pharma's almanac

A NICE INSIGHT MAGAZINE

Q2 2019 VOLUME 5 NUMBER 2

THE ADVANCED THERAPEUTICS ISSUE

INSIDE THE WORLD OF ORPHAN DRUGS

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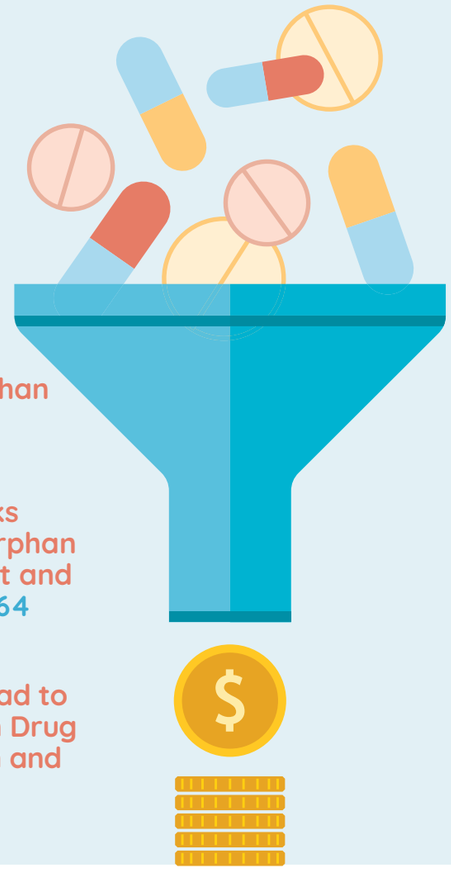
By **David Alvaro, Ph.D., Emilie Branch** and **Cynthia Challener, Ph.D.,** Nice Insight



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Nice Passion is a substantially different offering from all previous That's Nice brand extensions. We are shooting video and short films centered on individuals that work in the Life Sciences community, but the focus of each piece is a passion they pursue with total dedication away from work. Our four films so far have been shot at an airfield in France, on a remote mountain in New Hampshire, in suburban New York and, of course, on our epic cross-country adventure, Road To BIO.

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The print version of *Pharma's Almanac* is delivered to a targeted group of 20,000 leaders from all sectors of the industry who are implementing new strategies and technologies creating collaboration models with drug developers to deliver on the global mission to provide the reliable supply of safe effective pharmaceuticals and therapeutic agents worldwide. The custom print distribution includes individuals across big pharma, the biotechs, mid-sized and specialty pharma, virtual pharma–biotechs, as well as regulatory and governmental agencies, academia, and consumer patient touchpoints.

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→ A NOTE FROM THE EDITOR

ORPHAN DRUGS AND NEXT-GENERATION THERAPIES

→ BY **DAVID ALVARO, Ph.D.**, NICE INSIGHT

We are very pleased to introduce the "Advanced Therapeutics" issue of Pharma's Almanac. Inside, you will find thought leadership from a range of innovative and industry-leading companies that provide contract development and manufacturing services, supply chain logistics and other supportive services to the pharmaceutical and biopharmaceutical industries.

In any current forum discussing next-generation therapies, cell and gene therapies are certain to demand a considerable amount of bandwidth, and this issue is no exception. Our contributors herein address a diversity of considerations for these advanced therapies, including viral vectors and their manufacturing processes, the arrival of standardized off-the-shelf vector products and specific applications for cancer and aging patients. The evolution of supply chain logistics to make clinical trials and, ultimately, commercialization possible, as well as the overall state of the industry, and the recent mergers and acquisitions that are accelerating its maturation are likewise explored.

Regenerative medicines are only one piece of the current therapeutic landscape. This issue also features content on cutting-edge oral solid dose technologies, plasma proteins, sterile products and antibody–drug conjugates, among other topics.

Of course, as engaging as it is to focus on the technologies that are advancing the industry, the true excitement from innovations in pharma and biopharma comes from the benefits to patients, particularly when they are able to provide an unmet medical need or deliver life-changing or life-saving treatments to underserved patient populations. In this issue, our Nice Insight overview and the three-part feature explores the orphan drug market and some of the major challenges from the perspectives of development, manufacturing, regulatory incentives and commercialization. Addressing the needs of innovator companies developing orphan drugs – particularly the small and virtual biopharmaceutical companies most likely to require outsourced support throughout the life cycle from gene to vial – is a common thread woven across much of the issue.

The paradigm shift from the blockbuster drug era to our time of tailored treatments and personalized medicine reflects more than just a shake-up of the market and a call to evolve business models for this new ecosystem. It represents an ongoing opportunity to reorient the focus of the industry, not only toward patients in general, but toward those with the greatest unmet needs. P

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"Passion, in all its various forms, is what drives us. For some, it is the culmination of a lifelong ambition, while others may be fortunate to live it every day."

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THAT'S NICE CONTINUES TO SEEK OUT AND ADD NEW CONTENT TO NICE PASSION

Nice Passion is a different brand extension to all others at That's Nice. Very personal short films tell stories of individuals that work in Life Sciences, but pursue a separate passion with total dedication away from their day-to-day role.

Road to BIO *51-minute film, 14 chapters*
We launched Nice Passion with the film, Road to BIO. It tells the story of an epic 12-day road trip from Cambridge, Massachusetts to San Diego, California before the 2017 BIO International. Meet some of the crew at this year's show.

Flight of Freedom *5-minute short, 1 chapter*
In this film shot in France, a career scientist from a pharma innovator narrates his passion for restoring and flying a World War II-era plane. It is the freedom of flight, as a contrast to so much in modern life, which fuels this passion.

Everyday Exotic *8-minute film, 1 chapter*
This story appears to center on the realization of an exotic car dream, but actually focuses on having belief in your own convictions and breaking down society's barriers. Meet the exotic commuter at BIO International in Philadelphia.

Science of Nature *6-minute short, 1 chapter*
Through the week, the central character in this film works at the forefront of a scientific enterprise that can benefit all humans. On weekends, he lives away from every other human, inspired by solitude and unspoiled nature on a remote mountain.

WHERE DO ORPHAN DRUGS GO FROM HERE?

By **Nigel Walker**, Nice Insight

Since laws were implemented in the United States, Europe and Japan to encourage the development of drugs to treat rare diseases, the number of orphan drugs on the market has increased. In spite of this, development and approval times can be quite lengthy, and the treatments often carry very high price tags. The consensus is starting to build among many stakeholders that the programs need a major overhaul.

Steadily Growing Market

Following the inception of legislation promoting the commercialization of orphan drugs, development of new drugs to treat the approximately 7,000–8,000 known rare diseases has been financially incentivized through marketing exclusivity periods, tax credits and reduced fees.

Evaluate Pharma estimates that the current global orphan drug market is expanding at a compound annual growth rate of 11.3% – nearly twice that of the overall pharma market (6.4%) – and will reach a value of $262 billion in 2024.[1] By then, orphan drugs are expected to account for 20% of worldwide prescription sales and one-third of total R&D pipeline sales through 2024.

In addition, of all innovative drugs that have expanded the human drug target landscape from 1983 to 2017, orphan drugs account for more than 40%.[2] As of mid-2018, investigative drugs for the treatment of rare diseases also accounted for 40% of the 803 drug candidates undergoing clinical trials.

This growth is occurring despite declines in year-on-year price increases (which rose at 5.2% annually, compared to 9.2% for the top 100 non-orphan products), perhaps because the mean cost per patient was still nearly $150,000 in 2017.[1] Cancer treatments will account for approximately half of the global orphan drug market in 2024, followed by blood therapies at 12.5%.[1] Notably, four of the top five approved oncology drugs received orphan drug designations – and achieved blockbuster status.[2]

The U.S. Food and Drug Administration has granted more orphan drug designations than any other regulatory body, with many more coming since the implementation of the agency's orphan drug modernization plan beginning in 2016. Nearly 4,000 drugs received orphan drug designations in the United States in the period between 1983 and 2017, and more than 650 were approved for marketing in the United States during that time.[3] Between 2014 and 2017, orphan drugs comprised over 40% of the new molecule entities approved each year.[1]

Lengthy Development and Approval Times

A study conducted by the Tufts Center for the Study of Drug Development revealed that the time required to transition from first patent filing to product launch for orphan drugs is 18% longer on average than it is for all new drugs.[3] Development of drugs to treat ultra-rare diseases that affect only a few hundred patients takes even longer – 17.2 years on average versus 15.1 years for regular orphan drugs.

Of the 86 orphan drugs that received marketing approval from the FDA in 2018, 16 had been designated as an orphan drug for the treatment of a rare disease 10 or more years before approval, and waited 20 or more years to secure approval.[4] Many received orphan drug designation four to eight years before marketing authorization.

The Tufts study was based on 46 first-in-class orphan new molecular entities approved by the FDA between 1999 and 2012. Previous studies evaluated the time from filing of a new drug application to FDA approval, which does not take into consideration the challenges associated with setting up and running clinical trials. Some other difficulties include variability in the expression, severity and/or course of diseases that may not be well known and/or lack well-understood biologies; small and geographically dispersed populations; and lack of obvious endpoints and outcome measures.[3]

The fact that the study only looked at data through 2012 may have contributed to the lengthy development times, because recent advances in drug development and approval pathways were not accounted for, such as the FDA's Breakthrough Therapy designation for accelerated approvals, which was implemented in 2012.[3]

In addition, a 2017 study by Kaiser Health News and National Public Radio found that one-third of orphan drugs approved in the United States, since the

Drug development costs continue to rise, and resistance to high drug prices remains vocal and strident from patients, payers and the presidential administration. **These changes may reduce the attractiveness of orphan drug development.**

program began in 1983, were either repurposed mass-market drugs, or drugs that received multiple orphan approvals with dramatically reduced approval times. These approaches have been increasing in recent years as a strategy for extending patent protection. New approaches to study design, such as involving patient advocacy groups and the use of adaptive clinical trials, are also helping reduce development times.[3]

Questions about Costs and Pricing

Pricing decisions for some orphan drugs are raising serious concerns and questions among patients, payers and government officials.

Procysbi for the treatment of cystinosis, a rare, fatal childhood disease, is one example. Developer Raptor Pharmaceutical (since acquired by Horizon Pharma) licensed the tech from the University of California San Diego and worked closely with it and the cystinosis research foundation to develop the drug, which the company's board – against the wishes of then-CEO Christopher Starr and then Chief Medical Officer Patrice Rioux – launched in 2013 with a $300,000 price tag – a price that has risen 48% since then.[5] According to Horizon, the company has a program that covers deductibles and copays or the entire cost if insurance is lacking, so all patients who need Procysbi can receive it.

Despite cases like this one, there is evidence to suggest that the seven-year market exclusivity granted to drugs designated under the Orphan Drug Act of 1983 for rare diseases is working as intended. A study commissioned by the National Organization for Rare Disorders (NORD) and published by IQVIA Institute found that orphan exclusivity did *not* inappropriately prevent generics and biosimilars from entering the market.[6] Of the 503 approved therapies with an orphan indication at the time the research was conducted, 217 are no longer covered by orphan exclusivity or patent protection, and 116 of them have generic or biosimilar competition.

In addition, in 2017, median spending on the 101 orphan drugs without protection from competition and without competitors was found to be only $8.6 million per year per drug. Thirty of these drugs have since been discontinued because they were replaced by newer drugs or were insufficiently profitable.[7] The study also found that most orphan drugs have relatively low prices. When they do have very high prices, it is often because the patient population is quite small and there is little or no interest from potential competitors. Furthermore, it was determined that prices for orphan drugs are in general raised more slowly than prices for other branded drugs, both for therapies developed as orphan drugs and those for which an orphan indication is later added.

A recent study on the development costs for orphan drugs is raising some questions, however. It found that while the total out-of-pocket clinical costs and capitalized expected costs per approved drug were both higher for orphan drugs than nonorphan drugs ($55 and $96 million vs. $30 and $43 million, respectively); when the overall probability of clinical success was taken into account, both costs for orphan drugs were actually lower ($166 and $291 million vs. $291 million and $489 million, respectively).[8] The results were determined using data from 1163 trials evaluating 561 nonorphan drugs and 602 orphan drugs. No hard conclusions can be made, however, because significant variabilities in the trial designs, subjects and lengths of the studies may not all have been accounted for. Furthermore, the authors note that the cost of development must be considered in the context of the drug's therapeutic role.

Clinical trials for orphan drugs can be more challenging to establish because it can be difficult to find enough patients, but they also can be conducted with many fewer participants (as few as 20) than those for non-orphan drugs, which may require thousands.[9] Smaller trials can lead to faster approvals and lower costs.

Is There Manipulation of the System?

While the orphan drug exclusivity appears to be working, some believe that, in certain cases, orphan drug laws are being abused and exploited for economic gain. Two strategies raising concern are the repurposing of commonly used drugs and obtaining multiple orphan designations in different indications for the same drug.[9] It should be noted, however, that clinical trials must be performed before approval can be sought for any new indication.

In another approach, companies have divided common conditions into much smaller subsets defined by specific biomarker-defined characteristics. In 2016, a study found that 13 of the 84 drugs approved with orphan designations between 2009 and 2015 were for subsets of more prevalent diseases, with some also approved for other, related conditions.[9] As an example, Genentech's Avastin cancer treatment has 11 approved orphan uses.[10] This strategy falls under the category of personalized medicine for some and should be distinguished from orphan drugs that treat genuinely rare conditions, many of which are suffered by children.

Additional concerns include the avoidance of the traditional large clinical trials typically conducted for non-orphan drugs and the ability in some cases for drug makers to charge extremely high prices and realize significant profits.[11]

Recommendations for Refining the Process

The U.S. Government Accounting Office (GAO) investigated the orphan drug approval process and found that the FDA does not always take into account background information it should when determining whether a drug qualifies for orphan designation, particularly since the implementation of the agency's modernization plan.[10,12] In 15% of the approvals investigated, FDA reviewers failed to independently verify patient estimates.

The GAO recommends that the FDA ensure that all required information, such as regulatory history information, including adverse actions, reported to other regulatory agencies for reviews of orphan designation applications be consistently recorded and evaluated.[12] The FDA and the Department of Health and Human Services agreed with the GAO's recommendations.

Others would like to see more significant changes, because for many drugs that could receive orphan designation, the period of marketing exclusivity is unnecessary, given that they are unlikely to face generic competition.[13] Limiting financial incentives to tax credits would address this issue. It has also been proposed to give tax credits only to pharma companies that can demonstrate a small patient population and the lack of economic viability without receiving financial assistance. Others have suggested adding the ability to reclaim any tax incentives where it is clear they were not needed to facilitate development. Finally, implementation of price regulation for orphan drugs after patent expiry that have no generic competition has been proposed to control patient costs.

Another suggestion is to focus orphan drug approvals on rare diseases that have not yet received the attention of major pharmaceutical companies rather than on the size of the patient population.[11]

Will Governments Act?

In November 2018, Senator Orrin Hatch and Representatives Leonard Lance and G.K. Butterfield introduced a resolution that marked 35 years of success of the Orphan Drug Act and called for ongoing support of the law.

Senator Kay Hagan has also introduced a plan developed by the Biotechnology Industry Organization to expand the FDA's accelerated-approval program.[14] The proposal, which is included in the renewal of the Prescription Drug User Fee Act (PDUFA), would allow drug approvals based on phase II clinical trial results when data cannot be "ethically, feasibly or practicably generated" – a common scenario for orphan drugs.[15]

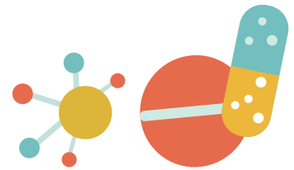
What Does the Future Hold?

On the other hand, the U.S. tax reform legislation passed in 2018 reduced the tax credit for orphan drug developers by half, from 50% to 25%. Drug development costs continue to rise, and resistance to high drug prices remains vocal and strident from patients, payers and the presidential administration. These changes may reduce the attractiveness of orphan drug development. Some companies have already made the decision to stop investing in rare disease therapies.

