — including selection, customization, factory-acceptance testing (FAT) and site-acceptance testing (SAT) — can range from six weeks to 24 months. This can prove exceptionally costly — and potentially unfeasible — when trying to re-outfit a facility and deliver final goods under a fast-tracked timeline, reducing the competitiveness of a CDMO in bidding for such accelerated projects. When dealing with OEMs outside of the United States — for which issues with customs and international tariffs are routine — this timeline can become even more extended.

In addition to increased timelines set by the FDA, a drug maker can push for production speed internally, and is especially likely to do so if the drug has already been granted commercial status. Changing market conditions can create a sudden need for rapid increases in capacity. Contract manufacturing organizations must respond to these external pressures and update processes accordingly. As production revolves around machinery, in order to keep costs low but also meet the demands of the market by revamping operations, a CDMO is benefited by a partnership with a trusted used equipment supplier.

PARTNERING WITH A USED EQUIPMENT DEALER
The secondhand equipment market can provide a wide range of readily available equipment to pharmaceutical companies and CDMOs, reducing the lead times needed for specification, delivery and installation. Working with a qualified used equipment supplier can lead to faster product launches, process upgrades, capacity expansions and critical equipment replacements, which can make or break a fast-tracked project itself or a CDMO’s ability to secure the program. Beyond decreased lead times, buying used equipment can significantly reduce capital expenditures — costs for used assets can be 40-70% less than new equipment.

With a constantly updated stock of the latest machines in major asset classes and an expert team that trains operators in how to manage their newly acquired equipment, Federal Equipment Company is a leading choice when a facility needs to be upgraded. Federal Equipment Company provides machines that can be shipped within a week, which is unprecedented in an industry where much longer lead times are considered standard.

We partner with top OEMs to assure that the right machine is selected and installed. To maximize both time and cost savings, the option of acquiring used, rather than new equipment, should be evaluated as early as possible during process design to maximize flexibility and avoid the time-consuming, costly design and specification stages involved in new equipment purchases.

THE BENEFITS OF A SINGLE PARTNER
At Federal Equipment Company, the breadth of knowledge that our experts bring to any deal and our comprehensive understanding of the equipment that we carry provide a wealth of additional value to our partners. We offer training for solid dose equipment via our partner Techneticals in our tablet and capsule formulations lab — which is available for rent. We
Fast Track, Breakthrough Therapy and Priority Review

Giving a drug Fast Track status facilitates the review process; a drug that has promising animal or human data and treats a serious condition for which there are limited or no treatment options can be fast-tracked.

A Breakthrough Therapy designation indicates that the proposed therapy demonstrates a significant improvement over the current treatments on the market. A Breakthrough Therapy may also be submitted for Fast Track status.

If a drug is given Priority Review, the FDA will evaluate its effects in six months, instead of the usual 10 under standard review. A Priority Review designation is assigned to a drug because it may improve the treatment, diagnosis or prevention of a serious condition.

A Breakthrough Therapy designation indicates that the proposed therapy demonstrates a significant improvement over the current treatments on the market. A Breakthrough Therapy may also be submitted for Fast Track status.

When a CDMO is facing an abbreviated timeline — whether from the FDA or a sponsor organization — product management and optimization are key. Especially as cell and gene therapies advance from the clinic into the commercial realm and as biologic therapies continue to maintain their blockbuster status — production timelines will be expected to decrease. Owing to the high cost of research and development for new drugs, CDMOs that partner with a trusted equipment dealer and reduce production costs by relying on used machinery will not only improve their timelines but also build their reputation in the industry. By partnering with a reliable equipment supplier, companies are reducing costs, saving time and optimizing their means of production.

About the Author

Justin Kadis
Business Development, Federal Equipment Company

Justin Kadis works in marketing and business development for Federal Equipment Company, a major supplier of used manufacturing equipment for a wide variety of industries. He graduated from Boston University with a Bachelor of Science in Business Administration degree with a concentration in marketing.

LinkedIn: www.linkedin.com/in/jkadis/
Email: justin@fedequip.com

When you think equipment, think Federal Equipment

REFERENCE

CRISPR-Cas9: MILESTONES. THE FIRST IN VIVO CLINICAL TRIAL IS NOW UNDERWAY

BY LYDIA MICHAUT, Ph.D., BIOAGILYTIX

THE BRILLIANCY STUDY IS A MAJOR STEP FORWARD FOR CRISPR GENE EDITING, AND THERE IS MUCH POTENTIAL FOR ITS USE, PARTICULARLY IN MANY IN VIVO APPLICATIONS.

This comes as no surprise, since the most common orthologs of Cas9 are derived from Staphylococcus aureus (SaCas9) and Streptococcus pyogenes (SpCas9), which are two common pathogens that humans encounters. Both antibody- and T cell-mediated immunity against Cas9 in healthy individuals have been described, and while several published papers report varied outcomes, they all point to the conclusion that anti-Cas9 immunity needs to be assessed as part of the gene therapy development process.

It is important to remember that, while the existence of anti-Cas9 antibodies indicates that the immune system has previously been exposed to intracellular bacterial proteins, they may not necessarily mean that the efficacy of Cas9-mediated gene editing will be compromised. However, understanding their prevalence and potential neutralizing effect will be critical as part of the risk-benefit analysis for individual patients, as the impact of preexisting immunity can range from no clinical effect to decreased treatment efficacy to severe adverse reactions. For example, in the case of in vivo delivery, Cas9 is expressed intracellularly and can react with Cas9-RNA complexes, which may trigger immune cells expressing Cas9 protein.

A recent study showed that anti-Cas9 T cells can react to Cas9 in circulation, generating cytotoxic T lymphocytes (CTLs) that can destroy infected host cells. The study also notes that in vivo gene editing typically uses viral vectors that lead to long-term expression and are more likely to mediate an immune response to Cas9 following therapy.

IMPLICATIONS FOR IN VIVO GENE EDITING

It is important to note that research around in vivo use of CRISPR-Cas9 is still nascent, as the technology itself is recent and evolving. Still, the BRILLIANCE study is a major step forward for CRISPR gene editing, and there is much potential for its use, particularly in many in vivo applications. Ensuring the efficacy and safety of gene therapies based on CRISPR-Cas9 gene-editing tools will require careful evaluation of the prevalence of pre-existing antibodies to Cas9 and monitoring for clinical adverse events following therapy.

REFERENCES


ABOUT THE AUTHOR

Lydia Michaut, Ph.D.
Scientific Officer, BioAgilytix

Dr. Lydia Michaut holds a master’s degree in molecular and cellular biology and a Ph.D. in immunology from the University of Strasbourg and has 15 years of experience in fundamental research directly contributing to important work in Balian Prize- and Nobel Prize-winning academic laboratories. She then spent 10 years at Novartis, where she acquired a deep expertise of clinical regulated bioanalytics supporting PK, PD, and immunogenicity assessments of large molecule therapeutics, including gene therapies, before joining BioAgilytix in early 2019.

LinkedIn www.linkedin.com/in/lydia-michaut-5819482/ Email info@bioagilytix.com

PHARMASALMANAC.COM 89
PHARMA'S ALMANAC: GLOBAL PHARMACEUTICALS. SUPPLY CHAIN TRENDS | 04 2019
Quotient Sciences has been employing its unique Translational Pharmaceutics® integrated platform to accelerate product development for more than a decade. This platform has significantly reduced costs and time to market compared with traditional development approaches. Time savings of >12 months and a financial gain of >$100 million were recently confirmed by systematic research conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD).

**REAL NEED TO IMPROVE THE DRUG DEVELOPMENT PROCESS**

Drug development efforts must become more effective and efficient to reduce the time and cost required to bring new drugs to market – a cost estimated by the Tufts Center for the Study of Drug Development (Tufts CSDD) to be $2.6 billion.1

One way to improve efficiency is to break down the barriers between product manufacturing and evaluation in clinical trials. Both pharmaceutical companies and the contract service sector are constructed using a siloed model, with departments or organizations having a focus on either manufacturing or clinical testing. The resulting gap of many weeks or even months between manufacturing and dosing of products drives inefficiencies into the development process and, in addition, once a trial is initiated, means there is typically no flexibility in dosing; only clinical trial materials manufactured in advance of the study can be used.

**AN INTEGRATED APPROACH BORNE FROM LISTENING TO CUSTOMER NEEDS**

Quotient Sciences was founded in 1990 as an academic spin-out evaluating the science behind oral and inhaled drug delivery. Quotient had developed an operational framework comprising a clinical pharmacology facility with an integrated formulation group with small-scale manufacturing capabilities. In the early 2000s, several customers were asking Quotient whether it would be possible to quickly develop new formulation prototypes with abbreviated CMC data packages and then rapidly assess those in the clinical unit. The idea was that, if this could be done in days or weeks rather than many months, it would significantly shorten the development time. Quotient discussed various approaches internally with regulatory, manufacturing and medical colleagues and in 2008 approached the UK authorities (MHRA) for an advisory meeting to discuss some of the concepts. The main objectives of the meeting were to see if we could create a suitable regulatory and operational framework for bringing more speed and flexibility to developing new investigational drug products, without compromising quality or patient safety. The MHRA was receptive to our proposals, and the platform Translational Pharmaceutics was born.

**WHAT IS TRANSLATIONAL PHARMACEUTICS?**

Translational Pharmaceutics is the integration of formulation development, real-time manufacturing and clinical testing. By combining the work of contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) in one offering, outsourcing and program management are simplified and streamlined, and development times and costs are reduced. Importantly, clinical data arising within a study are utilized in real time to inform which formulation compositions should be made and dosed next, increasing program precision and potential for success. Flexibility is fully maximized by the unique inclusion of a formulation design space in regulatory submissions, which allows the potential to optimize the quantitative composition of critical-to-performance excipients and dosage strengths relative to clinical performance.

Quotient Sciences has several global state-of-the-art facilities for the manufacture of clinical trial materials and for running adaptive phase I clinical trials, enabling rapid manufacture and flexible product dosing in real time. To bring Translational Pharmaceutics to the United States, a scientific advisory meeting was held with the FDA in 2018, and as a result we now perform Translational Pharmaceutics programs within both the UK and U.S. regulatory environments.

**WIDE APPLICABILITY**

To date, we have completed more than 400 programs using our Translational Pharmaceutics platform. Our scientific and operational teams work with each client to design and deliver customized solutions that accelerate both simple and complex drug development programs based on individual molecule needs.

Translational Pharmaceutics can be deployed across the development spectrum, to accelerate transition of molecules from first-in-human (FIH) to proof-of-concept (POC), to optimize formulation compositions during full development and on average, the Tufts CSDD analysis found that average time savings for such FIH programs from formulation development to the point of patient supplies were 15 months compared with conventional studies (11.5 months vs. 26.5 months).
as also part of life-cycle management pro-
grams (505(b)(2)) projects. Translational Pharmacaceutics is applicable to all types of formulations, whether “fit for purpose” phase or those requiring sophisticated drug delivery technologies. While oral dos-
age forms feature transit, since they represent the predominant route of admin-
istration, the platform has been used to deliver peptide, liquid, injectable, topical and ocular routes.

Examples of completed projects include:
• Evaluation and selection of solubilization technologies;
• Optimization of modified release (MR) systems;
• Improvement of taste, palatability and acceptability of age-appropriate formulations;
• Changing routes of delivery;
• Development of combination products; and
• Understanding quality-by-design of product and process variables.

MANY BENEFITS OF AN INTEGRATED DEVELOPMENT PLATFORM

The obvious benefits of our Translational Pharmacaceutics platform are time and cost out of the development process, as quantified by the recent Tufts CSDD study. Time is saved via a combination of set-up features including:
• Manufacturing clinical batches immediately prior to dosing,
• Managing formulation changes within a single clinical protocol,
• Maximizing potential for “first right time” by using clinically driven decision making,
• Sealing traditional manufacturing campaign(s) to match the needs of the clinical trial.

Additional benefits are also apparent, with the consumption of drug substance often reduced by as much as 85%, given that only small batches are needed and stability studies are often not necessary (or very limited). Furthermore, with Translational Pharmacaceutics, projects are led by a single project manager overseeing an integrated cross-functional project team focused on delivering all of the components of traditional CDMO and CRO services, providing multiple efficiencies, cost savings and de-risking the supply chain.

TUFTS CSDD REPORT RESULTS

Customer feedback indicated that our Translational Pharmacaceutics platform provided significant savings in time and money, but we had to quantify the benefits.

In 2019, Joe DiMasi and his team at Tufts CSDD performed a study of projects completed by Quotient Sciences using the Translational Pharmacaceutics approach, applying their advanced economic model, which quan-
tifies the relationship between time and cost in drug development. The results were recently published in the white pa-
per “Assessing the Financial Impact of Translational Pharmacaceutics: A Platform for Acceleration Product Development.”

The Tufts CSDD team evaluated data provided by Quotient for a range of proj-
ects conducted over the past decade, in-
cluding actual dates taken from executed Translational Pharmacaceutics project plans. A group of independent industry consultants provided benchmark data for 30 conventional timelines for similar pro-
gress to enable comparison and identifi-
cation of time and cost savings.

THE BENEFITS OF TRANSLATIONAL PHARMACEUTICS ARE CLEAR

We’re extremely proud that the Tufts CSDD research has drawn these con-
clusions about the financial benefits of Translational Pharmacaceutics. If we ever hope to play our part in in-
dustry’s aspiration to improve R&D effi-
ciency and accelerate the availability of more medicines for patients.

Costs benefits were identified for two aspects of each project: R&D savings and returns from development. The savings were achieved by reducing project timelines for early development by greater

than 12 months. The additional sav-
eges included a design space on the quantity of release-controlling polymer in the for-
mulation developed did not provide

advancement into patient studies. The novel design of this study also enabled use of a smaller test population. A single-center study in healthy adult volunteers was performed at Quotient Sciences with the starting dose of ME-401. This study was designed to determine safety, tolerability and human exposure from the preceding cohort. The pro-
toco also allowed for flexibility to dose alternate formulations of ME-401. Unit doses were only manufactured once the data from previous cohorts were avail-
able. A powder blend in a capsule con-
taining ME-401, filler, and buffers was developed, enabling the creation of a dose design space from which any dose for the study could be prepared. Follow-

ing completion of the FIH study, the iden-
tified dose formulation was immediately supplied into oncology patient trials.

On average, the Tufts CSDD analysis found that average time savings for each of the two together gave us quantified mean after-tax pre-approval R&D cost of $220.2 million, and $201.5 million per ap-
proach was highly meaningful, ranging

REFERENCES


TO DATE, WE HAVE COMPLETED MORE THAN 400 PROGRAMS USING OUR TRANSLATIONAL PHARMACEUTICS PLATFORM.

The Tufts Casdd study found that projects involving solubil-
ity enhancement can be completed 12

months faster, affording additional sales, use of a minimal number of subjects, and regulatory guidelines. Dose selection for subsequent drug was dependent on the safety, tolerability and human expo-
sure from the safety, tolerability and human expo-
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continued...
With an expert process development (PD) team and a phosphorus-rich infrastructure in mind, further reducing time and cost, AVID BIOSERVICES is well positioned to support projects from concept to commercialization and research to production scale. Our integrated capabilities ensure the rapid development and seamless transition of robust, cost-efficient and readily scalable processes from the lab to the clinic and into the plant.

**STRONG BIOLOGICS GROWTH**

**DRIVING PHARMA MARKET**

While small molecules still account for the largest percentage of drugs on the market, demand for biologics is growing at a rapid pace. A significant portion of the pharmaceutical industry pipeline consists of recombinant proteins and antibodies, as well as next-generation biopharmaceuticals, such as gene and cell therapies.