So what does it all mean for the future of orphan drugs? Thousands of rare diseases still lack treatments, and genomics technologies are facilitating the identification of novel drug targets. In many cases, the development costs for drugs to treat these diseases can be combined with limited generic competition to create incentives for drug makers – even if the financial advantages established by orphan drug laws are reduced. Taking all this into consideration, further growth of the orphan drug market can therefore be expected. P

Following the inception of legislation promoting the commercialization of orphan drugs, development of new drugs **to treat the approximately 7,000–8,000 known rare diseases has been financially incentivized through marketing exclusivity periods, tax credits and reduced fees.**

Development of drugs to treat ultra-rare diseases that affect only a few hundred patients takes even longer — **17.2 years on average versus 15.1 years for regular orphan drugs.**



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Mr. Walker is the founder and managing director of That's Nice LLC, a research-driven marketing agency with 20 years dedicated to life sciences. Nigel harnesses the strategic capabilities of Nice Insight, the research arm of That's Nice, to help companies communicate science-based visions to grow their businesses. Mr. Walker earned a bachelor's degree in graphic design with honors from London College.

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ACCELERATING THE DEVELOPMENT OF VIRAL VECTOR MANUFACTURING PROCESSES

→ BY **RICHARD O. SNYDER, Ph.D.,** AND **RAJIV VAIDYA, Ph.D.,** BRAMMER BIO AND **CLIVE GLOVER, Ph.D.,** AND **MATT NILOFF, M.S.,** PALL CORPORATION

As cell and gene therapies have the potential to rapidly advance through clinical trials to commercialization, there is increasing demand for practical manufacturing solutions for viral vectors that can be readily optimized and scaled. Through ongoing efforts, Brammer Bio and Pall Biotech are each developing and implementing state-of-the-art solutions designed to accelerate process development and scale-up for viral vector manufacturing.

NOT YOUR TRADITIONAL mAb PROCESS

While lower molecular weight biologic drug substances are often produced via fermentation, larger recombinant proteins and monoclonal antibodies (mAbs), which account for the largest fraction of biologics on the market today, are generally manufactured using well-established platform processes. As a result, production equipment has been designed for mAb manufacturing, and this space is well serviced by equipment suppliers.

Viral vectors are substantially more complex than recombinant proteins and mAbs, and very different biology is involved in their production. For instance, viruses often kill the cells that are used to produce them, which creates complications when scaling processes. Viruses are also substantially larger than recombinant proteins and mAbs, and are also highly charged.

BRAMMER BIO HAS LEVERAGED HARDWARE TECHNOLOGIES DEVELOPED BY PALL TO **PROVIDE ENHANCED SERVICES TO ITS CLIENTS THAT REQUIRE THE SCALE-UP OF VIRAL VECTOR MANUFACTURING PROCESSES.**

Consequently, the equipment and reagents used for mAb manufacturing may not be optimal for the production of viral vectors. While some aspects of the technology have applicability, very different culture formats – most notably adherent cell culture in plasticware – have typically been employed for viral vector development and clinical trial material production.

SUSPENSION VS. ADHERENT CELL CULTURE

In suspension cell culture, the cells are free floating in the culture medium, while, in adherent cell culture, the cells are attached to a substrate in a monolayer. Adherent cell culture is used for certain cells, including cell lines used for viral vector production that must be anchored in some way to enable cell survival.

Traditionally, suspension cell culture has been performed in stirred-tank bioreactors, while adherent cell culture has been achieved using roller bottles, flasks and plastic flatware, such as Corning's HYPERStack® or Nunc™ Cell Factory™ vessels. Indeed, the majority of viral vectors in the clinical pipeline were initially produced via adherent cell culture, and an extensive knowledge base has been developed around the optimized production of viruses in this manner.

Suspension cell culture formats have been developed for the manufacture of adenovirus (AV), adeno-associated viral (AAV), retroviral (RV), and lentiviral (LV) vectors in HEK 293 cells and other cell types. Suspension culture using insect cell systems has also been applied to the production of AAV vectors (Figure 1).[1] While these processes are scalable, the level of process understanding can be limited.

FROM PLASTICWARE TO BIOREACTORS

The challenge with adherent cell culture is the lack of scalability afforded by these processes. Production of large quantities of viral vectors on plasticware requires scale-out (vs. the ability to scale-up). Cost scales directly with the addition of more flasks or trays and more plasticware also takes up a larger footprint in the plant. These processes are highly labor-intensive, and scaling-out introduces the need for multiple rounds of manipulations, which can lead to more risk.

Bioreactors – whether adherent or suspension – are closed systems with reduced risk for contamination, since they require fewer seeding, transfection and harvest unit operations. They are also available in multiple sizes. The largest single-use bioreactors for suspension cell culture scale to 2000 L.

An example of the industrialization of adherent cell culture has been accomplished in the form of the Pall iCELLis® disposable fixed-bed bioreactor system, the largest of which is 500 m^2. This area translates roughly to a volume greater than 1000 L for a suspension bioreactor and is equivalent to 794 10-layer cell stacks or 5,882 roller bottles at 850 cm^2 each – *an order of magnitude increase in scale.*

TIMELINES DRIVE DECISION MAKING

The choice to manufacture viral vectors using an adherent or suspension cell culture system is based on several factors, though perhaps the most important driver is the timeline for the project. Regulatory authorities in many jurisdictions, including the United States, offer accelerated licensing approval pathways for cell and gene therapies, meaning that development and commercialization timelines can be shorter than those for traditional biologics.

The choice of culture system is driven by a number of factors, including the size of the product lot(s) needed in the clinic and marketplace, as well as the amount of time allotted for process development. Because adherent cell culture is familiar, and most viral vector processes are initially developed in flask-based systems, process development times, including scale-up in iCELLis® bioreactors, can be quicker. If scalability is more of a concern than a shorter timeline, then development of a robust suspension cell culture process might be preferred; however, it may require more time up front but it can, ultimately, pay dividends in terms of batch size.

Other factors that influence the choice between adherent and suspension cell culture production include the disease target, the dose for each patient, the size of the patient population and the expected market penetration. The platform that can best support production of the desired quantity of viral vector is a primary driver. For some gene therapies, clinical and commercial production in plasticware may be sufficient, while other indications require production in bioreactors for commercial supply.

There are challenges from timeline and technical perspectives when switching to a new production platform after clinical trials have been performed in humans, particularly the need to demonstrate comparability of the product manufactured using the original and replacement process. Consequently, some drug companies elect to invest the time up front to develop processes and analytical methods that can be readily scaled to a commercially viable process.

DOWNSTREAM PROCESSING

The upstream portion of viral vector manufacturing includes expanding the seed train, inoculating the terminal reactor and initiating production – steps that can take 3–5 weeks, and that are followed by 1–2 days required for downstream processing. The downstream portion is very important too, as it is essential to purify viral vectors from impurities to ensure that the final product is suitable for therapeutic use.

There are many variations in downstream processing, but a process generally begins with clarification of the harvested virus to remove cellular debris and other, larger impurities. The clarified harvest is then subjected to tangential flow filtration (TFF) to concentrate the viral vector particles and achieve buffer exchange. Chromatography is then performed to remove other remaining impurities, such as host-cell proteins, host-cell and plasmid DNA, etc. Ultrafiltration/diafiltration (UF/DF) via TFF is again performed to formulate the vector in the final buffer, and the formulated bulk vector is then subjected to sterile filtration and ultimately filling/finishing.

Manufacturers of hardware and consumables provide options to support most downstream unit operations for viral vector processing. For example, Pall's Allegro MVP system with fully disposable flowpaths and single-use sensors for control and monitoring of key parameters can be used to run most downstream processes, including TFF, buffer preparation, pH adjustment, membrane chromatography, UF/DF and filling. It provides control of fully automated process sequences for optimal operations, greater consistency in product quality, reduced labor costs and reduction of operator errors.

ANALYTICAL CHALLENGES

The complexity of viral vectors is much greater than traditional biologics. As a result, multiple orthogonal methods are employed to understand the physicochemical properties and quality of viral vector products. This multifaceted approach will continue unless breakthrough technologies are developed that enable the integration of the results from multiple analyses.

During process development, the "noise" in cell-based assays can also create challenges for the evaluation of process improvements. To overcome this difficulty, trending is performed to develop confidence that an improvement has been achieved. Fortunately, most methods used to determine physical properties, such as polymerase chain reaction (PCR) techniques, have greater accuracy.

BECAUSE ADHERENT CELL CULTURE IS FAMILIAR, AND MOST VIRAL VECTOR PROCESSES ARE INITIALLY DEVELOPED IN FLASK-BASED SYSTEMS, **PROCESS DEVELOPMENT TIMES, INCLUDING SCALE-UP IN ICELLIS BIOREACTORS, CAN BE QUICKER.**

Brammer Bio uses state-of-the-art technologies to verify the identity, strength and integrity of the genetic payload (e.g., vector genome), including digital droplet PCR[8] for quantification, which is crucial for proper dosing. Next-generation sequencing techniques help with understanding the nucleic acid impurities, while high-performance liquid chromatography (HPLC) methods have replaced gel electrophoresis for purity analyses.

EVOLVING TECHNOLOGY

Until recently, the systems used for viral vector production have largely comprised tools and technologies designed for other applications, particularly mAb production.

Newer analytical techniques are providing a better understanding of the critical quality attributes of the vectors that are monitored during process development and manufacturing. New resins for affinity chromatography of certain vectors (such as POROS AAVX resin from Thermo Fisher Scientific) have been introduced for purification, and filtration technologies that take into account the specific challenges posed by viral vectors are also under development.

Process controls tailored for viral vector production systems, which can have different cell culture profiles than mAbs and other recombinant proteins, are leading to more consistent processes and higher-quality products. Progress is also being achieved in developing better cell substrates for viral vector production.

Advances are being made on the drug product side as well, including formulation development, final product conditioning, fill/finish operations and labeling, storage and controlled transport – all of which present unique challenges for viral vectors. The goal is to ensure that the product reaches the patient with the greatest possible potency and safety.

OUTLOOK FOR THE FUTURE

Companies, including Pall, are working with viral vector manufacturers such as Brammer Bio to identify the needs for commercial viral vector production. They are actively investing in the development of new solutions and tools that are optimized specifically for viral vector upstream and downstream processing that will facilitate the manufacturing of these promising new treatments.

Brammer Bio has leveraged hardware technologies developed by Pall to provide enhanced services to its clients that require the scale-up of viral vector manufacturing processes. With a synergistic relationship, it is the patients who ultimately benefit from accelerating the development and commercialization of novel gene therapies.

SCALABLE ADHERENT PRODUCTION IN THE ICELLIS BIOREACTOR

The PALL iCELLis® 500+ bioreactor is an automated, single-use, fixed-bed bioreactor that provides a large cell growth surface area within a small footprint. The compact fixed bed is filled with proprietary macrocarriers made of class VI polyester microfibers. Due to the cell-cell interactions within the 3D environment of the fixed bed, iCELLis bioreactors can be inoculated at very low densities (3,000 cells per cm^2 or less), allowing for streamlined and simplified seed trains, fewer manual operations and reduced costs.

Evenly distributed media circulation is achieved by a built-in magnetic drive impeller, ensuring low shear stress and high cell viability. Media is pumped from the bottom through the packed bed and then cascades as a thin film down the outer walls, facilitating aeration and gas exchange. This unique waterfall oxygenation, together with gentle agitation and biomass immobilization, enables the compact iCELLis system to achieve and maintain high cell densities – achieving the productivity of much larger stirred-tank units. In addition, immobilization of the cells in the fixed bed combined with operation in perfusion/recirculation mode eliminates the need for centrifugation to harvest the cells, simplifying the downstream process.

Pall has investigated the production of various viral vectors using the iCELLis bioreactor and shown that it can enable the significant reduction of development timelines.[2-4] Other researchers have also demonstrated the use of the iCELLis fixed-bed bioreactor technology for large-scale production of AV,[5] AAV[6] and LV[7] vectors.

The iCELLis 500 bioreactor is available in sizes ranging from 66 m^2 to 500 m^2, and with a choice of packed beds with lower and higher densities. The iCELLis Nano system (up to 4 m^2) is also available for process development work and small-scale production. Moving from the small to larger bioreactors involves increasing the cross-sectional area of the fixed bed while maintaining a constant bed height. As a result, cell seeding and nutrient and oxygen delivery throughout the fixed bed are comparable. Pall has demonstrated that processes optimized in the iCELLis Nano scale directly to the iCELLis 500+ bioreactor with little additional work required.[2]

FIGURE 1A

Insect cell culture in Pall Allegro STR (●) vs. cylindrical vendor A bioreactor (●)

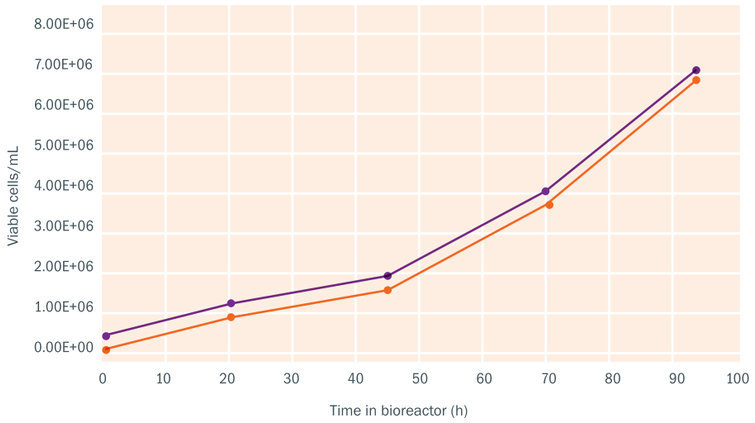

FIGURE 1B

Infected cell diameter in Pall Allegro STR (●) vs. cylindrical vendor B bioreactor (●)

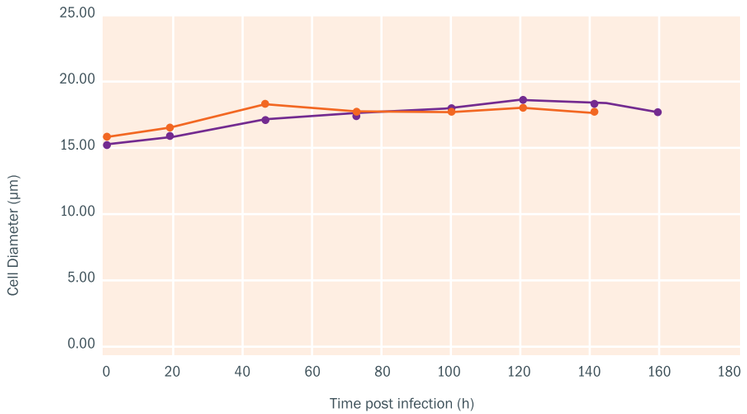

FIGURE 1

Figure 1. (A) Growth of insect cell line Sf9 in a Pall Allegro STR and cylindrical-vendor A* 200-L bioreactors. The cells were then co-infected with two baculovirus vectors to produce an rAAV5-GFP vector.

(B) The ~3 µm diameter change in the cells is an indication of the progression of the infection in the Pall Allegro STR and cylindrical-vendor B* bioreactors. Clarified harvest: Pall Allegro STR 2.48×10^{11} vg/ml, cylindrical-vendor A 2.50×10^{11} vg/ml. *"A" and "B" signify two different cylindrical bioreactors. P

ACKNOWLEDGEMENT

The Brammer Bio process development, analytical development and manufacturing teams performed the work presented in Figure 1.

PROCESS CONTROLS TAILORED FOR VIRAL VECTOR PRODUCTION SYSTEMS, WHICH CAN HAVE DIFFERENT CELL CULTURE PROFILES THAN mAbs AND OTHER RECOMBINANT PROTEINS, ARE LEADING TO MORE CONSISTENT PROCESSES AND HIGHER-QUALITY PRODUCTS. **PROGRESS IS ALSO BEING ACHIEVED IN DEVELOPING BETTER CELL SUBSTRATES FOR VIRAL VECTOR PRODUCTION.**

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Dr. Snyder was the founder of Florida Biologix, which was spun out of the University of Florida in 2015 and merged to create Brammer Bio in 2016. Dr. Snyder has been investigating virus biology, vector development, cGMP manufacturing and analytical technologies, and viral vector–mediated gene transfer for over 32 years. Dr. Snyder received his doctoral degree in microbiology from the State University of New York at Stony Brook and obtained his BA in biology from Washington University in St. Louis.

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Q&A: BUILDING A SUCCESSFUL CDMO BRAND

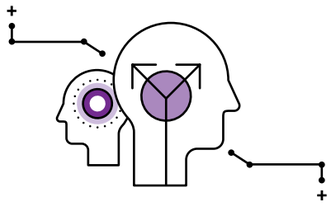
Mark Bamforth is the founder and departing CEO of Brammer Bio, which was recently acquired by Thermo Fisher Scientific. Previously, Mark founded and led Gallus BioPharmaceuticals, which was sold to Patheon in September 2014. We sat down with Mark to discuss his history of building valuable brands from the ground up.