Estimates for the value of the global biopharmaceuticals market vary somewhat, but they are all in the several hundred billion dollar range. One research firm predicts the market will expand at a compound annual growth rate (CAGR) of 8.59% from $237 billion in 2018 to nearly $390 billion in 2024.1

Biosimilars are an emerging segment of the biopharmaceutical market. According to research company Biophan Associates, in March 2019 there were over 1,500 follow-on biosimilars that have been approved, including over 1,000 biosimilars and over 550 biobetters.2 The growth in biosimilars is having an impact on biologics drug manufacturing, leading to an overall increase in outsourcing of approximately 15%.3

Today, Biophan reports that contract development and manufacturing organizations (CDMOs) manufacture e<33% of biopharmaceutical products.4 Since 2000, more than 15 new contract research organizations (CROs)/CDMOs have been established to provide biologics development and manufacturing services.5 The value of the global contract bioprocessing market is estimated to be expanding at a CAGR of 7.5%.6

**FROM EMBEDDED SERVICES TO DEDICATED CDO**

Unlike most new CDMOs that begin with smaller, early-stage projects and eventually move into commercial biologics manufacturing, Avid Bioservices’ first two clients had phase II/III commercial projects. Avid Bioservices’ focus on the embedded CDMO, we brought all of the expertise we had accumulated in biologics development and manufacturing for Peregrine products to the limited number of projects we accepted.

Since then, Avid Bioservices has transitioned into a fully dedicated CDMO focused completely on meeting the needs of our customers. We are committed to the continuous improvement of our own equipment and systems. We bring over 26 years of development and manufacturing experience and are personally invested in the success of our clients, from beginning to end.

**FULL LIFE CYCLE CAPABILITIES**

Avid provides fully integrated biomanufacturing services for our clients and can support a project from concept to commercial supply, including cell line optimization, protein characterization, upstream (batch, feed-batch and perfusion) and downstream processes — allowing us to use a wide range of expression systems, optimization, scale-up and validation, and can be tailored to meet the specific needs of our clients, from beginning to end.

Projects at Avid Bioservices fall into one of three categories: transfer in of established processes; transfer of existing processes that require optimization; or de novo upstream and downstream process development.

Each type of project involves a slightly different approach to process development. The key to success is having a conversation with the client at the earliest possible point to understand the specific needs and establish a target product profile. In addition to process knowledge, it is important to have experience developing and manufacturing a wide range of protein biotherapeutics using different CHO cell lines and other systems (NSO).

In addition to more conventional biotherapeutics like monoclonal antibodies, we have experience developing processes and production of unique molecules, such as Fc fusions and other fusion molecules, enzymes, vaccine subunits and other recombinant proteins.

Our manufacturing flexibility — in both upstream and downstream unit operations — allows us to accommodate these new and changing specialty biologic drug substances, which require processes that cannot be implemented using established platforms.

**HIGH-PERFORMANCE SOLUTIONS**

Advances in bioprocessing are occurring at a rapid pace. Within just the last decade, cell densities have increased dramatically. Titters as high as 10 g/L are now possible. The increased yields and productivity have been a boon for upstream production, but create challenges for downstream processing. A process on a 2,000-L scale with a titer of 10 g/L will afford 20 kg of protein that must be purified. In addition, in many cases, these high-producing cell lines take time to achieve their high production rates. This requires planned development and production timelines.

Avid Bioservices is actively working to develop proprietary technologies for these intensified projects intended to support high-performance systems that are robust, offer predictable performance and rapidly reach peak production levels. The goal is to achieve high cellular productivity and readily scalable downstream processes for more rapid production while still maintaining exceptionally high performance.

**FOCUS ON PROCESS DEVELOPMENT**

Projects at Avid Bioservices fall into one of three categories: transfer in of well-established processes; transfer of existing processes that require optimization; or de novo upstream and downstream process development.

Avid Bioservices is actively working to develop proprietary technologies for these intensified projects intended to support high-performance systems that are robust, offer predictable performance and rapidly reach peak production levels. The goal is to achieve high cellular productivity and readily scalable downstream processes for more rapid production while still maintain exceptionally high performance.

**WHILE SMALL MOLECULES STILL ACCOUNT FOR THE LARGEST PERCENTAGE OF DRUGS ON THE MARKET, DEMAND FOR BIOLOGICS IS GROWING AT A RAPID PACE.**

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1. Estimates for the value of the global biopharmaceuticals market vary somewhat, but they are all in the several hundred billion dollar range. One research firm predicts the market will expand at a compound annual growth rate (CAGR) of 8.59% from $237 billion in 2018 to nearly $390 billion in 2024.

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3. The growth in biosimilars is having an impact on biologics drug manufacturing, leading to an overall increase in outsourcing of approximately 15%.

4. Today, Biophan reports that contract development and manufacturing organizations (CDMOs) manufacture e<33% of biopharmaceutical products.

5. Since 2000, more than 15 new contract research organizations (CROs)/CDMOs have been established to provide biologics development and manufacturing services.

6. The value of the global contract bioprocessing market is estimated to be expanding at a CAGR of 7.5%.
Avid’s process development group collaborates closely with our analytical team, which enables us to establish the relevant process design space with a minimal number of experiments, and a minimal quantity of material. We also partner with equipment suppliers offering industry-leading systems and platforms, including GE, Thermo Fisher Scientific, Waters, Regenex, MilliporeSigma and Sartorius Stedim Biotech to ensure that the processes we develop are both efficient and cost-effective.

Our team of experts has years of product development and manufacturing experience that enable us to smoothly transition molecules onto the next phase, on time, and within budget. Our cell line, upstream, and downstream development processes combine to ensure our clients receive a well-characterized biologic with consistent product quality.

Recent projects have included rapid CHO cell culture optimization for a phase I clinical project resulting in >6 g/L titer and high capacity downstream process; cell culture optimization, downstream processing improvement and scale-up to 1000 L for a complex non-fcG immunglobulin with a complex glycoprofile; and phase-appropriate optimization of a process throughout clinical development (change in cell line, switch from a stainless-steel to a disposable bioreactor, media and feed optimization, scale-up to 1000 L and downstream process optimization) resulting in an overall 10-fold increase in comparable product yield.

NEW PROCESS DEVELOPMENT LAB
To support the growing number of clients with projects advancing through late-phase clinical trials towards commercial launch, we recently invested in an integrated pilot facility and process development lab to enable de-risking of the scale-up process for a seamless transition from the lab to commercial production.

The new PD lab, launched in early October 2018, has 30 identical state-of-the-art single-use and glass bioreactor systems ranging from 3 L to 15 L, which allows Avid to perform statistically significant process development, characterization and validation work in shortened timelines. The new equipment significantly accelerates our ability to develop and deliver cost-effective, robust, scalable and compliant processes and to drive efficient and rapid onboarding of new client programs progressing to manufacturing.

STRONG PARTNERSHIP APPROACH
Avid Bioservices strives to be a strategic partner with our clients, helping them to successfully deliver their products to the patients that need them. We aim to pave the way for the commercial launch of client products and take pride in our ability to think creatively and respond rapidly to any challenges that arise. Within the straits of quality, cost and time, our goal is always to provide the best service offering – development of optimized product and provision of high-quality product.

Indeed, quality is our passion and the paramount measure of our success. We deliver on our commitments to provide uncompromised compliance, deliver high-quality products to patients and achieve the key time-sensitive milestones that drive our clients’ successes.

Our robust quality systems are compliant with U.S. FDA, EU and ROW regulations, and we have an excellent 14-year regulatory inspection history. Avid’s Quality Control group serves as our internal oversight team, ensuring that each product receives the utmost attention to detail needed to achieve compliance.

Our focus on quality goes hand in hand with our excellent inspection and compliance history, providing you with peace of mind in your choice of a CDMO partner. We take your projects to the next level with our commitment to your commercial success.

REFERENCES

ABOUT THE AUTHORS
Richard Richieri
Chief Operations Officer, Avid Bioservices
Richard Richieri joined Avid as Chief Operations Officer in October 2019, overseeing process development, clinical and commercial manufacturing, technical support and facilities. Mr. Richieri previously spent 15 years with Avid Bioservices and its former parent company, Peregrine Pharmaceuticals, including the role of Senior Vice President of Manufacturing. He earned a bachelor’s degree in chemical engineering from the University of California, Los Angeles and a master’s degree in chemical engineering from the University of California, San Diego.

Email rrichieri@avidbio.com
LinkedIn www.linkedin.com/in/richard-richieri-1582634/

Magnus Schroeder, Ph.D.
Vice President of Process Development, Avid Bioservices
Dr. Schroeder joined Avid as the VP of Process Development in May 2018. He most recently served as a director at AGC Biologics a global CDMO organization, where he successfully supported client projects towards first-in-human clinical trials, commercial product launch and ongoing commercial supply. Dr. Schroeder earned his Ph.D. in biochemical engineering and his M.S. in molecular biotechnology from Biola University in California. He has previously served as a visiting scientist at Rensselaer Polytechnic Institute and at the University of Minnesota.

Email mschroeder@avidbio.com
LinkedIn www.linkedin.com/in/magnus-schroeder-4460531f

With over 26 years of process development and manufacturing experience, we are personally committed to your project success from beginning to end. Our team is dedicated to providing world-class customer service with the highest level of quality, from process development through commercialization.

We offer state-of-the-art facilities, utilizing the latest systems and technologies, quality processes, and platforms to ensure your project needs are met.

For more information, please visit avidbio.com

Our team of experts provide these services for your biologics:
- Cell Line Development
- Process Development & Optimization
- Analytical Development, Qualification, & Validation
- Clinical & cGMP Commercial Manufacturing

“We take your projects to the next level with your personal commitment for your commercial success.”
**FILL-FINISH SYSTEMS**

### FILL-FINISH FLEXIBILITY FOR SMALL-BATCH APPLICATIONS

Tighter regulation demands fewer interruptions and increased environmental monitoring and in-process-control (IPC) in drug production. Barrier separation systems are increasingly important to ensure process cleanliness and compliance. However, flexibility and repeatability are critical assets to small-batch developers, CDMOs/CMOs, and producers alike. Fill-finish systems designed to provide flexibility and repeatability offer greater efficiency, capability and traceability for small-batch applications. As competition and regulation continue to pressurize businesses in this space, advanced solutions, such as the uniquely configurable Flexicon FPC60 peristaltic fill-finishing system can deliver a competitive edge, with leading technology from Watson-Marlow Fluid Technology Group.

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**ABOUT THE AUTHOR**

Steve P. Adams  
Product Manager, Flexicon, Watson-Marlow Fluid Technology Group  

Mr. Adams is the product manager of Flexicon, a part of the Watson-Marlow Fluid Technology Group manufacturing specialized filling equipment from precision benchtop fillers to fully automated systems for aseptic applications in the biopharmaceutical industry. Steve has a BS in biology and several years of experience in medical device product development in sterile applications.

LinkedIn  
www.linkedin.com/in/steven-p-adams  
Email  
Steven.Adams@wmftg.com

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**SMALL-BATCH DRUG DEVELOPMENT**  

**FILL-FINISH SYSTEMS**  

Greater efficiency and lower costs are driving a growing number of inventive drug developers to turn away from large-batch, mass-market developments toward the important and lucrative segment of small-batch, personalized medication and orphan drugs. Simultaneously, regulators continue to increase the complexity of regulation, especially in data recording, traceability and cGMP. As a result of these two phenomena, drug development and production costs climb. Competitive developers and manufacturers must create a wider variety of formulations at an efficient rate while constantly meeting the high standards enforced by regulators. Their tools, including fill-finish systems machines, must accommodate these goals by providing exceptional flexibility and repeatability while adhering to increasing complex regulation.

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**SMALL-BATCH DRUG DEVELOPMENT AND PRODUCTION REQUIRES FLEXIBLE, REPEATABLE FILL-FINISH SYSTEMS**

A growing number of inventive drug developers are turning away from large-batch, mass-market developments toward the important and lucrative segment of small-batch, personalized medication and orphan drugs. Simultaneously, regulators continue to increase the complexity of regulation, especially in data recording, traceability and cGMP. As a result of these two phenomena, drug development and production costs climb. Competitive developers and manufacturers must create a wider variety of formulations at an efficient rate while constantly meeting the high standards enforced by regulators. Their tools, including fill-finish systems machines, must accommodate these goals by providing exceptional flexibility and repeatability while adhering to increasing complex regulation.
Plasmid DNA was key to the development of biologic drug manufacturing. Today, it plays a critical role in the production of next-generation cell and gene therapies and vaccines. With its plasmid DNA manufacturing expertise, Aldevron has helped facilitate the advance of these important therapeutic classes. The company continues to invest in additional capacity and novel capabilities to support biopharma manufacturers into the future.

THE PIVOTAL ROLE OF PLASMID DNA

By Robert Reames, Aldevron

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WHY PLASMIDS?
Plasmids are small extrachromosomal double-stranded DNA units that are typically circular in shape and are found across bacterial species. They behave independently of chromosomal DNA and are capable of self-replication. Generally, plasmids contain a few genes that encode proteins for cellular activities that are necessary for bacterial survival. Many are involved in establishing resistance to antibiotics, digesting foreign substances and killing other bacteria. Most notably, they can be picked up from the environment and transferred between bacteria via horizontal gene transfer (HGT), providing a unique nonsexual mechanism for the transfer of genetic information between individual bacteria and across species boundaries.

FROM AWARENESS TO UNDERSTANDING
While scientists were aware of the existence of independent strands of DNA in bacterial cells as early as the 1940s, the significance and function was not well understood. The term plasmid was coined in 1952 by Joshua Lederberg, who used it to refer to “any extrachromosomal hereditary element” when he observed virus particles picking up bacterial genes and transferring them to another host by a process he called transduction.

Once the double-helical structure of DNA was discovered and it was understood that DNA is the carrier of genetic information, the nature of plasmids as strands of DNA that can pass on traits became clear. Several plasmids were identified in the 1960s, including fertility and resistance (R) plasmids.

EASY TO MANIPULATE
Plasmid DNA was first isolated in 1967, and researchers across disciplines have been manipulating it ever since. Plasmids are attractive as genetic engineering tools because they are stable and easy to genetically modify. They have 1,000–30,000 DNA base pairs, so they are relatively easy to handle. They do not degrade when cut and can return to their original shape, making it easy to insert new DNA sequences into existing plasmid backbones. And because they self-replicate in bacterial cells, growing large quantities of bacteria is an effective strategy to produce large amounts of DNA.

PRODUCTION OF THERAPEUTIC PROTEINS
The first pharmaceutical application of plasmids was achieved in the 1970s. A foreign recombinant DNA was introduced into bacteria, enabling them to produce therapeutic proteins. Production of human insulin via transgene-containing plasmids in Escherichia coli was first accomplished in 1978. By 1986, advances in expression vector and transfection techniques led to the use of plasmids for the expression of foreign genes in mammalian cells, enabling the manufacture of more complex proteins and other biomolecules.

GENERATION OF TRANSGENIC ANIMALS AND PLANTS
In 1981, plasmid DNA was used to generate the first transgenic animal. Mice expressing thymidine kinase from herpes simplex virus were created by injecting recombinant plasmid DNA into fertilized mouse embryos. Transgenic plants followed in 1983 – first to improve the properties of crops, but then as a means for enabling plant-based drug production.

MANUFACTURE OF VACCINES AND GENE THERAPIES
By 1991, researchers were exploring the use of plasmid DNA for gene therapies. Compared with recombinant viruses, plasmids are attractive because they can deliver large quantities of DNA while presenting a low risk for oncoviruses and immunogenicity. They are also easier to manufacture in large quantities simply to be fairly stable. Unfortunately, they are inefficient gene transfer vectors when used in vivo. Today, most gene therapies are delivered in the form of viral vectors, which are manufactured using several different plasmids.