1. CAN YOU TELL US A LITTLE BIT ABOUT THE INSPIRATION THAT LED YOU TO FOUND GALLUS BIOPHARMACEUTICALS, YOUR FIRST VENTURE?

I spent 22 years with Genzyme, a biotech product company, and, at the end of my tenure, I began considering starting my own company. I'd been involved with an entrepreneurial organization called the Saltire Foundation, and the more I heard others speak about their entrepreneurial journeys, the more I became interested in taking that step myself. Many of the companies I was involved with were product companies or innovators, though I had realized clinical and product development weren't the best fit for me. My whole career had been spent in manufacturing and operations with a life science focus, which led me to conclude that I should look at biologic contract manufacturing as a space to develop the next stage of my career.

I had investigated sites for Genzyme and was aware of some that were still up for sale. In April 2010, I reached out to Johnson & Johnson and told them I'd be interested in acquiring a site of theirs in St. Louis.

After that, my first learning experience was finding the right investors. Contract manufacturing was fairly straightforward; we were basically going to carve out the existing operations with a focused leadership team and about 160 employees. However, we still had to add business development and process development teams to support the site and invest to build out clinical capacity. It took about 13 months before we were fully funded and off the ground.



2. HOW DID YOUR EXPERIENCE AT GENZYME PROVIDE YOU WITH INSIGHT INTO WAYS TO INCREASE EFFICIENCY IN MANUFACTURING AND HOW A CDMO COULD BRING MORE VALUE TO CUSTOMERS? HOW DID THAT COME TO FRUITION WITH GALLUS?

Gallus was focused on mammalian culture and monoclonal antibodies, but there was a phenomenon that was really starting to mature around 2010–2011: single-use or disposable technology. Before I had funded the business and closed on the acquisition of that site, I had set up a partnership with Xcellerex, which is now a part of GE, to deploy their single-use platform at the St. Louis site. The benefit of single-use technology was it had a somewhat lower capital cost and faster deployment than the slow build-out of stainless steel-based bioreactors; it was generally a more flexible approach for multi-product manufacturing, which helped me develop a plan that would allow us to quickly create additional capacity to support new clients.

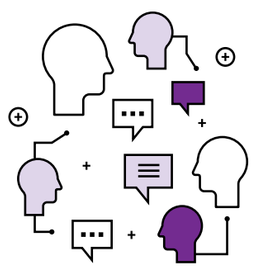
3. AS YOU WERE BUILDING THIS BRAND, WHAT WAS YOUR APPROACH TO GROWTH AND THE FORMATION OF STRATEGIC PARTNERSHIPS?

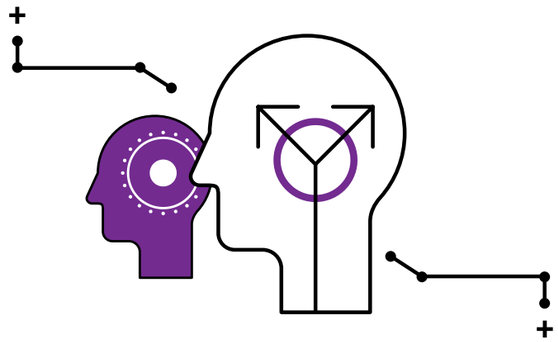
Gallus offered the high-quality pedigree of the site and the commercial manufacturing team. Business growth was slow for the first two years, because we were in the process of building both the organization and its reputation while continuing to supply J&J with commercial product. Until we really established more critical mass and built out the plant over the first year to 18 months, it was hard to gain traction with clients.

By the third year, we hit an inflection point. We expanded the use of our process development space and our clinical capability, and were signing up more clients, including for late-stage clinical molecules. These clients were attracted by the commercial pedigree of the site and team and that they could launch their products at Gallus and be supported throughout the life cycle.

Three years in, we acquired a company called Laureate Biopharmaceutical Services, based in Princeton, New Jersey. Most of Laureate's clients were in phase I/II clinical trials with monoclonal antibodies. This acquisition broadened our pipeline and client base and also gave us more credibility; they had been in business for 12 years. This helped to accelerate our growth and attract more business to Gallus.

Going into our fourth year of that journey, we paid attention to the inbound interest in the company and decided to have a conversation about a transaction. In the end, we went ahead with it and the company was sold to Patheon. We fit into their network of commercial biologic sites and deep customer relationships, thus ensuring the ongoing growth for the Gallus team.





4. CAN YOU DISCUSS THE INSPIRATION FOR THE CREATION OF YOUR SECOND COMPANY (BRAMMER BIO)?

At Gallus, we had a partnership with a cell therapy company. We explored the cell therapy space and talked to about half a dozen potential clients and made some proposals, but we didn't have a high degree of credibility because we had no activity in that space, so none of those opportunities came to fruition. Once Gallus was sold, I decided to create Brammer Bio to focus on cell therapy, and, after another 13-month journey with the support of a partner and others, really came to appreciate that the strongest opportunity was to supply the viral vectors needed for both gene-modified cell therapies and gene therapies.

Exploring acquisition opportunities jumpstarted Brammer Bio, especially when we were reintroduced to the Massachusetts-based private equity group Ampersand Capital in early 2016. Ampersand had invested in Florida Biologix in November 2015, helping the founder, Dr. Richard Snyder, to spin the company out from the University of Florida. Ampersand recognized that this was a fantastic organization comprising about 100 people with excellent technical experience focused on early stage development for gene therapies. The opportunity was really to build a late-stage pipeline with the existing clients and to attract new clients. Of course, I spent much of my career doing late-stage clinical supply and commercial supply and so the relationship was symbiotic. We merged with Florida Biologix to create Brammer Bio at the end of Q1 2016.

5. DID YOU HAVE A SENSE AT THE TIME THAT YOU WERE IN A REALLY SWEET SPOT IN TERMS OF TIMING, BETWEEN THE INITIAL SURGE OF INTEREST IN THESE THERAPIES AND THE CURRENT EXPLOSION IN THIS SPACE?

Back in the early 1990s, Genzyme was a pioneer in gene therapy for cystic fibrosis and conducted some of the first in-human clinical trials. Genzyme was also a pioneer in regenerative cell therapy, and had the first FDA-approved cell therapy product in the late 1990s. In 2006, I established a site for clinical gene therapy manufacturing for Genzyme. In 2016, it became clear that the demand for viral vectors was really starting to build. In the summer of 2016, we negotiated to acquire two sites from Biogen and bring about 100 people over with commercial biologics experience. We announced this in November 2016 and completed the deal on January 1, 2017. That action drove a lot of inbound inquiries from companies that were entering phase III clinical trials and needed to establish a commercial source. They viewed it as less risky to switch to us than to continue with CDMOs that lacked commercial experience. In early 2017, it was clear that viral vector demand was starting to explode; we made the strategic decision to not return to cell therapy manufacturing. We committed to a $200 million capital investment program to provide the capacity needed for clients. We started the development of a second commercial site in Lexington, Massachusetts.

6. AT WHAT POINT DID YOU REALIZE JUST HOW MUCH VALUE YOU HAD CREATED WITH THIS BRAND, AND HOW DID THAT LEAD TO THE ACQUISITION BY THERMO FISHER SCIENTIFIC?

We'd grown the company from 100 people to 600 people over three years and we'd invested $200 million (which is an extraordinary amount for a relatively small company), so we'd taken a lot of risks to be ahead of the curve. I didn't do this all alone, of course; I had partners I was working with and a strong leadership team that played a very crucial role in executing on these plans because, if you don't execute, you quickly find that you're not going to grow rapidly — execution is core to maintaining momentum and growth.

We were faced with a strategic decision at the end of 2018, which was to either raise additional capital for investment in further capacity — beyond what we were already doing with the first $200 million — and over the next 2–3 years double the size of the team again, ourselves, or we could do this as part of a larger organization with deep resources. We had received inbound inquiries from companies that were interested in getting into this space which we decided to explore more deeply. Early in 2019, we concluded that the better route was to become part of a larger services organization.

We knew that we had created something special, but when you're on a trajectory that is basically an exponential curve, you're faced with a unique dilemma. It's not like being in a business where you've got a steady 10–15% annual growth. Instead, you've got this exponential growth so the discussion becomes: do we wait a year? The challenge was funding the next stage of growth, which would take 2–3 years. That was the dilemma of having something that's going very well, and so we ultimately decided to accept the offer from Thermo Fisher Scientific, which has deep resources and experience that will accelerate our growth to serve clients.

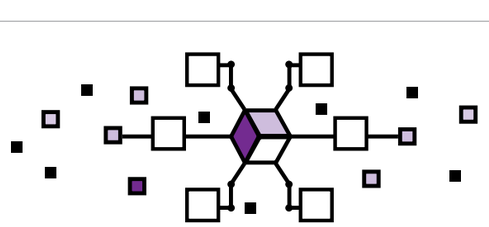
7. YOU'VE REALLY BUILT TWO VERY VALUABLE BRANDS ESSENTIALLY FROM SCRATCH. WHY DO YOU THINK YOU'VE BEEN ABLE TO HAVE SUCH SUCCESS DOING SO, AND WHAT HAVE YOU LEARNED ALONG THE WAY?

The humbling piece of this industry is that it's all about execution. Of course, having a vision and a plan is vital, because you can't get investors on board if you don't have a plan—but, once you've got the investment in place to support that plan, it's all about execution. In our business of serving clients, they are entrusting you with their product, which, in the case of smaller clients, may, in essence, be the company—it's an awesome responsibility that a service provider takes on.

For me, customer service and engaging with the client is crucial. With Brammer Bio, we focused on values comprising the acronym "BEST," which stands for Brilliant science, Extraordinary service, Setting standards, and Trust, empowerment, accountability and me. When you recruit people from innovator companies, you have to explain the differences in being part of a service organization, and what matters is delivering on client commitments. Similarly, when we provide our early stage development and clinical supply, clients may be waiting for that first GMP batch in order to get it into the clinic and prove that they have a product. Fundamentally understanding what a service business looks like and how to organize around that is key.

The other piece of this success is that every employee has a bonusable element of their compensation tied to two things: the financial performance of the company and the operational performance, which includes everything we have to do to deliver. We have a track record of being able to pay that bonusable amount each year throughout both Brammer's and Gallus' histories. Achieving this is about keeping the goals visible to everyone in the organization and connecting those goals to individuals, while emphasizing personal and team responsibility.

Another lesson I learned at Genzyme is that you can't wait until you have perfect information. You've certainly got to do your analysis, speak to people, and be aware of opportunities and strengths, but, at some point, you have to go with your gut and trust what you're going to create. You have to believe that the business will grow. Of course, you learn lessons along the way that can reshape what you're doing, but, fundamentally, you've got to go with your experience and intuition. If you wait until everything is sewn up, you'll be too late — others will have already done it.



8. CAN YOU TELL US ANYTHING ABOUT YOUR PLANS FOR YOUR NEXT VENTURE?

I continue to believe that there are areas in manufacturing and delivery that challenge the life sciences, in general. A tremendous amount of the pipeline is in smaller, innovator companies who don't want to invest in manufacturing themselves, for example. I believe there continue to be opportunities to support those innovators through the application of manufacturing excellence. Whether in a direct or supporting role, there's an opportunity for me to help the industry continue to grow and bring products to patients to improve and save lives.

9. WOULD YOU LIKE TO DISCUSS YOUR COMMITMENT TO SCOTTISH ENTREPRENEURSHIP AND THE SALTIRE FOUNDATION?

I've been involved with Entrepreneurial Scotland and the Saltire Foundation for 11 years. The Foundation creates opportunities for seniors at Scottish universities to pursue internship opportunities abroad and for more seasoned applicants to visit Babson College in Massachusetts to learn about a global view. The program encourages these entrepreneurs to return to Scotland with the tools needed to build companies. It's a challenge for a small country to build businesses of scale that really have a global role to play, and so I encourage those who are already doing so to encourage others to do the same as a way of giving back.

ABOUT THE AUTHOR

Mark Bamforth
CEO, Founder, Brammer Bio

Mark Bamforth is the cofounder and CEO of contract development and manufacturing organization (CDMO), Brammer Bio. In 2010, Bamforth founded and led Gallus BioPharmaceuticals. Gallus became a premier CMO, delivering clinical and commercial biopharmaceuticals to product companies worldwide. He has a BS in chemical engineering from Strathclyde University and an MBA from Henley Management College.

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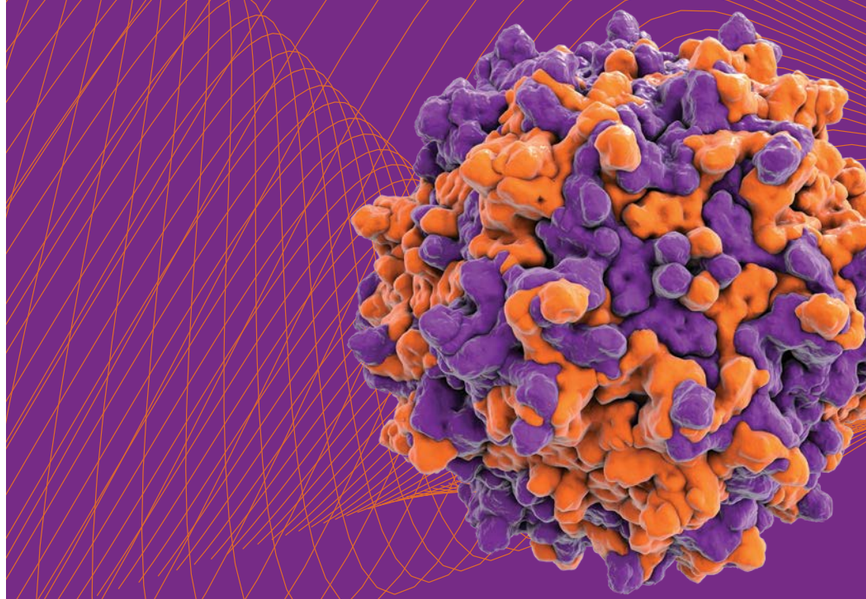

BEST-IN-CLASS VIRAL VECTOR CONTRACT MANUFACTURING

Brammer Bio is dedicated to providing clinical and commercial viral vectors for in vivo gene and ex vivo gene-modified cell therapies, from process and analytical development through commercial approval. We have a highly skilled team of scientists with expertise from over 100 client projects to tackle the challenges posed by these novel technologies and help accelerate their transition from the clinic to patients, while focusing on meeting cGMP standards. Brammer Bio is *Helping to Cure.*®

www.brammerbio.com

KEYS TO SUCCESSFUL STORAGE, MANAGEMENT AND TRANSPORT OF BIOLOGICAL MATERIALS

→ BY **GULAM JAFFER,** YOURWAY

Biological materials are shipped from collection and production sites to other locations for analysis and/or further processing. These materials require special handling, and their storage and shipment — generally at very low temperatures — must be achieved in compliance with various local, national and international regulations. Partnering with an experienced and reliable logistics provider can ensure the successful management of biological materials, even for the most complex supply chains.

TYPES OF BIOLOGICAL MATERIALS

Items classified as biological materials can be derived from both humans and animals, such as blood, plasma, tissue, urine and feces samples. The material obtained via leukapheresis for the production of cell and gene therapies also falls into this category, as do biologic drug substances that are used to formulate final drug products, such as viruses and viral vectors. Finally, developmental drugs and vaccines that contain living cells and/or live/attenuated viruses and viral vectors are also considered biological materials.

GENERAL LOGISTICS CONSIDERATIONS

The storage, handling and transport of biological materials require extensive knowledge about the properties and characteristics of the materials themselves and the conditions under which they can be safely stored and shipped. They also require comprehensive understanding of the local, national and international regulations for their transport and applicable customs requirements for each country involved.

Transport of these materials requires identification of appropriate primary and secondary packaging materials, compliant labeling, preparation of essential documents and knowledge of expected taxes, duties and other fees. Additionally, transport often requires managing a range of other considerations, given the temperature-sensitive nature of these materials and the often time-sensitive nature of the shipments.

Scheduling sample pickup and delivery necessitates coordination among multiple sites and identification of appropriate modes of transport. Real-time monitoring and tracking of packages are essential to ensure that they are handled appropriately, maintained at the correct temperature and successfully travel the desired route. Achieving visibility throughout the shipment process is also crucial for establishing a chain of custody and identity.

The use of quality management systems ensures compliance with Good Distribution Practice (GDP) for the transport, storage and distribution of biological with international quality and other requirements across the supply chain.

SPECIAL REQUIREMENTS FOR PERSONALIZED MEDICINES

The FDA is expecting to approve 10–20 new cell and gene therapies per year by 2025.[1] In addition to the Fast Track, Breakthrough Therapy and Priority Review designations available for traditional biologics, the Regenerative Medicine Advanced Therapy (RMAT) designation provides a further accelerated approval pathway for cell and gene therapies that treat disease states posing serious or life-threatening consequences.

Next-generation personalized medicines present additional challenges for logistics management. They must be stored and shipped at refrigerated (sometimes below –50 °C) temperatures. In many cases, biological material collected from a specific patient is processed and then returned to that same patient, which requires a secure chain of identity.

The FDA has published several guidance documents regarding the development, manufacturing and approval of cell and gene therapies. Given the complexity of the supply chain for personalized medicines and the need for end-to-end visibility, additional guidances are expected regarding the temperature-controlled logistics needed for these next-generation treatments.

MANAGING TEMPERATURE-CONTROLLED LOGISTICS

A temperature-controlled supply chain enables storage, shipment and delivery of temperature-sensitive materials under refrigerated (or frozen) conditions without interruption. It requires scientific knowledge and understanding, the implementation of advanced packaging and information technologies and effective logistical planning capabilities. Key elements include suitably designed temperature-controlled packaging with incorporated real-time monitoring systems, refrigerated modes of transport and storage facilities, an effective quality assurance system and open and transparent communication and collaboration across the supply chain.

An unbroken temperature-controlled supply chain is essential to ensuring product safety, efficacy and quality for drug products and biological samples collected for diagnostic purposes or for use in the production of next-generation medicines. Continuous advances in technology are leading to improved product integrity and safety, increasing the efficiency of the pharmaceutical supply chain. This helps to ensure that the right biological materials are delivered at the right times to the right locations, and, for personalized medicines, to the right patients.

TRANSPORT REGULATIONS

Regulations for the international shipment of biological materials originate with the International Civil Aviation Organization (ICAO). The Dangerous Goods Regulations established by the International Air Transport Association (IATA) are recognized by the ICAO as the field guide for practical reference by industry.[2]

Under these guidelines, biological materials fall into one of two categories within the classification division 6.2. Category A materials are infectious substances that contain pathogens that can affect humans or animals. These materials contain pathogens that are capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans or animals.

Category B biological substances are infectious materials that do not meet the criteria for inclusion in Category A and do not cause life-threatening or fatal disease or permanent disability in humans upon exposure. These represent the bulk of pharmaceutical industry shipments. Some biological materials (typically patient specimens and blood for transfusions) with a minimal likelihood of containing pathogens are exempt from certain requirements.

The requirements for shipping Category B biological substances are outlined in IATA's Danger Goods and ADR's Packaging Instructions 650 (road) regulations. All materials must be packaged in a leak-proof primary container, with sufficient absorbent material in place around liquid materials to absorb the entire contents if the container should break. The primary container and absorbent must be placed in a secondary leak-proof container and surrounded by an outer rigid packaging material. It must also be appropriately marked as a Category B biological substance.

IATA's Perishable Cargo Regulations (PCR) serves as a reference guide for all stakeholders involved in the packaging and handling of perishables for air transportation. Chapter 17 Air Transport Logistics for Time and Temperature-Sensitive Healthcare Products requires the implementation of a quality management system, service-level agreements and specific training. IATA created the Center of

Excellence for Independent Validators in Pharmaceutical Logistics (CEIV) program to help organizations understand the requirements.

ADVANCES IN TEMPERATURE-CONTROLLED PACKAGING TECH

There are three main types of packaging solutions for temperature-sensitive biologic materials: active (dynamic), semi-active and passive (static).[3] Active packaging relies on an external power source to maintain a constant temperature. 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 an electrical power source. Passive packaging comprises eutectic plates of a PCM within an insulating material.

Standard temperature ranges for the shipment of biological materials include deep-frozen (below –50 °C), frozen (–50 °C to –20 °C), refrigerated (4 °C to 8 °C) and room temperature (15 °C to 25 °C). The rapid development of next-generation medicines and increasingly strict regulations are driving the demand for higher-performance, smart packaging solutions that are fit-for-purpose across numerous supply chains, including those that extend into emerging markets.[3]

Today's temperature-controlled packaging solutions are much more efficient and robust than traditional passive packaging that used chilled and frozen water surrounded by bulky insulating foams. The use of lightweight vacuum-insulated panels (VIPs) and PCMs provide greater reliability in a smaller space for increased payload efficiency. While they are more expensive initially, they have proven to be more cost-effective over the long term.[3]

Most of these packaging solutions also contain integrated data collection and transmission capabilities linked to web-based asset management software systems for real-time monitoring and tracking of the environmental condition (e.g., vibration, light, humidity, pressure, temperature, orientation) and location of a package as it moves through the supply chain. The data is not only used to ensure proper handling and delivery; historical information enables data-driven logistics decision making and can be leveraged to improve packaging design.[4]

Given the greater cost of these smart packaging solutions, there is a movement toward utilizing reusable systems. The asset-management software systems are thus also being leveraged to facilitate reverse logistics.[3]

A TRUSTED AND RESPONSIVE LOGISTICS PARTNER

An effective logistics provider must be aware of the critical nature of all biological samples and be able to supply the appropriate packaging to meet any temperature requirements, identify optimal shipping lanes and confirm import and export requirements. They must also have the infrastructure available to ensure the integrity of these shipments from the moment they are packaged and depart the site through to final delivery.

Yourway has the biological, warehousing and logistical expertise and capabilities to meet customer needs for temperature-controlled storage and 24/7 package pickup with no weight, size or value restrictions.

Yourway does not, however, simply offer logistics, warehousing and packaging support. At Yourway, we take an integrated solutions management approach, leveraging our experience and expertise to provide an array of customized solution-based offerings, including project management support, planning and optimization guidance, comparator sourcing, ancillary supply sourcing, forecasting and returns/reconciliation management. We offer highly customized solutions that ensure high-quality, responsive, tailored support from start to finish.

Yourway's temperature-controlled transport specialists enable the shipment of phase I, II, III, and IV materials, finished goods and production raw materials. Over the last five years, Yourway has substantially expanded our international resources and global network to be closer to clients and to provide them with even more responsive global service. Our experienced network of agents and associates located around the world clear and deliver shipments to their destinations as soon as they arrive. Yourway is also committed to facilitating reverse logistics, including reclamation and value recovery, returns and reconciliation and, where appropriate, storage, consolidation, destruction or disposal.

Yourway's worldwide service also includes documentation support and the provision of regulatory advice regarding country-specific requirements. Customs fees are managed proactively and paid by Yourway, regardless of the cost – shipments are never held up waiting for the client to pay fees. Overall, Yourway's proactive management approach helps our customers avoid delays of all kinds during the shipment of critical clinical trial materials. P

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 clients' high-value, high-priority clinical materials.

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Tracy Kinjerski
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From mAb Developer to Successful Biologics CDMO

In its short history as a fully dedicated contract development and manufacturing organization (CDMO), Avid Bioservices has experienced dramatic growth. With our legacy as a commercial pharmaceutical manufacturer, our robust regulatory track record and our broad technological capabilities and expertise, we are uniquely positioned to support client projects throughout the life cycle.

Commercial Manufacturing Legacy

Southern California–based Avid Bioservices was initially founded as a wholly owned subsidiary of Peregrine Pharmaceuticals to leverage excess manufacturing capacity and has been approved for commercial manufacture since 2005. In January 2018, the company relaunched as a dedicated biopharmaceutical CDMO and adopted Avid Bioservices' name.

Avid supports the development and manufacture of biologic drug substances (e.g., monoclonal antibodies, recombinant enzymes, glycoprotein) via mammalian cell culture, with a full-service offering including upstream and downstream process development (PD), extensive analytical support and manufacturing capabilities from clinical to commercial scale. Additional cell-line development capabilities are being developed internally and via collaborations.

Avid was approved for commercial manufacture 14 years ago, setting us apart from most industry CDMOs. We have extensive experience in validation and launch preparation. In fact, in just the second half of our last fiscal year, we completed three process performance qualification campaigns for different customers. To this extensive commercial experience, we have added business operations expertise and expanded PD capabilities.

Collaboration is Critical

As a CDMO that was previously a drug development company, we are familiar with the challenges faced by our clients. Importantly, many of our staff were involved in legacy Peregrine Pharmaceuticals projects and have relevant experience developing CMC packages and working with regulatory agencies. We emphasize a collaborative approach, keeping the patients in mind from the very start of a project and advising clients on the feasibility of their timelines and the best approaches to accomplish our shared goals.

Clients also benefit from our agility and flexibility. Our approach and level of engagement, even including our management team, allow us to rapidly respond to our evolving client needs and to effectively manage projects throughout their life cycles. Our flexible facility layout and accommodating management makes it possible for us to readily support projects of all sizes, including orphan indications and other smaller-volume projects.

As a result, Avid Bioservices collaborates with both small biotech companies on IND-enabling projects and large biopharma firms looking to transfer projects moving to commercialization, and also as a reliable second supplier for existing products.

At the Leading Edge of Technology

We recognize the value afforded by advanced technologies. We are in the process of evaluating and applying novel process technologies that provide value to our customers, and we will continue to be at the leading edge of technology adoption. CDMOs must continually balance upstream and downstream capacity for a variety of products and processes that pose many different challenges. We are thus in a unique position, as we have transitioned into a dedicated CDMO. Avid works closely with vendors and innovators to identify new solutions for increasing efficiency and productivity while driving down costs and ensuring the highest level of safety.

Moving Rapidly toward Profitability

Over the last 18 months, we have expanded our PD capabilities and upgraded existing equipment and services. Currently, we are scheduling some manufacturing projects 2–3 years into the future. While 50% of our newer 84,000-ft² facility has yet to be equipped, we anticipate the need for a capacity expansion to meet future project requirements. Various programs are underway to increase throughput in our existing facilities, and we are evaluating our options for expansion. Avid is moving rapidly toward cash generation and a positive EBIDTA.

Tackling Key Industry Issues

The rapid growth in the biopharmaceutical industry is posing challenges that all players in the field must address. First, it is imperative that everyone focus on developing the talent that is needed to support continued growth in the sector. Avid has numerous initiatives with local universities, community colleges and public–private partnerships to ensure we have access to the right people.

Second, manufacturing capacity is limited today. Demand is also rising. It is incumbent upon sponsor companies looking to bring products to the IND stage to plan for and secure production capacity as far in advance as possible. Avid is fortunate over the short term to have new facilities and capacity available. However, we are also planning well in advance to ensure we can meet future customer needs. P

INTEGRATED OUTSOURCING FROM RSMs TO APIs

→ BY **SCOTT MARTIN** AND **RANDALL ANDREWS,** ALBEMARLE FINE CHEMISTRY SERVICES

As active pharmaceutical ingredient (API) complexity has increased, so too has the raw material supply chain. Drug manufacturers must ensure that these materials meet strict regulatory guidelines regarding impurity levels, that their quality is well documented to mitigate risk and that they can be traced throughout the supply chain. An integrated supply chain with transparency among sponsors and suppliers ensures that regulatory starting materials (RSMs) are well characterized and free of impurities that can impact the final drug product.

INTEGRATED MANUFACTURING OF RSMs AND APIs

Albemarle Fine Chemistry Services (FCS) is a manufacturer of APIs for a range of custom and generic products. We produce high-quality APIs that meet and surpass the updated regulations regarding impurities – including heavy metals and genotoxic compounds. Our success in production is a result of our robust R&D, analytical services, engineering and quality teams. These capabilities are further bolstered by the integration of operations between our cGMP manufacturing facility that produces APIs and our ISO fine chemical facility, which produces many of the RSMs incorporated in the manufacture of our APIs. This integration simplifies the supply chain and provides an unparalleled level of transparency into starting materials, which gives us the ability to identify and control impurities earlier in the API manufacturing process, as well as collaboration for implementing potential process optimizations that will impact the quality of the API.

Albemarle's site in South Haven, Michigan, is FDA-registered and implements cGMP in the production of more than 40 products – from custom APIs and advanced intermediates to a family of generics. Albemarle's facility in Tyrone, Pennsylvania performs custom manufacturing and routinely handles highly hazardous materials, such as chlorine, anhydrous ammonia, thionyl chloride, *N*-butyl lithium and others. Tyrone supplies RSMs ranging from small pilot (10 kg) to commercial (100 metric tons) quantities.

The teams at the South Haven and Tyrone sites collaborate and communicate to identify opportunities for improvement, set production schedules and address logistical issues. Albemarle's project sponsors benefit from this integration, particularly as it relates to identifying impurities, method development, process development, scale-up, regulatory compliance and speed to market.

CONTROLLING IMPURITIES

The integration of the Tyrone and South Haven operations makes Albemarle FCS one of the most capable and flexible broad-based chemistry operations in North America, which is essential as materials and compounds become more complex. As the chemistries required to synthesize these compounds become more advanced, there is a corresponding increase in the stringency of requirements to identify, characterize and control residual impurities. Albemarle's integrated supply chain excels in addressing this ever-increasing standard in the APIs we manufacture for our customers. This is possible because we understand our capabilities and chemistries at both facilities and are well positioned to choose the most effective and efficient actions to reduce impurities and run our processes in control.

Core strengths of Albemarle FCS include analytical and R&D capabilities at both sites that allow us to perform development work in collaboration with our customers. We are continually working to develop and refine analytical methods to identify impurities with increasing stringency and to determine the optimal upstream and/or downstream process modifications to control, minimize or eliminate them. The quality of incoming RSMs from the Tyrone site are tightly controlled through the predetermined acceptance criteria; any deviation from those criteria can be quickly addressed because of the integration between the two sites. In addition, when a deeper investigation is required, the two sites can work closely together to determine the root cause and implement the appropriate corrective actions.

Regulatory agencies expect manufacturers to have a comprehensive understanding of the process used to produce the RSMs they use to manufacture drug substances, but it is not typically possible to achieve the necessary transparency with an external supplier. The integration of both of these operations under the Albemarle umbrella, however, achieves a new level of transparency that has far-reaching benefits. When the Tyrone facility considers process optimizations for a particular RSM, the impact of the process change is evaluated by both sites to determine the level of testing required to approve the optimized process. This collaborative environment ensures that any impact to the final API due to optimization of the RSM manufacturing process is fully understood.

PROCESS DEVELOPMENT FOR SAFETY AT ANY SCALE

Once the chemistry for a given API has been determined, we work on developing optimal processes at both sites, with safety and quality always our primary concerns. Sometimes, we have to suggest alternative chemistries to ensure that we are running a process that is robust enough from a safety design perspective. It is important to address such safety issues up front when approaching scale-up, as it becomes more challenging and costly to change chemistry to optimize operational safety as a new API approaches validation.

FORECASTING AND SCALE-UP

Speed to market is a high priority for many of our customers. Forecasting production schedules is an added advantage of this integrated supply chain. The two sites meet regularly to ensure that the production schedules and quantities are in alignment for meeting the customer's expectations. In addition, the teams at the two sites can move quickly to respond to changes in customer demand and work with the customer to ensure success in delivering the API.

FAST TRACK PATHWAYS AND APPROVALS

The communication between the Tyrone and South Haven teams is also beneficial to sponsors who are fast-tracking a product to market. When a product is being fast-tracked, everything moves on a compressed timeline, which makes it even more critical to make the most informed choices and prepare for contingencies from the start. The two Albemarle sites typically coordinate to discuss a fast-track filing and make adjustments as quickly as possible. Without this integration, the process would be delayed as sponsors send out data and wait for feedback.

Regardless of the approval pathway, a product approved in the United States is not automatically approved in Europe, as was common in the past. Being prepared with the proper analytical and R&D expertise and the analytical equipment on-site allows us to anticipate these potential gaps and respond quickly with solutions. Our regulatory teams work with customers to develop processes and methods to ensure the compliance and quality of their APIs, because their products are as important to us as they are to them. P

ABOUT THE AUTHORS

Scott Martin
President, Albemarle Fine Chemistry Services

Scott Martin has been President of Albemarle Fine Chemistry Services since 2016. Previously, he held a number of positions at Albemarle, beginning as Vice President of Fine Chemistry Services, followed by Vice President roles in the Catalyst, Fine Chemicals, Manufacturing Performance Chemicals, and Manufacturing Catalyst and Corp. Engineering divisions. Before joining Albemarle, Scott was President of Chemfirst Fine Chemicals, and he led its integration into Albemarle's existing pharma and agricultural businesses.