Also in the early 1990s, scientists were learning about the ability of plasmid DNA to stimulate both humoral immunity (antibodies) and cell-mediated immunity (T cells) and thus the potential for plasmids to be used as vaccines. In this case, the plasmids are designed to produce specific proteins from the relevant pathogen and then purified. As with gene therapies, using plasmids avoids the need to work with or introduce infectious agents into the body, and they are stable and can be readily manufactured at large scale. However, they tend to induce weaker immune responses.

DNA vaccines are under development for a number of different diseases, from infectious diseases, such as HIV-AIDS, Ebola, malaria and influenza, to various cancers and neurological diseases.

GENE EDITING AND PLASMID DNA
Integration of plasmid DNA into the genome allowed for further manipulation. Today, gene knock-out, knock-ins, over-expression, disease models, conditional mutants and fluorescently labeled proteins are all facilitated by the use of plasmid DNA.

In 2002, plasmid DNA was engineered to synthesize small RNAs, enabling the suppression of gene expression in mammalian cells via RNA-mediated interference (RNAi). Gene editing within rodent cells was achieved in 2011 by coinjecting single-celled embryos with sequence-specific zinc-finger nucleases and relevant plasmid DNA. Mammalian cells transfected with plasmid DNA expressing Cas9 and guide RNA were produced in 2013, enabling the gene editing system CRISPR/Cas to rapidly and precisely edit genomes inside living cells.

WE CAN PROVIDE PLASMID DNA FOR DISCOVERY RESEARCH, CLINICAL AND COMMERCIAL APPLICATIONS.

ADVANCING PLASMID MANUFACTURING AT ALDEVRON
Aldevron has been producing plasmid DNA since its inception in 1998. We began offering research-grade material only, and then expanded into custom manufacturing of plasmid DNA for preclinical, clinical and commercial applications.

We have proven experience producing plasmid DNA needed for viral vectors (AAV, lentivirus), DNA vaccines, CAR-T cell therapy, gene editing, cloning, DNA vaccines, personalized cell therapies and other applications. Companies pursuing truly novel products, such as Sarepta with its gene therapy treatment for Duchenne muscular dystrophy and Genprex with its...
plasmid DNA treatment for lung cancer, turn to Aldevron as their plasmid DNA supplier.

We can produce supercoiled, linearized, minicircle, nanoplasmid and bacmid plasmid DNA and have the capacity for thousands of small-scale plasmid preps per day and large-scale capacity for manufacturing hundreds of grams per lot. We can provide plasmid DNA for discovery research, clinical, and commercial applications.

Earlier in 2019, we added approximately 4,300 ft² of laboratory and production space to our Freiberg facility, expanding our capacity and adding a new Beacon Op-tofluidic platform to support rapid execution of species-agnostic single B cell antibody discovery. In April 2019, we added 1,000-L fermentation capacity to the Wisconsin plant, which will be online by the end of 2019, and plan to further expand the footprint of that site.

In July 2019, we were excited to partner with EQT; a leading private equity firm based in Europe. EQT is supporting Aldevron through investments in additional production capacity, R&D and initiatives and by leveraging its strong healthcare expertise, global presence and network of industrial advisors. EQT now owns a majority interest, with our founders, management and TA Associates retaining a minority stake.

Winning the War on Talent with Behavioral Interviewing

C ompetition for top talent is fierce in the pharma industries; however, the right recruitment firm can help find the perfect match.

War for Talent Is Here

The job market in the pharmaceutical industry is incredibly competitive. Companies are looking for very specific talent to fill leadership positions and must pursue candidates using a streamlined and efficient process. With limited candidates available—the cost of a vacant executive position in the many millions—you must also be able to make hiring decisions quickly.

Using our behavioral interviewing approach, we have achieved a fill rate of over 98% and an average of less than 3.3 candidates interviewed for a successful hire.

Social Media Is Insufficient

An understanding of the industry, the company and the skills and abilities of candidates is essential to make effective matches for leadership positions—this cannot be achieved without established relationships across an industry network.

The Role of the Recruiter

In addition to identifying the best and brightest candidates in the market, effective search and recruiting firms help their clients determine actual and specific candidate needs. Recruiters share their industry-wide experiences and bring new perspectives that help ensure clients pursue the right hiring strategies. With their extensive industry networks, they have access to a broad pool of top talent. Search firms apply proven methods for identifying and interviewing potential candidates, enabling the identification of the best matches for any given position.

The Key Corporate Services Process

With 20 plus years of experience recruiting in the pharma and biotech outsourcing sector, Key Corporate Services provide our clients with job candidates that make a real and lasting impact on their businesses. We start by understanding the company’s history, culture, market position, value proposition, goals and what it is trying to achieve with the hire. We then learn about the various stakeholders involved and the specific position, value proposition, goals and what it is trying to achieve with the hire. We then learn about the various stakeholders involved and the specific position, value proposition, goals and what it is trying to achieve with the hire. We then learn about the various stakeholders involved and the specific position, value proposition, goals and what it is trying to achieve with the hire. We then learn about the various stakeholders involved and the specific position, value proposition, goals and what it is trying to achieve with the hire. We then learn about the various stakeholders involved and the specific position, value proposition, goals and what it is trying to achieve with the hire.

The Benefits of Behavioral Interviewing

When hiring, it is essential to avoid being limited by traditional descriptors. It’s better to use a behavioral predictor of future success that sets and experience levels alone. Using our behavioral interviewing approach, we have achieved a fill rate of over 98% and an average of less than 3.3 candidates interviewed for a successful hire. That means our clients hire the right person more quickly, save time and money and add productive members to their staff faster than the competition.

Why Key Corporate Services?

Key Corporate Services is specialized in the pharma outsourcing sector and has been building an extensive network of contacts for more than 15 years. These contacts allow us to engage with virtually every candidate in the sector, provide search and recruiting services to the pharma outsourcing sector for a long time to come.

ABOUT THE AUTHOR

Robert Reames
Director of Technical Operations, Aldevron

Robert Reames is the Director of Technical Operations at Aldevron. He joined the organization in 2007 as Production Scientist for recombinant protein purification. Since then, he has served various roles in the company, which include R&D, Production Management, and Associate Director for GMP Manufacturing. Robert graduated from Minnesota State University Moorhead in 2007 with a BS in biochemistry and biotechnology.

LinkedIn: www.linkedin.com/in/rreames6480912/
Email: reames@aldevron.com

REFERENCE

Founded in 1998, Italian contract manufacturer Labomar provides novel quality, front-line solutions to its customers in the nutraceutical, food supplement, medical food, medical device and cosmetics markets. With the recent acquisition of Canadian CMO ImportFab, the company is now in a position to directly offer our proprietary delivery technologies to North American customers.

PHARMACY ROOTS
My family has owned a pharmacy in Istrana, in the province of Treviso, Italy for more than 100 years. I spent a lot of time in the pharmacy as a child and began working there as a young man. In speaking with customers, it was quite clear that many of the products on the market did not really meet their needs. To address this, I began developing products for the store, using a small laboratory in the pharmacy and eventually a GMP lab created in my family’s home. Customers of the pharmacy liked the products, and soon there was demand for them at other pharmacies as well. Eventually, it was necessary to move to a bigger space, and Labomar was officially established in 1998.

TWO DECADES OF RAPID GROWTH
Over the last two decades, the company has grown significantly to produce nutraceuticals, supplements, medical foods, medical devices and cosmetics. Today, we have a network of five facilities, including our headquarters, three cutting-edge production sites with state-of-the-art machinery and technology, 16 transformation centers and 15 complete packaging lines and the Labomar R&D Center. We employ 200 people and have 13 registered patients. We support 180 customers, market products in 28 countries and have the capability to produce up to 30 million units per year.

WIDE RANGE OF PRODUCTS AND SERVICES FOCUSED ON WELL-BEING
For Labomar, well-being is a wide-ranging concept: a good life philosophy that is built up day-by-day with safe and effective products. We also value a positive and stimulating working environment, in which passion and cooperation thrive.