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Randy Andrews is the Plant Manager of the Albemarle Tyrone facility. He received his B.S. in chemical engineering from Pennsylvania State University and has over 30 years of experience in the custom manufacturing environment. His areas of expertise include process development, process and project engineering, control system development, and operations management. The custom manufacturing environment allows him to utilize his passion for continuous improvement to improve cost, throughput and efficiency.

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BIOPROCESS OF THE FUTURE: WHAT'S IN IT FOR BIOMANUFACTURERS?

Market forces, capacity constraints, and government policies have driven the bioprocess industry to evaluate new technologies in mAb production with goals to maximize manufacturing flexibility and efficiency while minimizing risk and product cost. Focus is needed on technologies offering the highest return on investment based on ease of implementation, regulatory acceptance, and cost of goods (COG) reduction.

We sat down with Merrilee Whitney, head of the BioContinuum™ Platform for Next Generation Bioprocessing, to hear how MilliporeSigma is addressing the paradigm shift toward intensified, connected and continuous bioprocessing in today's evolving biopharma industry.

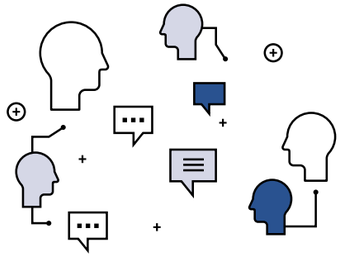
Merrilee Whitney,
MilliporeSigma
www.emdmillipore.com/BioContinuum

1. HOW WOULD YOU DESCRIBE TODAY'S BIOPHARMA LANDSCAPE?

We are seeing unprecedented pressures on biomanufacturers: from the incredible amount of growth in the molecules coming through the pipeline to the uncertainty associated with regulatory change and acceptance, coupled with the cost pressure that they are experiencing with an increased number of entrances into the marketplace. As an answer to this evolution, we brought to life the BioContinuum™ Platform representing our belief in and commitment to the change that is happening within the industry, to meet these challenges that our customers are facing.

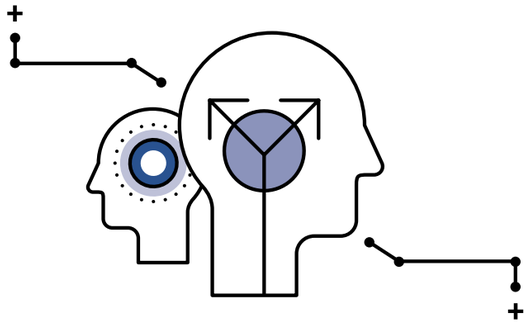
2. IS FULLY CONNECTED, FULLY CONTINUOUS PROCESSING THE ANSWER TO THE CHALLENGES BIOMANUFACTURERS FACE TODAY?

Nowadays, a lot of the discussion in the industry is around fully connected, fully continuous processing being the answer. Our unique point of view is that this will be an evolution over time, starting with process intensification. As a matter of fact, it is starting right now. There are solutions in our portfolio today that will enable biotherapeutic manufacturers to see real benefits in terms of their cost of goods and facility flexibility. Every solution that we already have in the portfolio and are continuing to develop is designed with a very holistic perspective of not only how all these different solutions work in an mAb process today but also how they can be connected and put together for a fully connected, fully continuous process in the future.



3. WHAT ROLE IS COLLABORATION PLAYING IN ADDRESSING BIOMANUFACTURERS' CHALLENGES OF TODAY?

Collaboration is going to be key in how we are able to actually realize the benefits of these technologies as an industry. What will be immensely important will be the collaboration between suppliers such as ourselves and biomanufacturers, as well as regulators. There are going to be many unanswered questions that we as an entire industry need to work through together. And as MilliporeSigma is taking a very holistic view to how this evolution in the industry will happen, we are perfectly poised to collaborate with both customers and regulators to bring this vision of Next Generation Bioprocessing to fruition.



4. WHAT ACTUALLY IS THE BIOCONTINUUM™ PLATFORM?

As stated earlier, the BioContinuum™ Platform represents our belief in and commitment to the evolution of bioprocessing. Together with our customers and regulators, we strive to accelerate access to biopharmaceuticals for patients worldwide.

Whether developing an intensified, connected or continuous bioprocess, the BioContinuum™ Platform provides the building blocks to help our customers achieve their bioprocessing goals. This holistic and forward-looking view of biomanufacturing actively incorporates connected software, controls and analytics across our portfolio of technologies to make the factory of the future a reality.

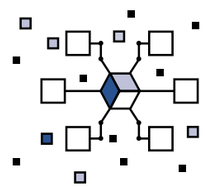
The BioContinuum™ Platform is an expanding offering of proven and novel technologies, applications and expertise enabling biotherapeutic manufacturers to confidently enter the era of next-generation processing by delivering increased speed, greater flexibility and enhanced quality while reducing the costs and risks of navigating the evolving biopharma landscape.

5. WHAT IS PART OF THIS PLATFORM?

The BioContinuum™ Platform comprises several elements. First, there are process intensification–enabling products, integrated solutions and applications, such as perfused seed train, intensified protein A capture, a complete flow-through polishing toolbox or single-pass tangential flow filtration applicable for a multitude of applications. Second, there is a key element around expertise, whether that's how you implement and validate these technologies in your processes or regulatory aspects where we can work in partnership with the regulators and our customers. Finally, there is a critical element when we start to discuss connecting process steps and getting to a fully continuous process in 5–10 years, which is the software, automation and analytics that's required to get all of this to work together seamlessly.

6. WHAT IS THE VALUE OF THIS PLATFORM TO END-USERS? WHAT'S IN IT FOR THEM?

We are working with BioSolve® modeling so that we can develop individual scenarios with our customers to demonstrate actual benefits that can be realized in their particular cases and with their specific challenges. But, across the industry, we are seeing very real and tangible benefits of the adoption of process intensification today: for instance, 90% reduction in facility footprint, 90% reduction in capital expenditure, 70% reduction in the time it will actually take to build one of these facilities of the future. However, it is not just about the facility footprint and construction time, but also on how to positively impact operating expenses moving forward. Some customers have seen as much as a 90% reduction in their operating expense.



7. DO YOU HAVE ANY FINAL THOUGHTS?

The final message I would want to leave people with about MilliporeSigma's BioContinuum™ Platform and where we are as an industry is process intensification is here today and it is real. We are implementing these solutions with our customers right now with very positive impact. That being said, we are developing those solutions with an eye to the future, so if a customer does want to develop a fully connected, fully continuous process in the future, we are developing those building blocks that they can utilize today and tomorrow.

ABOUT THE AUTHOR

Merrilee Whitney
Head of the BioContinuum™ Platform
MilliporeSigma

Merrilee holds degrees in International Relations and Chemical Engineering from Bucknell University. Her career has spanned multiple industries, beginning with Xerox, before moving on to bring hollow fiber UF systems to the U.S. market at Ionics and Koch Membrane Systems. In 2006, Merrilee began her career at MilliporeSigma as the Product Manager for the Millistak+® product line. Throughout her 12 years, she has managed multiple product lines including clarification, aseptic, virus filtration, and Single Use & Systems. Merrilee currently serves as the Head of the BioContinuum™ Platform, driving the strategy execution of Process Intensification Technologies, Software & Automation, and Analytics to meet the evolving needs of biologics manufacturing.

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NEW FACILITY PRESENTS MANUFACTURING SOLUTIONS FOR RECOMBINANT PROTEINS

BY **PAUL MAGRETA,** GRIFOLS

With new, state-of-the-art facilities, extensive tech transfer experience and ongoing investments, Grifols provides contract development and manufacturing services for the production of bulk recombinant proteins for use in diagnostics, therapeutics and vaccines.

PROTEIN MANUFACTURING IN A CUSTOM FACILITY AT GRIFOLS

Our new, $80 million Consolidated Manufacturing Facility (CMF) is located in Emeryville, California. Surrounded and supported by complementary functions and facilities on the Grifols campus, CMF was designed, built and validated to extend our three decades of reliable current Good Manufacturing Practice (cGMP) production of recombinant proteins into the future. The flexible, multiproduct design of CMF and the available manufacturing capacity created an opportunity to leverage our technical expertise and Grifols' commitment to quality to provide contract services to biopharma companies as a recombinant protein Contract Development and Manufacturing Organization (CDMO).

CMF features 25,000 square feet of Good Manufacturing Practice (GMP) production space, including two separate fermentation suites for *Escherichia coli* and yeast, three purification suites and a bulk fill area. The facility layout, designed and built by Grifols Engineering, allows for future process-fit flexibility, easy segregation and rapid process changeover. Production suites with dedicated air-handling systems are physically isolated to minimize risks of cross-contamination. The facility consolidates all of the functions required to support GMP production of recombinant proteins, including warehousing, utilities and maintenance operations, which helps create efficient communication and cross-functional interactions and fosters a collaborative culture that enhances our agility and responsiveness to new projects.

To integrate and simplify process control, real-time monitoring and data trending, we installed advanced automation systems throughout the facility, including a distributed control system (DCS) and a central data historian. Touch screens are available to operators both inside and outside of each manufacturing suite and provide clear visibility into our manufacturing operations and facilitate on-the-floor troubleshooting and analysis.

LEVERAGING OUR EXPERTISE TO SUPPORT CUSTOMER NEEDS

We are well positioned to provide development and manufacturing services to customers seeking recombinant protein production, including therapeutic biologics and vaccines. The location of our facility – in the heart of the San Francisco Bay Area biotech hub – positions us as a go-to recombinant protein CDMO for the local small and virtual biotech companies that lack internal resources, including access to a modern manufacturing facility.

CMF is staffed by highly experienced individuals with diverse expertise and educational backgrounds who have been rigorously trained to support efficient GMP operations. The CMF teams are supported by complementary functions including R&D, process development, analytical laboratories and in-house regulatory support, allowing us to provide a comprehensive range of the services that smaller biotech customers need to get from gene to the clinic and beyond.

EXTENSIVE TECH TRANSFER EXPERIENCE

Grifols received approval from the U.S. Food and Drug Administration (FDA) to relocate existing immunodiagnostic manufacturing operations to the new CMF in July 2018. This first submission enabled commercial GMP fermentation, purification and bulk fill operations in the facility. It also allowed for the production of one recombinant Hepatitis C virus (HCV) antigen. At the conclusion of this transition, we will have transferred 21 different products into CMF, six of them licensed by the FDA.

The contemporaneous transfer of multiple products to the facility was a multi-year effort that required a clear strategy and detailed planning. A risk-based matrix approach was developed to define the tech transfer activities necessary to relocate 21 products. During the project execution, we gained valuable knowledge and experience that can be applied to future transfers to and from the facility to ensure efficient and robust tech transfers. Through these efforts, we have realized a capable multi-product facility for recombinant protein production.

EXPANDING CAPABILITIES VIA ONGOING INVESTMENTS

In parallel with the tech transfer of the existing products, we are finalizing the design for a new pilot plant. This space – expected to be operational by the end of 2019 – will be refurbished and custom-designed to support pilot and small-volume clinical and commercial manufacturing of recombinant proteins.

Additionally, we have opened new laboratory space for our research and development teams and purchased new equipment to expand our capabilities in mammalian cell culture. Cell culture capabilities will also be included in the pilot plant and in future CMF plans.

BUILDING ON THE GRIFOLS QUALITY CULTURE

Quality is prioritized across all Grifols businesses and is critical for each product we produce. Our quality management system (QMS) is continuously monitored via monthly key performance indicators, quarterly management reviews and internal audits. Our operations are routinely challenged by audits performed by regulatory agencies and customers, which provides further validation of our regulatory compliance. We leverage the Grifols quality tradition to provide the most reliable quality support for our contract manufacturing customers while maintaining a focus on patients as the most important beneficiaries of our commitment to quality.

THE FLEXIBLE, MULTIPRODUCT DESIGN OF CMF CREATED AN OPPORTUNITY **TO PROVIDE CONTRACT SERVICES TO BIOPHARMA COMPANIES AS A RECOMBINANT PROTEIN CDMO.**

ABOUT GRIFOLS

Grifols is a global healthcare company founded in Barcelona in 1940, committed to improving the health and well-being of people around the world. We produce essential plasma medicines for patients to treat rare, chronic and, at times, life-threatening conditions. The company provides a comprehensive portfolio of solutions in transfusion medicine and also offers hospitals, pharmacies and healthcare professionals information and services that deliver efficient, expert medical care.

Grifols, with more than 21,000 employees in 30 countries, is committed to a sustainable business model that sets the standard for continuous innovation, quality, safety and ethical leadership in the industry. P

ABOUT THE AUTHOR

Paul Magreta
Business Development, CDMO Services
Grifols

Paul Magreta has over 20 years of experience in the design, start-up and operation of biopharmaceutical manufacturing facilities, and is currently responsible for developing the recombinant protein CDMO business at Grifols in Emeryville, California. Prior to Grifols, Paul led Global Process Engineering at Novartis Vaccines and Diagnostics, and had previously worked in Process Development, Manufacturing Sciences and Technology, and Process Engineering at Genentech. He has a B.S. in chemical engineering from the University of Michigan.

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REDUCING WASTE WITH LEAN DELIVERY IN FACILITY DESIGN AND CONSTRUCTION

→ BY **MATTHEW KHAIR** AND **J. LEE EMEL,** CRB USA

Applying a lean delivery approach to the design and construction of new facilities can reduce waste, lower costs and improve speed to market.

LEAN DELIVERY IN THE CONTEXT OF FACILITY DESIGN AND CONSTRUCTION

Lean thinking is centered on the successful reduction or complete elimination of waste throughout multiple aspects of a business. Applied to capital projects, lean delivery entails removing redundant or wasteful activities that add time or cost to projects. By applying a lean mindset and fully integrating the delivery team, it is possible to achieve huge savings in schedule, reduced risk and improved cost certainty.

Traditional capital project delivery breaks an overall project into individual scopes of work and fragments the overall project team. Originally built out of a need to implement "checks and balances" on a project, traditional project delivery in its worst applications can devolve into contract-driven, adversarial relationships manifested out of distrust. Priorities are set by individual entities, often in conflict with overall project success, and risk is compartmentalized and fully felt by individual team members.

Implementing a lean mindset in project delivery helps counter some of the unfortunate trends that have grown out of the traditional model. An immediately apparent difference is that risk is more broadly shared in a lean model. Shifting away from a model predicated on rigidly defined terms and expectations ultimately helps reduce conflict that can lead to multiple change orders and consequentially higher costs, among other problems. With an integrated, lean approach to project delivery, everyone involved in the project shares risk – and thus responsibility. This simple distinction can result in a significant cultural shift where all parties are focused entirely on successful delivery with a clear understanding that project success will naturally lead to individual success.

Another important distinction of lean delivery is the simultaneous implementation of work, rather than approaching it sequentially. Parts of a project are not pursued by individuals independently and passed on to the next person or group. Rather, as much work as possible is completed simultaneously, with the elimination of unnecessary steps where possible and a communal end goal.

Lean capital projects are implemented in two main phases: the planning/scoping and execution phases. Both require early involvement of all major players to truly harness the power of this delivery model. In the planning/scoping phase, the team develops the scope and goals of the project, cost and schedule targets, as well as a construction strategy that maximizes parallel efforts, and a partnering strategy with the equipment supplier and subcontractor community. More importantly, the entire team comes together to build the culture for the project and agree on how to best leverage each other's talents to ensure success. The overall schedule is confirmed and commitments are made around scope, cost and delivery.

LEAN THINKING IS CENTERED ON THE SUCCESSFUL REDUCTION **OR COMPLETE ELIMINATION OF WASTE THROUGHOUT MULTIPLE ASPECTS OF A BUSINESS**

In the execution phase, the team uses lean tools to help drive the project based on the plan. Lean tools facilitate planning and integrated work and are designed to bring team members together and enable the delivery of the

IMPLEMENTING A LEAN MINDSET IN PROJECT DELIVERY **HELPS COUNTER SOME OF THE UNFORTUNATE TRENDS THAT HAVE GROWN OUT OF THE TRADITIONAL MODEL.**

project on time and at the targeted cost. Examples include the use of core teams, colocation of staff, the establishment of measurable goals at the start of the project, performance benchmarking, risk-sharing propositions, pull planning and continuous improvement. These various tools are applied to the project to drive results.