This approach has led the development of many innovative, ready-to-market products targeting a broad array of therapeutic applications, such as gynecology, proctology, neurology, cardiology, gastroenterology, oncology, dermatology, wound care, orthopedics, pediatrics, eyesight wellness, weight management, cough and cold, and much more.

Labomar’s nutraceutical products are developed using patented technologies that increase the bioavailability of the active ingredients and regulate their absorption. Probiotic formulations from Labomar are based on probiotic species with proven scientific evidence for specific therapeutic areas.

Our medical devices (classes II A, II B and III) are intended for topical use and oral administration. Labomar developed formulations of foods for special medical purposes, which are intended to replace (either in part or totally) the foods eaten by persons suffering from metabolic or functional pathologies, with the special needs of these patients in mind, paying particular attention to the organoleptic aspects to enhance acceptability. Cosmetic products from Labomar are designed for resolving skin problems, as well as combating the signs of aging and improving physiological parameters.

Labomar also works closely with customers to develop customized and specific solutions, which can be formulated in many different types of dosage forms, including liquids (syrups, suspensions, emulsions, nanoemulsions, gels), tablets (regular, chewable, micro, orally dispersible), sublingual, coated, modified release, SCIENTIFIC RESEARCH AND THE CONSTANT DEVELOPMENT OF NEW, PATENTED TECHNOLOGIES ARE AT THE CORE OF WHAT WE DO.
AND FURTHER GROWTH.
INTERNATIONALIZATION
AN ADDITIONAL STEP
on producing daily on top-quality raw materials and in-
market research and trend analyses, our
rigorously scientific documentation.
rewarding new, ready-to-market products based
Our patented Raw Counters for the
administration. To that end, we have acquired the Food and Drug Administration and Health Canada, provides contract manufacturing and packaging services for liquid, semi-solid and cream pharmaceutical, cosmetic and nutraceutical products. The integration of their capabilities with Labomar presents a unique opportunity to increase the total turn-
over and company size, while expanding into new areas of the pharmaceutical market. We will now be able to bring our novel technologies and products to the United States, Canada and Mexico while also expanding our current direct access to the North American market.

CONTINUED INVESTMENT FOR FURTHER GROWTH
The acquisition of ImportFab raises the
in the coming years. To that end, we have acquired 100% of ImportFab Inc., a Canadian company based in Montreal that has been operating in the North American phar-
and installing new equipment necessary to transfer our technologies, Labomar is expanding our headquarters and adding new production areas for nutraceuticals and probiotics in Italy. We are also investing in an R&D accelerator program that is designed to attract young people and talent from foreign countries with inter-
ideas for developing of sup-
ments, cosmetics, medical foods and other products.

PHARMASALMANAC.COM 107106
**BREAKTHROUGH TECHNOLOGIES**

What breakthrough technologies have had a transformative effect on your business in 2019?

The challenges involved in biologic drug development differ greatly to those of small molecule drugs, and today’s innovators are more often focused on discovery, so they need to outsource other activities to progress programs.

At the same time, larger biopharma companies are seeking to forge more long-term relationships with fewer suppliers.

Following a year-long initiative and consultation exercise, Catalent’s biologics launch the OneBio Suite, an integrated biologics development solution designed specifically for those innovators looking for increased speed to the clinic and on to the market, while also reducing complexity and risks from projects.

OneBio offers innovators a single, integrated provider, reducing timelines and complexity associated with contract negotiation, site inspections and handoffs and poor communication between multiple vendors. The platform leverages Catalent’s advanced technologies and expertise to support programs from cell line development through to fill-finish, packaging, clinical supply and commercial launch under a single contract, program manager and harmonized quality systems.

OneBio Suite draws upon Catalent’s proven track record of progressing biologic drugs to market, which includes over 120 global clinical trials and 10 commercially marketed biologics using the company’s proprietary GFx® cell line development technology and 25 approved products through fill-finish and commercial supply to global markets.

One of the most exciting technological or scientific advancements that have influenced our business strategy in 2019 is our novel epigenetic regulator program. Unlike gene therapies, which target and modify DNA directly by inserting specific genes into patient’s cells, epigenetic regulators control or modify gene expression through processes that do not alter the sequence of DNA directly. Our lead asset DUR-928 is a small endogenous molecule that plays an important role in regulating cellular functions such as lipid homeostasis, inflammation and cell survival. DUR-928 has shown positive results in a phase Ia trial for the treatment of alcoholic hepatitis, a devastating acute condition with high mortality rates and limited therapeutic options. We are also advancing programs in other indications that could benefit from DUR-928, such as non-alcoholic steatohepatitis (NASH) or psoriasis. We believe that epigenetic regulation is a powerful and untapped treatment approach for many challenging diseases.

James E. Brown, D.V.M.
President and Chief Executive Officer,
DURECT Corporation

One breakthrough technology that has had a transformative effect on our research and development efforts this past year has been advances in next-generation sequencing (NGS) technologies, including single-cell RNA sequencing (scRNA-seq).

When combined with ongoing advances in bioinformatics, the complex data sets generated by scRNA-seq have great potential to identify previously unrecognized cell populations and relationships between genes that could help uncover new targets for researchers to focus on. We received a grant from the French National Research Agency to collaborate with academic researchers at premier cancer centers in France to use scRNA-seq and bioinformatics approaches to validate new targets linked to myeloid cells, an important type of suppressive immune cells. This grant and subsequent collaborations could have a positive impact on development of new therapies for immune-related diseases, such as cancer and autoimmune diseases. We’re eagerly anticipating additional breakthroughs with NGS technologies that could provide researchers with novel targets to leverage innovative new treatment options for all patients in need.

Alexia Peyrolers
Chief Executive Officer, GSE Immunotherapeutics

Although continuous flow has been utilized in a variety of industries for over a century, the pharmaceutical industry has been slow to adopt this technology for historical and regulatory reasons. The advantages that continuous flow has for chemical synthesis include both safety and efficiency, and there are a number of examples of pharmaceutical companies looking to leverage the technology for process improvements in clinical phase development.

Shawn Conway
Director of Engineering Research & Development, Cambrex

Cambrex identified a need for continuous process development capabilities within the CDMO industry and took the decision to establish a continuous flow Centre of Excellence at its site in High Point, NC. The site has installed a number of continuous flow reactor platforms and, as a result, now has several continuous flow projects underway with pharma customers of varying sizes. Customers have access to a dedicated engineering group and the process development work carried out in High Point can be seamlessly transferred to Cambrex’s drug substance manufacturing facilities in the U.S. and Europe, where commercial scale equipment can be used for scale-up.
Q: What breakthrough technologies have had a transformative effect on your business in 2019?

In recent years, technological advances in the immuno-oncology field have been focused on the development of checkpoint therapies, bispecific antibodies and, most notably, cell therapies such as CAR-T or TCR-T approaches.

While initial progress is encouraging, these treatment options present challenges that pertain to specificity, safety and durability of response, as well as manufacturing challenges in the case of cell therapy approaches. A primary driver of our motivation at Cue Biopharma was to develop an alternative therapeutic approach that could mitigate the challenges discussed above and hence provide a differentiated and superior path for the future of immunotherapy that would significantly improve upon what current therapies can accomplish, with broad applications within and beyond immuno-oncology. To that end, we have been engineering a class of injectable biologics to selectively engage and modulate targeted T cells within the patient’s body to transform the treatment of cancer and autoimmune diseases. Our breakthrough technology, the Immuno-STAT™ (Selective Targeting and Alteration of T cells) platform, represents a fundamentally different mechanism for leveraging T cells to treat diseases with the potential to be more targeted, more powerful and safer, while at the same time far less costly and cumbersome than cell therapies.

In 2019 at Charles River, we announced a strategic partnership with Atomwise, bringing their unique, structure-based artificial intelligence (AI) technology, based on convolutional neural networks for hit identification and optimization, to our partner projects.