Multiple design "mini-releases" allow fabrication of as many components as possible in parallel with construction of the building structure, such as equipment, piping and modular structures. The releases are aligned to the build strategy to allow just-in-time delivery to the site, where organized assembly takes place.

TEAM BUILDING IS FUNDAMENTAL

Establishing the right team to implement a lean delivery project is essential. The team members must be committed to the lean delivery approach, or they will often default to protecting their own interests and operating in a more traditional, parochial manner. All team members must also understand the value of lean delivery tools and how to use them.

The main tenet of lean delivery is that every team member is aware of what needs to be accomplished daily, in order to release work for others who are downstream of their activities. With lean delivery projects, results are required every day and every week, and there is an expectation that each person on the team will constantly deliver.

Fundamental to the lean delivery concept is the notion that everyone on the project team has a common goal and a piece of ownership in the project. Because each team member's individual success is dependent on the performance of every other team member, a significant level of trust and accountability is essential – not only among the design and construction experts, but also suppliers, subcontractors and owners.

One of the most effective ways to achieve this goal is to define the vision, culture statement and charter for each project, which helps team members understand the goals of the project and the importance of each person's role in bringing it to fruition. Prequalification of external partners can also help build a level of trust. In some cases, the use of outside consultants to facilitate initial project meetings with new partners can be valuable for building bonds and breaking down barriers.

In many cases, team members find they enjoy working on lean projects because everyone on the team is aligned from the start of the project and there is collective ownership. Conflicts are minimized, and a solution-oriented mentality that transforms challenges into opportunities to problem-solve is universally adopted. Issues become transformative events that lead to an organic deepening of relationships across all parties. Teams also know that everyone involved cares about each person being successful so the overall project will be successful. With direct, open and transparent communication among all parties, each team member often comes to better appreciate the skill sets and expertise that each person brings to the project, which results in better designs. This knowledge sharing can also accelerate the personal growth of team members. Overall, participation in lean delivery projects can present career-changing opportunities.

STANDARDIZATION, MODULARIZATION AND OFF-SITE CONSTRUCTION

Off-site construction is one of the more powerful lean solutions that you can employ on any integrated design/construction project. The more work you can push off-site, the greater the opportunity to create parallel, overlapping workstreams. This work can also be performed more efficiently in partner shops without being impacted by site conditions. As a result, the quality of the work improves, completion dates are more certain and cost is more predictable.

Reducing the concentration of craft labor on-site also reduces risks and improves overall safety. In our current market, where there are real shortages in qualified labor, it allows the project team to better align scopes of work with companies that have the bandwidth to execute them.

To that end, the industry is finding ways to modularize and standardize facilities that were once thought to be truly customized. The use of more standardized modular components for the delivery of custom designs helps reduce costs and accelerate project timelines. Some examples include electrical panels, automation codes, duct routing above similar spaces, air handler sizing and cooling coils.

A changing landscape that is embracing cell and gene therapies continues to challenge that thinking, but, with the right combination of technical and delivery SMEs, it is possible to adapt to whatever challenges arise.

CONSIDERABLE BENEFITS FOR PHARMA

In the pharmaceutical industry, the biggest area of waste in the delivery of manufacturing projects is time. Pharmaceutical companies are in business to get life-changing and life-saving drugs to their patients as rapidly as possible. At CRB, we have used our lean delivery model to cut project schedules in half – reducing typical three-year design/build/qualify timelines to less than 18 months.

In addition to significant time reductions, we have seen much better cost control, less construction waste and safer job sites. There is also a huge improvement in the overall team experience. Lean delivery projects are much more enjoyable for people to work on.

Because lean delivery projects involve an entirely new, integrated approach, clients must be willing to embrace this new mindset. If the client is not ready to embrace the lean approach, they will not be able to achieve the same results. It can be difficult initially to convince drug manufacturers that have a focus on cost minimization, systems installed and teams in-place whose performance is solely based on cost savings.

For example, if the client's procurement team requires hard bids on every contract and piece of equipment, they will lose the collaborative advantage of early involvement by these key partners. It has been shown that a perceived initial savings in buying out a contract is almost always offset by change orders and cost escalation. In projects where there are tremendous cost constraints, people are driven into very competitive situations that often result in the need for one change after another, which creates tensions and negative impacts on scheduling and cost.

Eventually, however, even the most conservative companies will come to accept the lean delivery concept, because the data speak volumes. When a lean delivery approach is used and suppliers are included on the project team, costs and timelines can be more easily controlled. Contracts are established that create ownership and accountability and allow companies to make a fair profit.

CRB AND LEAN DELIVERY

As a firm that has been focused primarily on the life sciences industry for the past 30+ years, we have been involved in the delivery of just about all types of research, development and commercial manufacturing facilities. We have also been able to build a stable of experts across our company that we can leverage to solve just about any problem our clients throw at us.

The use of lean delivery is in its infancy in the pharmaceutical industry, but CRB is ahead of the curve. We have had some great successes using our lean, ONEsolution approach, but there are still more opportunities for improvement. CRB is very excited to be part of leading this revolution in how projects are delivered for our industry, and we hope to continue to demonstrate how to significantly beat traditional delivery metrics to those clients who may still be skeptical. We have built our company around this delivery approach and believe that it is the model that will transform capital projects for the pharmaceutical industry.

THE USE OF LEAN DELIVERY IS IN ITS INFANCY IN THE PHARMACEUTICAL INDUSTRY, **BUT CRB IS AHEAD OF THE CURVE.**

In the end, it is not just about getting the project done, but about helping our clients to be successful making drugs that improve and save patients' lives. P

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SUPPORTING SMALL AND EMERGING PHARMA THROUGH COLLABORATION AND SPECIALIZED EXPERTISE

→ BY **MARGA VIÑES,** GRIFOLS

Growth in the pharmaceutical industry is no longer exclusively driven by large pharmaceutical companies. The switch in the marketplace from a focus on blockbuster drugs to an emphasis on therapies that treat orphan and rare diseases has led to the rise of small and emerging pharma companies founded to advance novel medicines for specialized patient populations. These innovators require the support of contract service providers that recognize their unique requirements.

THE RISE OF SPECIALTY PHARMA

Advances in genomics have led to ongoing discoveries about the role of genetics and genetic mutations in disease mechanisms. The identification of novel drug targets that enable the development of highly specialized – and even personalized – medicines is behind many new drug candidates currently in the pipeline. These drugs – often with orphan drug, priority review, breakthrough therapy and other accelerated approval designations – are, in many cases, based on small molecule APIs developed by small or emerging companies, sometimes in collaboration with charitable foundations and/or universities and institutes.

According to the Tufts Center for the Study of Drug Development, smaller pharma and biotech firms developing small molecule drugs have higher clinical approval success rates than large companies.[1]

ONE NICHE: SMALL MOLECULE INJECTABLES

While most small molecule drugs are formulated for oral administration, for some chemical APIs, there are advantages to developing parenteral products – and demand for small molecule injectable drugs is increasing.[2] Drugs delivered parenterally into the bloodstream, including heart medications, antibiotics and analgesics, provide an immediate therapeutic effect, which is often crucial for patients being treated in hospitals, particularly in emergency rooms. Patients who cannot take medications by mouth also benefit from the administration of drugs by injection or infusion. Parenteral administration is also a desirable alternative for drugs that degrade in the stomach or intestines.

Parenteral formulations can be prepared as admixtures that must be manipulated into the correct dose before administration, or they can be prepared in premixed bags. Using premixed bags reduces the risk of medication error and microbial contamination, and producing these premixed bags in highly automated GMP facilities offers an even higher level of quality.

THE NEED FOR IN-DEPTH EXPERTISE

The thousands of small and emerging pharma companies across Europe and North America developing novel small molecule drugs often have limited resources, personnel and expertise with regard to the full drug development and manufacturing process. They often rely heavily on contract development and manufacturing organizations (CDMOs), outsourcing much of their process and formulation development, validation, regulatory compliance and manufacturing activities.

CDMOs that provide integrated services across all phases of the drug development and commercialization cycle provide the best support to these firms. For small companies looking to advance small molecule injectables, the ideal CDMO will also have extensive knowledge and the specialized expertise required to rapidly develop robust, high-quality manufacturing processes that are readily scalable and ensure the highest product quality and consistency.

THE VALUE OF QUALITY

The processes involved in the manufacture of sterile parenteral products are highly complex. The stability of the parenteral solutions must be assured, which requires the completion of extensive compatibility and stability studies. Products packaged in plastic must also undergo extractable and leachable testing to ensure that contamination of the drug product does not occur. Sterility must be confirmed via microbial contamination studies. Cold-chain management is also required for some parenteral products. These issues can only be addressed on an ongoing basis if the CDMO has a well-established culture of quality and effective quality systems in place.

FLEXIBILITY AND UNDERSTANDING MATTER

With many new drug candidates receiving designations allowing for accelerated approval pathways, CDMOs supporting small and emerging pharma companies developing small molecule injectable drugs must have the process understanding and physical capability to implement projects within dramatically shortened timelines. They must also have flexible capacity to support projects as they move from the clinic to commercialization.

In many cases, specialized products developed as orphan drugs or therapies designed to treat rare diseases will target small patient populations. The quantities of these drug products required at the clinical stage, and even for commercial production, can be much smaller than those for more traditional medications – as low as 100,000 units, for instance. The ideal CDMO for clients developing these products welcomes these smaller volumes but also has the ability to expand production to millions of units if or when the volume demand increases.

THE IMPORTANCE OF RELATIONSHIPS

Smaller pharma companies that rely heavily on outsourcing require CDMO partners that are willing to establish strategic partnerships based on open communication and transparency. It is also essential that the relationships between the different departments within the CDMO are strong, because there is much less time to develop and validate manufacturing processes and analytical methods. Good relationships with FDA representatives are equally important, particularly for drugs developed under accelerated approval pathways.

THE GRIFOLS DIFFERENCE

Grifols was one of the first companies in Europe to obtain approval for the parametric release of parenteral solutions. Parametric release is authorized for companies that have historically shown excellent sterility test results and high consistency in their overall quality systems. It also facilitates reduced timelines for product release, allowing our clients to get their products to the clinic and market more quickly.

Collaboration is emphasized at Grifols through the use of an integrated project management strategy. Cross-functional teams with representatives from R&D, quality assurance, manufacturing, quality control, regulatory and sales and marketing collaborate to consider all potential consequences before implementation of even the smallest changes. The result is the avoidance of unexpected problems and the need to make corrections, preventing unwanted delays and keeping projects on schedule. P

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THE RENAISSANCE OF MICROBIAL FERMENTATION

BY **VLADAS ALGIRDAS BUMELIS,** NORTHWAY BIOTECHPHARMA

Initially, many smaller biologic drug substances — including recombinant proteins and peptides — were produced via microbial fermentation. However, with the advent of cell-culture systems, interest shifted to mammalian systems to produce larger proteins and antibodies. Now, the introduction of smaller, complex next-generation molecules, such as bioconjugates, antibody fragments and other scaffolds, is once again driving interest in fermentation as an effective manufacturing platform.

STATE OF THE FERMENTATION MARKET

Just 10 years ago, of the slightly more than 150 recombinant pharmaceuticals approved through 2009 for human use by the FDA and/or the EMA, more than half were manufactured via microbial fermentation using bacteria or yeast.[1]

Since then, the biopharmaceutical industry shifted to focus largely on the development of mammalian cell culture systems for the expression of antibodies and other large proteins that require posttranslational modifications. In 2018, nearly 70% of biologics production capacity (in terms of volume, excluding blood/plasma products) utilized mammalian cell culture, primarily monoclonal antibodies (mAbs) produced using Chinese hamster ovary (CHO) host cells.[2] The other 30% of capacity involved expression in microbial systems, with most processes relying on *Escherichia coli*.

Interest in microbial production is increasing. Microbial-produced biopharmaceuticals generated revenue of around $100 billion in 2017, and the segment is expanding at a significant 6% CAGR.[3]

The expansion of the market for microbial fermentation reflects growth across product categories. The market for microbial fermentation for protein drugs increased from $44 billion to a projected $60 billion in 2020, while the markets for peptide hormones and vaccines increased from $18 to $28 billion and from $10 to $19 billion, respectively, over the same period.[4] Many large pharmaceutical companies, including AbbVie, GlaxoSmithKline, Sanofi and Eli Lilly, leverage both microbial and mammalian manufacturing for their products, while others, such as Merck and Bayer, rely overwhelmingly on microbial systems.

The rate of outsourcing of fermentation processes to CDMOs is also on the rise.[2] The value of the global contract pharmaceutical fermentation services market is predicted to surpass $4.0 billion by the end of 2026, expanding at a CAGR of 5.9%.[5] Most biologics CDMOs specialize in either microbial or mammalian system, with only a handful (e.g., AGC Biologics, Fujifilm Diosynth Biotechnologies, KBI Biopharma, Emergent BioSolutions, Northway Biotechpharma) offering both systems.

A key factor in the renewed interest in microbial fermentation for biopharmaceutical manufacturing is the development of next-generation therapies based on smaller biologic drug substances, including antibody fragments, antibody–drug conjugate (ADC) payloads and small peptide fragments. Advances in genetically engineered microbial strains have also contributed to higher yields for biopharmaceutical production.[3]

ADVANTAGES OF FERMENTATION

When choosing cell culture or fermentation as the manufacturing method of choice, the size of the biologic drug substance is often a major factor, as is whether significant posttranslational modifications (PTMs) are needed.

Microbial fermentation in bacteria, yeast or fungi is generally preferred for smaller biologics (e.g., peptides, proteins, cytokines, growth factors, plasmid DNA, nucleic acids, single-domain antibodies, peptibodies and non-glycosylated antibody fragments). In these cases, processing times are typically much shorter, and media costs can be significantly lower than those associated with cell culture. The microbes are genetically engineered to produce large quantities of the desired biomolecules at concentrations much higher than can be achieved via expression in mammalian cells.

The high-cost, long-development timelines and lower expression levels associated with mammalian cell culture are contributing to the resurgence in interest in manufacturing processes using microbial organisms.[6] In addition, most CHO systems are not effective for the production of complex, next-generation drug substances, such as single-domain antibodies, peptibodies and antibody fragments, with the right properties in clinically relevant amounts. Microbial fermentation is a better option in many cases.

Overall, microbial fermention–based manufacturing provides faster development, higher yields and quality, reduced variation between batches, better scaleability, and lower production costs.[7] Mammalian systems, however, present clear advantages for certain types of proteins – such as trans-membrane, membrane-bound, and glycoproteins – owing to the absence of endoplasmic reticula in bacteria to facilitate proper translation and conformation.

MEET THE MICROBES

E. coli, the most prominent microbe used for fermentation, has been shown to be highly robust and economical for the production of biologic drug substances.[1] *Saccharomyces cerevisiae* and *Pichia pastoris* are the most commonly used yeasts for pharmaceutical manufacturing. Interest in *P. pastoris* has grown due to its combination of prokaryotic growth characteristics and eukaryotic-like PTMs; it is used for the production of vaccines, antibody fragments, hormones, cytokines, matrix proteins and biosimilars.[1]

RECENT DEVELOPMENTS

To prevent the accumulation of the expressed recombinant proteins as insoluble aggregates or inclusion bodies, bacterial expression systems have been engineered to secrete the biologic drug substance into the periplasm or media for more rapid purification at higher yield and with a greater likelihood of obtaining the product in the desired conformation.[8]

Several companies, including VTU Technology and Research Corporation Technologies, are developing advanced *P. pastoris* yeast expression systems for the production of drug substances. These microbial platform systems include innovations like promoter libraries that allow for the fine-tuning of gene expression by carefully matching promoters and target genes, as well as the genetic deletion of undesired glycosylation pathways, and the introduction of human-like genes that direct the glycosylation process.

FERMENTATION AT NORTHWAY BIOTECHPHARMA

Northway Biotechpharma has been offering contract development and manufacturing fermentation services to the pharmaceutical industry for nearly 15 years. We are a full-service CDMO with capabilities in strain and cell-line development, process development and scale-up for clinical and commercial GMP manufacture of biologic drug substances. Northway Biotechpharma provides support for the development and production of both branded biologics and biosimilars.

In keeping with the increasing demand for microbial fermentation for manufacturing biologics, we are looking into investing in expanding our fermentation capacity by installing 5,000-L stainless steel bioreactors at our site in Vilnius. We are also pursuing the development of platform technologies and knowledge to further streamline our operations and reduce project timelines for our clients. P

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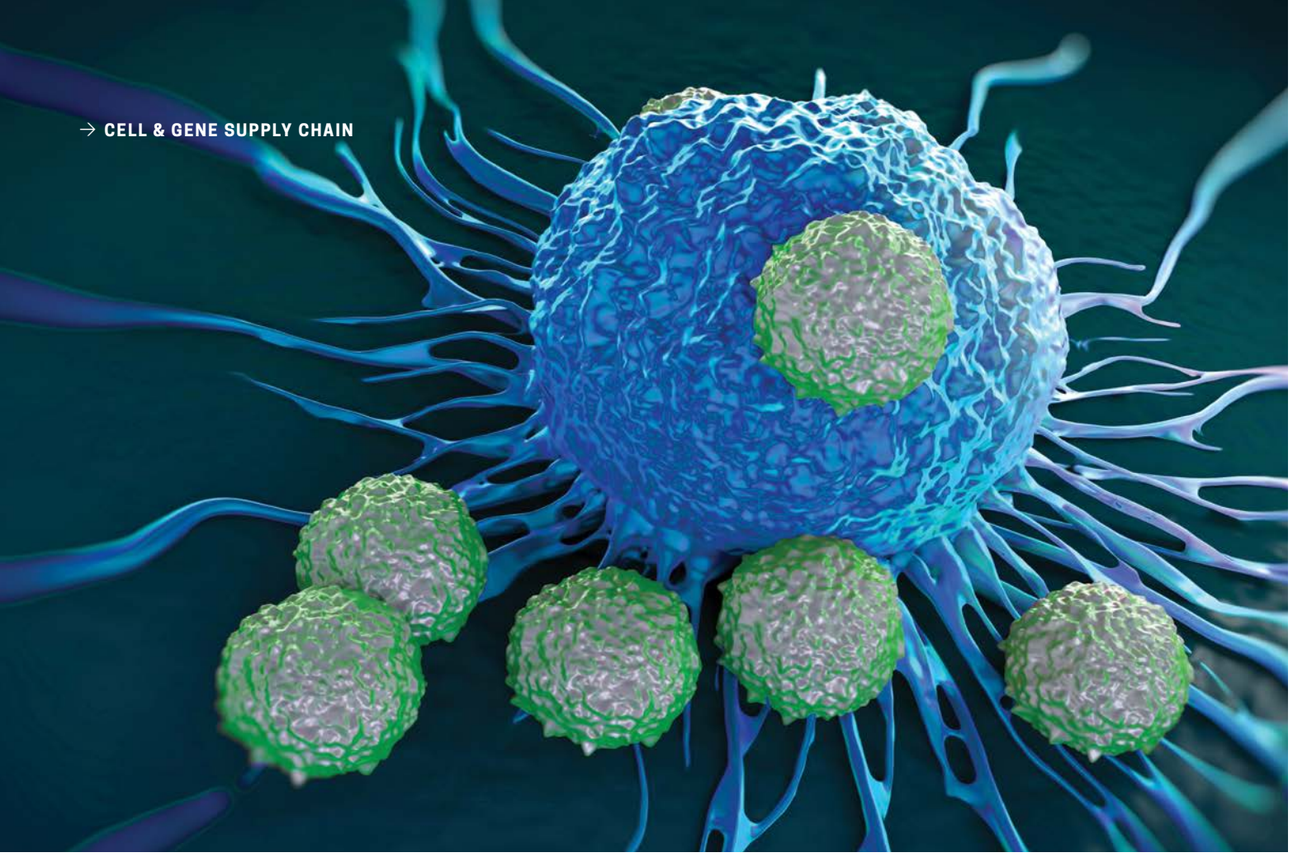

MANAGING THE COMPLEXITY OF THE SUPPLY CHAIN FOR CELL AND GENE THERAPIES

→ BY **SASCHA SONNENBERG,** MARKEN

The emerging cell and gene therapy industry is disrupting conventional supply chain models and requires significant changes to the supply chain. The development of advanced therapies means the design of logistics solutions for optimal management and oversight to achieve and deliver mission-critical milestones. Biological material produced for autologous and allogeneic therapies must be shipped under stringent temperature controls within extremely tight timelines, and with the chain of identity, and chain of custody, assured. Marken is developing technologies designed to address complex logistics and provide optimal supply chain solutions for the fast-growing cell and gene therapies market.

RAPIDLY EXPANDING MARKET

With hundreds of potential products advancing through early into late-stage clinical trials and scaling up to commercialization, the market for cell and gene therapies is expected to grow dramatically in the coming years. While only three cell and gene therapies have achieved FDA approval to date, former FDA Commissioner Scott Gottlieb predicted an approval rate of 10–20 cell and gene therapy products per year by 2025.[1] The value of the global market for cell and gene therapies is predicted to expand at a compound annual growth rate of nearly 22%, growing from $6.02 billion in 2017 to $35.4 billion in 2026.[2]

AUTOLOGOUS AND ALLOGENEIC SUPPLY CHAIN CHALLENGES

With autologous therapies, biological material is collected directly from the patient via apheresis. The material is transferred to the manufacturing site, where the cells are genetically modified and produced in large quantities. The personalized therapy is then shipped back to the clinic and administered to the patient. Both the initial material and therapy must be shipped under liquid nitrogen (LN2) or refrigerated conditions in a very short period of time – for the cell collection, the typical door-to-door transport time is 40–50 hours or less. The therapy transfer requires strict temperature and chain of identity monitoring.

The same is true for allogeneic therapies, once the cells have been modified, grown and processed into the final medicinal product. The ability to deliver material to the manufacturing site and/or back to the clinic depends on the location of the two sites and the availability of modes of transport.

Autologous cell therapies create scheduling challenges as well. In many cases, these products are produced at a contract manufacturing organization (CMO). Coordination between the material collection, transport and receiving hours at the CMO is a vital element managed manually in early stages and often supported by IT solutions when scaling up to phase III or commercial stage.

Allogeneic therapies are produced from cells that are collected from a healthy donor, stored under liquid nitrogen at a low temperature and shipped to a clinical site to treat a patient with a successful match. A just-in-time delivery process, including secondary packaging, labeling and QP release (in the EU) is necessary.

Errors along any point of the process or supply chain can be potentially devastating for patients and highly costly for clinical trial sponsors. Analysts estimate that manufacturing of approved CAR-T treatments can cost $200,000–800,000 per dose. Innovative therapies that may not only treat but potentially cure cancer and genetic diseases are promising, but if those therapies cannot be distributed to patients (or the patients cannot be brought to the therapies) they have no value.

RISE OF SMART TECHNOLOGIES

The development of smart packaging is a critical element of the supply chain solution. Monitoring and tracking systems embedded in the shipping solution allow real-time access to shipment data such as location, temperature, shock and orientation. If activated, predefined alarm points trigger automated messages, allowing interception of the shipment and the initiation of actions required to keep everything under control. Using GPS, data locations, such as airports or clinics, can be geo-fenced. When shipments enter or leave geo-fenced areas, automated notifications can be sent, assuring that defined individuals are aware of arriving shipments and notified of any excursions.

IT ADVANCES REQUIRED

The challenges and needs for cell and gene therapy supply chains are creating demand for more advanced IT solutions. For many of these drug products, and particularly for autologous cell therapies, logistics are a crucial element in ensuring that the right medication reaches the right patient within a highly specific time frame.

Many factors must be considered in the cell and gene therapy supply chain, such as when the patient should come to the clinic, how long the apheresis collection will take, when the material can be picked up from the clinic, the opening hours for the manufacturing site, the duration of the production process, when the drug product can be picked up and the locations of the two sites, among others. This information is used to identify the best mode of transport and to achieve lane mapping and lane verification.

One of the biggest challenges in autologous therapies is the fact that each batch is produced for one patient. Scaling up does not involve producing more volume in terms of quantity, but rather in terms of the number of batches. Scheduling is also dramatically different when moving from early to late stage and commercialization. At early development stages, scheduling is typically handled with manpower; planners coordinate requests coming in from clinics with available manufacturing capacities and manage the logistics interfaces that connect the various elements of the supply chain. When scaling up, adding more resources does not offer much benefit. The complexity is too great; effective IT systems are essential. When properly linked to the logistics systems, available data can be utilized to automate and forecast upcoming requests.

> THE FATE OF MILLIONS OF PATIENTS AND BILLIONS OF DOLLARS THUS RESTS ON THE BIOPHARMA INDUSTRY'S **ABILITY TO MASTER THE COMPLEX SUPPLY CHAINS THAT UNDERPIN THE DEVELOPMENT OF ADVANCED THERAPIES.**

MORE DECENTRALIZED APPROACH EXPECTED

There are instances where a lane-mapping exercise will lead to the conclusion that no route is available by which the successful delivery of material and/or drug product can be guaranteed within the acceptable time frame. In some cases, the problem can be overcome by collecting the patient sample at an earlier time, or requiring the CMO to offer more flexibility in accepting/dispatching material in order to make it possible to meet existing flight options.

As more cell and gene therapies reach the market, patients may need to be brought closer to the manufacturing site, or a decentralized supply chain approach may need to be implemented. As manufacturing technologies continue to evolve and

THE PROMISING NATURE OF ADVANCED THERAPEUTICS AND THE CHALLENGES THEY POSE MAKES IT NECESSARY **TO CHOOSE A SUPPLY CHAIN PROVIDER THAT HAS A TRACK RECORD OF MANAGING THESE LOGISTICALLY COMPLEX CLINICAL TRIALS**.

allow easier control and implementation of modular facilities, the latter option will become more feasible.

As the field of cell and gene therapy expands to address aging and other general conditions, there will be even greater demand for decentralization to enable the delivery of these remedies to the wider population.

FACILITATING COMMERCIALIZATION OF NEXT-GEN THERAPIES

The fate of millions of patients and billions of dollars thus rests on the biopharma industry's ability to master the complex supply chains that underpin the development of advanced therapies. The promising nature of advanced therapeutics and the challenges they pose makes it necessary to choose a supply chain provider that has track record of managing these logistically complex clinical trials.

One of Marken's core services is collecting and delivering biological samples. We are now leveraging that experience and sophisticated technologies for the collection of apheresis materials and the delivery of novel cell and gene therapy products. Clinics can use our Allegro portal for data entry and shipment requests. Marken's new Smart Box, a custom-designed thermal box, provides the best protection available for high-value shipments of clinical drug products, clinical drug substance and cell and gene therapies, combined with 24/7 tracking visibility using any one of three different GPS tracking devices. It is the first truly configurable container capable of utilizing any GPS tracking device available, including Marken's own SENTRY device, which reports location, temperature, movement and shock as often as once per hour. The box can also accommodate Bluetooth technology for temperature monitoring and identification.

Marken also recently introduced an automated closed-loop packaging solution that allows materials to travel at any temperature to any destination with an integrated and automated packaging returns process. The new service allows critical drug shipments traveling in reusable and valuable packaging to return to their point of origin for reconditioning and repositioning with much greater efficiency.

As the clinical supply chain subsidiary of UPS, Marken's access to UPS's expansive airline and fleet networks increases Marken's ability to source appropriate shipping lanes. Shipments are collected by Marken, placed on UPS flights and then carried to their final destination by Marken. The hybrid solution, which covers Europe and the Americas, gives Marken end-to-end oversight and offers more flexibility and resources. In Brazil, the introduction of the service extended the latest pickup times by up to five hours, giving more time to prepare and package samples.

Marken is actively working to develop advanced solutions that facilitate scheduling within the cell and gene therapy supply chain. We are collaborating with a leading supply chain software company, which has developed integrated software technology that effectively and easily orchestrates the cell therapy supply chain for autologous and allogeneic therapies. The interface between the operating systems allows users to automatically schedule or amend material collections in line with manufacturing capacity, and each healthcare provider's treatment schedules. Clinicians are then able to view the progress of therapies through each stage of the supply chain with a single, integrated system.

Marken utilizes historical data to forecast shipment times and requirements, optimizing the demand planning and scheduling process.

The implementation of smart technologies, along with our extensive network, has given Marken the opportunity to address cell and gene therapy supply chain issues before they occur. Marken is focused on not only providing supply chain logistics for the transport of these advanced, life-saving therapies, but also on providing comprehensive solutions. Marken is continually growing and expanding to meet the complex and ever-changing needs of these and other industry therapies as they evolve. They are a committed and global supply chain partner for those organizations on the cutting edge of developing patient-centric treatments and therapies for diseases. P

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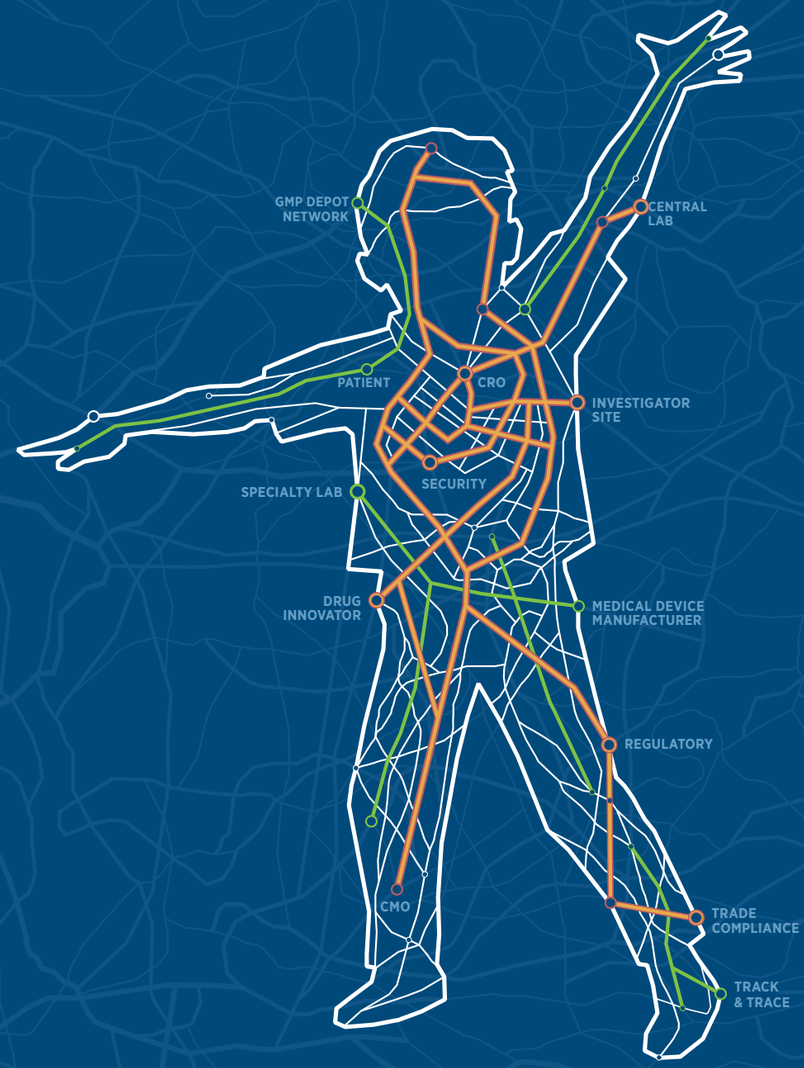

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REVISITING THE GLOBAL SERIALIZATION LANDSCAPE

→ BY **MICHAEL KINSELLA,** SERVIER

Serialization continues to be one of the most pressing issues in the industry. Following an internationally recognized mandate to implement a system of track and trace into the supply chain, countries established their own best practices to ensure compliance on national levels. However, these differing regulatory requirements have created confusion in the industry on an international scale. Countries have been pressured to change their operations and bring on staff with new areas of expertise in order to meet specific standards within a short period of time.

AN INTERNATIONAL APPROACH TO SERIALIZATION

The need to serialize is changing the way business is conducted throughout the supply chain. That countries are not aligned in their serialization requirements globally has only further muddied an already complex situation. For example, in Russia, the government plans to have full control over sales unit traceability throughout the supply chain. If a pharmaceutical manufacturer wants to produce and commercialize a finished drug product, they have to request government crypto codes before production begins and then complete up to 60 data transactions, from production line to dispensing activities, through a government database. This is a very different model from the European Union, where an end-to-end model is implemented. In this model, serial numbers are coded onto the sales units by the manufacturing organization and eventually decoded upon dispensing. A definitive feature of this end-to-end model is that the reporting demands during transport are less rigorous (unlike in Russia). In Russia, the model of full control also extends beyond pharmaceuticals to all commercialized goods, including alcohol, tobacco, cosmetics and luxury items.