For our industry, the development of abuse-deterrent technology and nanotechnology for cannabinoid-derived therapeutics is evolving to be transformative in treating high unmet medical needs.

These technologies are not only instrumental in enhancing the solubility of THC and CBC products that have been shown to relieve symptoms of pain and inflammation, but are of critical importance given the widespread opioid crisis. For example, the potential of cannabinoid-based medicines as an alternative to opioids for pain management is significant and of particular concern worldwide, as chronic pain is associated with more than $900 billion USD in healthcare costs per year. The use of deterrence technologies, particularly non-opioid alternatives, allows us to formulate and harness multiple delivery systems for cannabinoid-derived therapeutics in a safe manner while optimizing patient care. As more companies from Big Pharma begin to explore cannabinoid-based therapies, the industry will depend upon abuse deterrent technology and nanotechnology to identify prescription-strength alternatives for healthcare providers and patients.

We are also developing advanced polymers and 3D printing processes that can be leveraged by pharmaceutical companies to create personalized medicines in an oral solid dosage form. Similar activities are also underway to support the development of biosimilar implantable medical devices with patient-specific parts that can match the patient’s natural healing process. Other core technology areas being pursued include the production of advanced foods and biofabricated materials utilizing microbial fermentation processes, the use of lipid nanoparticle technologies for the delivery of nucleic acids such as mRNA and tissue engineering for wound healing and organ repair.

The power of this technology is an exciting step forward for Charles River into the AI arena, as it opens up the opportunity to predict binding to protein targets for vast numbers of compounds, including synthesis-on-demand libraries, within a matter of days. Access to such large regions of chemical space becomes very important for those protein targets that are traditionally considered challenging for hit finding and highly competitive “hot targets” where access to novel chemical space is highly desired.
During the last decade, the biopharma industry has made significant advancements in the discovery and development of new therapeutics; however, there are still many patients suffering from diseases, and they are still looking for effective treatment options.

Most diseases involve complex mechanisms, including changes in the epigenome, the chemical modifications to DNA and related proteins that regulate the expression of genes within a person’s genome. An increased effort, represented by an increased number of scientific publications, has been dedicated to understanding epigenetic mechanisms and disease in recent years.

As we enter 2020 and beyond, more robust computational approaches are under development that will allow us to build even better predictive models of gene expression and regulation to continue to unveil complex mechanisms of disease. At DURECT, we believe that epigenetic therapy is increasingly promising, and we are excited to move our therapeutic programs and bring it to a market that has struggled with manufacturing capacity. Recognizing this trend, Catalent has extended its capabilities through the $1.2 billion acquisition of Paragon Bioservices.

Gene therapy manufacturing outsourcing has many advantages for drug developers, as relatively low volumes are required to fulfill each program’s demand. However, stringent regulatory requirements and high-quality standards are required to manufacture these therapies safely and efficiently. Using a partner with deep experience, cGMP compliant manufacturing capacity and commercial-ready process development expertise is far more cost-effective than building and managing a new facility from the ground up.

Camera technology is being used in AVI and during fill trials to eliminate drift/pilling that adversely impact product integrity and risk of particulate transfer to container handling systems. New speculation software is still in development, but once it is a proven technology, the vision of in-line viable and non-viable particle measurement, without a microbiological testing process step that delays batch processing for weeks, will be reality.

Serialization identity technologies that utilize invisible UV imprints on containers and closure seal surfaces will reduce risk of counterfeit drugs. The recent application of computer systems for translating the mechanism of disease interaction and modeling formulations to mitigate impact will eventually change how drugs are developed and delivered, by reducing time in drug development and speeding time from R&D to the clinic and from clinic to the patient.

We believe that technologies that harness the breadth and the depth of the immune system will play a key role in providing next-gen therapeutic solutions for patients suffering from autoimmunity, cancers, chronic infections and other inflammatory disorders.

Approaches that will have the greatest impact are those that go beyond incremental improvements for patients and aim for more transformative breakthroughs that build upon fundamental biological nodes of immune modulation and dysregulation. A key consideration for immunotherapies will likely focus on specificity of biological signals and on platforms that can exploit the same for therapeutic solutions.

To that end, Cue Biopharma has developed the Immuno-STAT™ biologics platform that builds upon nature’s cues for T cell activation and modulation. It is an excellent example of biological form following function that harnesses the intrinsic specificity of the immune system, thereby potentially eliminating the negative side effects of global indiscriminate immune modulation and/or the need for ex vivo manipulation of T cells. The immuno-STAT platform builds upon a deep understanding of T cell biology and function, which we believe is potentially why this approach is poised to disrupt the biopharma industry.

Anish Suri, Ph.D.
Chief Scientific Officer, Cue Biopharma

Recent advances in the development and commercial use of gene and cell targeting therapies that are reliant upon lipid nanoparticle (LNP) delivery technologies have the potential to redefine treatment modalities across a range of disease areas. In particular, there is a surge in the number of customer projects relating to the development and production of complex parenteral drug products for the delivery of nucleic acids, such as mRNA. We expect that LNP-based delivery of genetic drugs will continue to enable the development of exciting new personalized drug treatments over the coming decade.

Another promising area of focus is tissue engineering, where technologies for 3D printed scaffolds, cell nutrition and advanced biomaterials are being combined to create new solutions that can repair or replace damaged tissue and organs. Evox has established an R&D hub for tissue engineering in Singapore to strengthen its competencies in this arena to ensure we are ready to serve as a global development partner and solutions provider.
Brazil already manufactures APIs for the local consumption. We see Brazil exporting its APIs and becoming an API manufacturing powerhouse supplying the global pharmaceutical industry over the next 10 years. Among the key strengths of Brazil are ANVISA standards, which are very high and recognized by the European Union, strong local API know-how, a talent pool of chemists and engineers and a competitive cost structure. C2 PHARMA is investing heavily to collaborate with Brazilian companies to market their APIs outside Brazil.

Andrew Badrot
Chief Executive Officer and Founder, C2 PHARMA

In one word: Brazil. We see Brazil as a burgeoning country to export APIs.

W e are in the initial stages of applying AI in hit identification and optimization at Charles River, so it is a little early for definitive data on the levels of success for our partner programs.

In AI, the next steps forward will be on the implementation strategy and how AI technologies at different stages of the process can be seamlessly integrated within organizations. However, the challenge still remains to demonstrate the current and emerging applications of AI prospectively impacting the drug discovery process. A level of skepticism towards AI in drug discovery exists, primarily due to the associated hype, and this skepticism will gradually be alleviated through demonstrated success stories on live drug discovery programs. Despite this, we anticipate that the application of AI technologies in our organization will grow significantly in the near future. AI will have a major positive impact upon our ability to find hits for challenging targets, ultimately resulting in quicker timelines to transition projects into hit-to-lead and lead-optimization phases.

We have been great advances in artificial intelligence (AI) technology over the past few years, the full impact of AI has yet to be truly felt in the biopharma industry.

While there have been great advances in artificial intelligence (AI) technology over the past few years, the full impact of AI has yet to be truly felt in the biopharma industry.

Heading into 2020 and beyond, we believe we will see more practical applications of AI, such as machine learning algorithms optimized for distilling the most salient information from large data sets. In the oncology space specifically, there are a growing number of tissue banks that contain samples of tumors from thousands of patients. In order for researchers to fully benefit from resources such as these, AI-driven bioinformatics approaches will have to be developed and put to use when processing these samples to ensure that they are of maximum value. We’re currently working with researchers at the Léon Bérard Cancer Center in Lyon, France to analyze gene expression in the human tumor microenvironment and the composition of tumor infiltrates based on tissue samples from cancer patients. The findings from this collaboration will be used for the selection and validation of innovative targets for early development of new drug candidates for hard-to-treat cancers.
ABITEC is a global leader in the development and manufacture of specialty lipids and sur- factants. Through their world-class technical, scientific, laboratory and manufacturing expertise, they deliver the highest quality solutions in stabilization, emulsification and lubrication. ABITEC’s first-class ISO certified facilities in Janesville, WI and Paris, IL, along with their corporate location in Columbus, OH, are home to nearly 70 employees who are passionate about creating premium ingredients.

AC Immune SA is a Nasdaq-listed clinical-stage biopharmaceutical company, which aims to become a global leader in Precision Medicine for neurodegenerative diseases. The company is utilizing two proprietary discovery platforms, SupraAntigen™ and Morphomer™, to design, discover and develop small molecule and biologi- cal therapeutics as well as diagnostic products intended to diagnose, prevent and modify neu- rodegenerative diseases caused by misfolding proteins.

Albemarle Fine Chemistry Services provides custom manufacturing of APIs and advanced intermediates for the API pharma- ceutical, agricultural and specialty chemi- cals industries. With world-class facilities, ex- ceptional process development and scale-up capabilities, and exemplary customer service, Albemarle is the perfect production partner for your custom project, offering a range of manu- facturing services backed by highly skilled R&D teams to assist with synthesis route selection, process development and analytical support.

Aldevron is a leader in advancing biological sci- ence. Their custom development and manufac- turing services have provided scientists around the world with the essential components to ac- celerate research and open up their laboratories for groundbreaking research and breakthrough discoveries.

Aldrich is the Almac Group is an established contract development and manufacturing organization (CDMO) providing an extensive range of integ- rated services across the drug development lifecycle to the pharmaceutical and biotech sec- tors globally. Their innovative services range from R&D, biomarker discovery and development, commercialization, API manufacturing, formula- tion development, clinical trial supply, RT (IVRS/ IVMS) through to commercial-scale manufacture.

Alranra is a spin-off company from the Paul Scherrer Institute (PSI) and ETH Zurich pioneering a novel antibody-dog- competitive (ADC) linker technology. Their linker platform enables the attachment of any payload to the ‘off the shelf’ antibodies without the need of prior antibody engineering. Their innovative approach has the potential to set new bench- marks in terms of development, performance and economics.

Avid Bioservices is a full-service contract de- velopment and manufacturing organization (CDMO), providing process development and cGMP clinical and commercial manufactur- ing services for leading biotechnology and pharmaceutical industries. Avid is a trusted partner for expert solutions and reliable results, with 30 years of biologics development and manufacturing experience, backed by an excellent regulatory track record for products approved in 15 countries.

Atranta Bio is building the best-in-class micro- biome contract development and manufacturing organization (CDMO) through the establishment of a facility dedicated to process development and cGMP clinical supply with a commercial- ization capability. Its aim is to support the pio- neers in the development of healthcare therapies based on the biotrophic perspective (BPR) tar- geting gut health and microbiome-related diseases by providing development and manufacturing services that bring effective treatments to the market and patients in need.

Avidity is a biopharmaceutical company committed to the development of innovative products that have the potential to restore the health of people with cardiovascular disease. The company has three programs in the mid to late stages of clinical development that are based on its autologous CD34+ cell therapy platform to treat coronary microvascular dysfunction, critical limb ischemia and no-option refractory disabling angina.

AppleBio is a full-service network of engineers, architects, constructors and consultants as- sisting advanced technology organizations in the planning, design, construction and op- eration support of facilities across the globe. AppleBio serves clients in biopharmaceutical, pharma- ceutical, science and technology, food, nutra- ceuticals and consumer products, providing support across the full project lifecycle.

Araris Biotech AG is one of the world’s leading subcon- tractors in the industrial & household, cosmet- icals and pharmaceuticals fields. Their story be- gan in 1950 in France, in the heart of Ardèche region, with a team of passionate enthusiasts that moved into the world of chemistry and developed its core business: research, formu- lation, manufacturing and filling. From the very beginning, Araris has focused on creation, in- novation and mastering processes to offer its customers cutting-edge expertise.

Aminc is an established contract development and manufacturing organization with a track record of success. Aminc has partnered with leading biotechnology and pharmaceutical companies worldwide. Aminc’s clients include some of the world’s largest companies, and they have a reputation for delivering high-quality services on time and on budget.

Aravis is a clinical-stage biopharmaceutical company committed to the development of innovative products that have the potential to restore the health of people with cardiovascular disease. The company has three programs in the mid to late stages of clinical development that are based on its autologous CD34+ cell therapy platform to treat coronary microvascular dysfunction, critical limb ischemia and no-option refractory disabling angina.

Arbaban is a spin-off company from the Paul Scherrer Institute (PSI) and ETH Zurich pioneering a novel antibody-dog- competitive (ADC) linker technology. Their linker platform enables the attachment of any payload to the ‘off the shelf’ antibodies without the need of prior antibody engineering. Their innovative approach has the potential to set new bench- marks in terms of development, performance and economics.

Arthromyx is a biopharmaceutical company committed to the development of innovative products that have the potential to restore the health of people with cardiovascular disease. The company has three programs in the mid to late stages of clinical development that are based on its autologous CD34+ cell therapy platform to treat coronary microvascular dysfunction, critical limb ischemia and no-option refractory disabling angina.

Astrida is a biopharmaceutical company committed to the development of innovative products that have the potential to restore the health of people with cardiovascular disease. The company has three programs in the mid to late stages of clinical development that are based on its autologous CD34+ cell therapy platform to treat coronary microvascular dysfunction, critical limb ischemia and no-option refractory disabling angina.
ImmuneGene is developing first-in-class cancer therapies. The company is using the tumor-educated immune cell response from patients. Their proprietary discovery engine identifies antibody-target pairs by interrogating the patient response with unparalleled depth, breadth, and speed. Using this rich source of target pairs, ImmuneGene is developing new cancer therapies and exploring uncharted areas of cancer biology.

Ocugen, Inc., is a clinical stage biopharmaceutical company focused on discovering, developing and commercializing a pipeline of innovative gene therapies, biologics and small molecules. Ocugen, Inc. is developing new cancer therapies and exploring uncharted areas of cancer biology.

ProQR is dedicated to changing lives through the creation of transformative RNA medicines for the treatment of severe inherited retinal diseases, such as Leber’s congenital amaurosis. ProQR’s therapies are growing their pipeline with patients and loved ones in mind. ProQR is leading the innovation in RNA-targeted therapies to combat some of the world’s most devastating diseases.

MWL is a spin-off company from University of Twente. The company is an award-winning, global leader in fluid management technology and has over 60 years of engineering experience. They are providing leading-edge solutions for medical and biotech industries. Headquartered in Altena, the Netherlands, with additional strategic locations worldwide, Yourway specializes in time- and temperature-sensitive clinical drug product and biological sample shipments.

Yourway is an integrated biopharmaceutical supply chain solutions provider offering a full range of primary and secondary clinical packaging, comparator sourcing, logistics, storage and distribution services for the global pharmaceutical and biotech industries. Yourway specializes in time- and temperature-sensitive clinical drug product and biological sample shipments.

Servier provides fully integrated manufacturing and supply chain services for small molecules & drug product, from development and clinical supply up to commercial launch. Servier possesses late-stage of the art facilities, a proven track record in chemical synthesis, pharmaceutical formulation, development and manufacturing, and a complete range of services offering full flexibility. Services include process and analytical development, pilot production and industrial scale-up, regulatory dossiers, in collaboration with the Servier network.

Theralase Technologies Inc. is a clinical stage pharmaceutical company focused on the research, development and commercialization of light activated Photo Dynamic Componet (PDC) and the associated drug formulations intended for safe and effectively destroy cancer. Founded in 1994, Theralase’s operations are divided into two divisions: medical laser technology division that manufactures and commercializes medical laser systems, and the R&D of Photodynamic Therapy for the anti-cancer technology.

PROVEO provides full integrated manufacturing and supply chain services for small molecules & drug product, from development and clinical supply up to commercial launch. PROVEO is a global pharmaceutical de-
The journey may test your every ability
But the ending prize is a sea of tranquility
Savor reward for your toil that is done
As you gaze towards the next horizon

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