The different traceability requirements globally also reflect a varied range of motivations in implementing these systems. Preventing counterfeit products and circumventing fraud might be the main motivator for one country, while preventing over-reimbursement is the primary concern for another. The approach to serialization and how the process is overseen differs from one country to the next, including which organization is tasked with ensuring manufacturer compliance. In the United States, the Food and Drug Administration must confirm whether companies comply with serial requirements; in the EU, serialization oversight is monitored by health authorities from each member state, and, in Russia, the Ministry of Trade tracks compliance directly.

In addition to the different driving motivations, regulatory agencies, oversight committees and available technology and resources in serialization, in Europe, certain countries have accepted a short grace period for serialization, where companies will not be fined if they have not achieved full compliance, while other countries, such as Germany, Poland and Austria, have a much stricter position today when it comes to enforcement.

Companies may now have to upgrade or reinvest to comply with a series of evolving international standards and solutions. Interestingly, in Europe, not all manufacturing organizations are currently connected to a European manufacturing hub. It may take several more months to get all remaining manufacturers on-boarded with the EU hub. Solutions deployed in Europe will not fully meet the Russian crypto coding requirements, and some companies may have to completely revisit (or at least upgrade) their capabilities to remain compliant.

ADDRESSING A HESITATION TO SERIALIZE

In Europe particularly, a lack of early communication and training support for all stakeholders involved has penalized the readiness across the pharmaceutical supply chain. National enforcement of serialization has varied significantly, with some countries intending to implement fines and others taking stricter or laxer approaches.

Becoming compliant with serialization involves multiple steps, including checking data, ensuring printing quality, an absence of duplicates and connecting an interface with existing systems. For some companies, changing systems where there is a lack of expert staff or appropriate resources in place can represent a great risk, especially considering the consequences from an investment and process perspective.

In order for serialization efforts to be successful, a learning period is a must for companies to build and fully master the new processes and solutions, which are integrated into their operations. Most countries, including the United States and Turkey, have introduced a phased approach to traceability to allow for actors to build their maturity step by step. However, the EU mandated compliance on a single date, which represents an ambitious target for all actors involved.

The expansion of serialization requirements down to the unit dose level is likely to be met with even greater resistance than the original global sales unit mandate. Among other reasons, this is because packaging lines are mostly not equipped with unit dose serialization functionality.

AS A MAJOR PLAYER IN THE GLOBAL SUPPLY CHAIN AND A LEADER IN SERIALIZATION, **SERVIER HAS THE EXPERTISE AND RESOURCES REQUIRED TO HELP OUR GLOBAL CUSTOMERS MEET TRACK-AND-TRACE REQUIREMENTS IN ALL MARKETS**

Serialization at the unit dose level would pose considerable challenges without major investment from the industry. Serialization of secondary packaging, while adding the additional unit dose serialization level, requires fundamental changes and investment across operations. Servier has already begun pilots on unit dose printing for lot and expiry.

Even though serialization solutions are fully validated, roles and responsibilities will have to adapt to manage these solutions – for example, a line operator/technician with a mechanical background will need to be well trained on the software.

SERVIER'S GLOBAL ADVANTAGE

As a major player in the global supply chain and a leader in serialization, Servier has the expertise and resources required to help our global customers meet track-and-trace requirements in all markets. Servier is present in a total of 148 different countries. This large-scale global exposure has made us aware that a singular solution for multiple markets is impossible, which pushed us to take a modular approach to serialization, developing a core system that is an aggregate of the requirements of different countries.

A CONNECTED INDUSTRY AND THE PROMISE OF SERIALIZATION

The ultimate benefit of serialization is that it will make the industry significantly more connected. Serialization allows

companies like Servier to understand who all of our partners in the supply chain are – and where they are. It gives companies the opportunity to centralize information to ensure the visibility of product flow in the supply chain and the transfer of ownership.

Serialization carried out correctly allows for endless possibilities. It forces companies to reflect on the interconnectedness of processes and systems while empowering the end user. At Servier, our production facilities are becoming more connected because of serialization, which could lead to real-time tracking of product management and supply chain activities. This can be a very powerful tool if companies execute the process correctly, but it can also be a Pandora's box – you are no longer selling only physical boxes, you are also selling data – and this data is a new company asset. Unfortunately, many organizations do not have this kind of expertise to rely on and, as the industry becomes more digitized, will have to build this skill set into their operations with strategic training and hiring.

Almost all of our clients rely on Servier's expertise and guidance in serialization, as very few have superior systems at maturity. We are also working with small CDMOs encountering track and trace for the first time, who do not fully understand what is required and rely on us to provide guidance.

Our clients' demands and strengths shift depending on the size of their organizations. Small companies can be quite agile and responsive, while larger organizations naturally tend to have more constraints to take into account. Our approach to dealing with both is to meet the standard minimum requirements first, build a relationship and take it step by step. Each of our client projects is handled on a case-by-case basis.

EVEN WHEN AN ORGANIZATION INPUTS GOOD DATA, **ATTENTION IS NECESSARY THROUGHOUT THE PROCESS TO GET GOOD DATA OUT.**

GOOD DATA IN AND GOOD DATA OUT

When dealing with the abundance of data that is a by-product of serialization, a strong security network is an ultimate priority. At Servier, we address data security before anything else and implement multiple controls to ensure that a breach is never a possibility. In addition to our automatic interfaces, we use complementary manual checking processes to verify the authenticity of data on initial data loading. Our primary focus is having the appropriate data in our system, which means ensuring that the data entered at the source is correct and having total oversight over all updates. Systems are now connected production to distribution, and, in Europe, we keep a record of all transactions.

With serialization, each organization is more and more connected. The key is managing the interface and ensuring data management, security and integrity in all transactions. Even when an organization inputs good data, attention is necessary throughout the process to get good data out.

BUILDING A NETWORK THROUGH SERIALIZATION

An interconnected industry reinforces the value of the Internet of Things (IoT), which has become a reality in the pharmaceutical industry. At Servier, we are building a network through serialization that provides solutions and opportunities. A comprehensive network was absent in the industry, but, as a result of serialization, real-time tracking could become the standard – which means real-time communication with our stakeholders. The continuity of this network is also critical for patients.

SERVIER HAS TAKEN A PROACTIVE APPROACH TO SERIALIZATION **AND IS WORKING TO EDUCATE OUR CLIENTS AT EVERY PHASE OF THE PROCESS.**

Servier has taken a proactive approach to serialization and is working to educate our clients at every phase of the process. We have developed e-learning tools, including webinars and videos. Perhaps most importantly, we pay special attention to the human elements of the new processes. For example, an employee focused on packaging compliance now has to be aware of data interfaces, data exchange and data coding. This is very much an end-to-end process, and changing one part of the process has an impact on upstream and downstream activities and individuals. For serialization implementation to be successful, managing the people within the process is key. P

ABOUT THE AUTHOR

Michael Kinsella
Program Director Serialization & Packaging, Supply Chain, Servier

An engineer by background, with a combined 25 years' experience in aeromotive, automotive, medical device, packaging equipment, pharmaceutical blister and bottle packaging, **Michael** started his Servier experience in the Irish production site and currently works in Servier headquarters' supply chain department. Michael is primarily managing Servier's global serialization program. Servier has already rolled out serialization solutions for the U.S., Europe, South Korea, China and Saudi Arabia, Gulf region, and manages Turkey and Argentina through partners—our next big challenge is to meet the Russian deadline by January 1, 2020.

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Exploring the Efficacy of Stem Cells in Reversing Age-Related Frailty

With the elderly population growing – both in the United States and globally – there is mounting pressure to develop treatments that address unmet needs in geriatric populations. Regenerative medicines, including allogeneic stem cells, show promise in treating aging frailty in elderly populations, but the regulatory path forward presents challenges.

Aging Frailty is a Growing Concern

The U.S. Census Bureau predicts that 78 million people will be older than 65 by 2035; globally, the over-60 population will double by 2050 and triple by 2100, outpacing their younger counterparts.[1] Yet, for a condition that plagues this population – aging frailty – there is no FDA-approved treatment, leaving them susceptible to poor clinical outcomes, such as institutionalization, falls, fractures, hospitalization and even death. Frailty is associated with sarcopenia, or loss of muscle mass, and elevated biomarkers in the blood that indicate chronic inflammation.

Stem Cell Therapy for Aging Frailty

Longeveron has been studying the potential of stem cell therapy to treat patients with aging frailty, exploring the immunomodulatory effects of mesenchymal stem cells (MSCs) in suppressing inflammation and reversing chronic aging-related disorders. As reported in 2017,[2] the results of phase I and phase II clinical studies were published in *The Journals of Gerontology*. These studies evaluated the safety and tolerability of intravenously infused allogeneic MSCs derived from the bone marrow of young healthy donors in patients with aging frailty.[3,4] Now, thanks in part to a two-year, $3.8 million grant from the National Institute of Aging, we are recruiting for an expanded phase IIb study in aging frailty. This marks the first multi-center, randomized, placebo-controlled trial using stem cells to treat aging frailty. The study's aim is to demonstrate the efficacy of Longeveron's allogeneic MSC infusion in ameliorating the signs and symptoms of the condition in patients aged 70–85.

MSCs, once isolated from donor bone marrow, are culture-expanded *in vitro* and cryopreserved. Once ready for use, the stem cells are thawed, washed and tested for viability prior to infusion into clinical trial subjects. MSCs are multipotent, self-renewing cells that differentiate into bone, fat and cartilage tissue and are essential for self-repair. As these cells migrate within the body, MSCs are believed to secrete chemical signals that induce tissue repair, reduce inflammation, modulate the immune system and promote the formation of endothelial tissue. This mechanism of action is being tested in elderly patients to determine the biological effect and the ability to reverse or reduce the severity of aging frailty and to prevent or reduce adverse health outcomes.

Clinical Trials Exploring Efficacy

Our phase IIb trial was originally slated to include 120 subjects in four treatment arms; however, thanks to the NIA grant award, Longeveron was able to expand the study to include a fifth LMSC dose and increase enrollment to a total of 150 subjects. Enrollment is anticipated to be completed in the late summer / early fall of 2019. The trial will assess the effects on physical function and mobility, as limitations in these areas increase with advancing age and worsening sarcopenia. Many aging frailty patients experience difficulty in performing basic activities of daily living, such as navigating stairs, crossing the street or even rising from chairs without the risk of falling. Our society urgently needs new treatments that can prevent or reverse the physical deterioration that often leads to an individual becoming dependent on others for care. We are one of the few organizations conducting clinical studies in these areas, and we believe that a regenerative medicine approach holds great promise.

The endpoints in the trial design include lower body strength, grip strength, mobility, endurance, balance, walking speed and fear and risk of falling. In addition, changes to pro- and anti-inflammatory molecules in the blood are being measured in the hope of identifying a potential biomarker. Assessing these endpoints helps determine whether the patient is experiencing deteriorating health. The effect of intervention on the long-term clinical outcomes will require a multi-year study, but the current phase IIb trial is focused on these more intermediate endpoints to determine efficacy over 6–12 months.

After the phase IIb trial results are known, Longeveron will, in consultation with regulatory authorities and advisors, evaluate the next steps toward eventual commercialization. P

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SUPPORTING COMMERCIALIZATION WITH SPECIALIZED TECHNOLOGIES

→ BY **JOSEPH SZCZESIUL** AND **PATRICK HATEM,** UPM PHARMACEUTICALS

As the complexity of APIs and drug formulations continues to increase, drug manufacturers more frequently need to engage contract development and manufacturing organizations that can support them with specialized technologies from the proof-of-concept stage through clinical trials and on to commercial production.

HIGHLY POTENT CAPABILITIES

Many small molecule APIs in the pharmaceutical pipeline today have increased potency. These compounds can affect workers and the environment at very low concentration levels and therefore require special equipment and handling capabilities to ensure proper containment and prevent their release into the air.

UPM Pharmaceuticals has capabilities for processing potent compounds from development to commercial quantities. Manufacturing takes place in glove boxes with table-top equipment at bench scale and moves up to compound-dedicated suites with appropriate air flow controls and outfitted with the necessary full-scale containment equipment.

HORMONE MANUFACTURING

Hormones are another class of compounds that can affect operators at low exposure levels, whether via inhalation, ingestion, or absorption through the skin. Strict requirements therefore exist regarding manufacturing and handling procedures (for raw materials, intermediates, and finished products, as well as quality control testing) and the use of environmental controls.

UPM has three compound-dedicated suites for solid dosage manufacture of hormone products. The main principles for dealing with hormones include isolation, containment, and employee protection. The manufacturing equipment is analogous to what would be used for standard solid dose granulating, milling, blending, compression and coating processes, but with containment provided by split butterfly valves and sealed transfer connectors. The equipment is dedicated to each suite, and each suite is isolated from the rest of the manufacturing facility by airlocks or is accessible only through external doors.

Currently, UPM manufactures hormone products for both development stages and commercial production, with suites dedicated to the manufacture of liothyronine, levothyroxine and estrogen products.

EXPERTISE IN CONTROLLED SUBSTANCES

Requirements for the manufacture of controlled substances impact all aspects of drug development, manufacturing and distribution. Avoiding diversion through the use of appropriate controls and record-keeping is crucial. An in-depth understanding of the regulations, long-standing positive relationships with regulators, and a track record of successfully working with controlled substances can accelerate product development and commercialization.

UPM has a long history of manufacturing and distributing many different types of controlled substances and takes a proactive approach to managing these products. We are vested in providing more than just capacity for the production of controlled substances. We work closely with our customers to make sure they understand all aspects and implications of the Controlled Substances Act (CSA).

UPM's in-house training program ensures that operators and other employees who handle controlled substances understand the importance of following company procedures to ensure compliance with the CSA and avoidance of any diversion of controlled substances. Our analytical laboratory is approved to handle Schedule I-V controlled substances and listed chemicals, and conducts formulation development and stability/degradation testing. Our R&D group also investigates abuse-deterrence solutions for controlled substances that both the Drug Enforcement Agency and the U.S. Food & Drug Administration have promoted.

The ability to support controlled substance projects in-house from the proof-of-concept stage through to commercialization/product launch, including formulation development, process and method development, validation and warehousing, does away with the requirement for complicated technology transfer of these challenging projects off-site to other vendors. Clients save both time and money while getting their products into the hands of patients more quickly.

FACILITATING ORAL PEPTIDE FORMULATIONS

Peptides are attractive as APIs because they are naturally ubiquitous in the body, play specific functional roles, are well-tolerated and exhibit reduced systemic toxicity. In addition, they often have greater potency and specificity with reduced side effects and greater efficacy compared with small molecule drug substances. It should be no surprise that there are over 100 peptide drugs on the market and many more in development.

The challenge with peptides, like other biologics, is that drug formulations typically must be administered via injection to achieve high bioavailability. Researchers are developing approaches to the formulation of oral peptide drugs using specialized excipients, such as enzyme inhibitors and permeation enhancers, mucoadhesive polymeric systems and carrier systems (such as emulsions, nanoparticles, microspheres, and liposomes), among other technologies.

Because the formulation development of oral peptide drugs is so challenging, many pharmaceutical companies rely on CDMOs with specialized expertise in this field. With our extensive experience in formulation development for oral drug delivery, including knowledge of specialized excipients, UPM is ideally suited to tackle the challenge presented by peptides. We also have the latest chromatography column technology available for peptide analysis and have developed proprietary methods to ensure that the techniques are appropriate, robust, and readily transferrable to commercial quality control.

In addition, UPM has low-humidity suites designed to provide the type of controlled environment required during the manufacture of water- and moisture-sensitive peptide products. We also have low-humidity solutions in our packaging area and use heavy (thick-wall) bottles, desiccants, oxygen absorber and nitrogen purging to stabilize final products during storage.

UPM has been involved in the formulation development of two of the few FDA-approved oral peptide products. We invested in large-scale manufacturing capacity specifically for the commercial production of one of these peptides. Three additional oral peptide drugs are at the IND stage at UPM.

STREAMLINING DEVELOPMENT WITH POWDER-IN-CAPSULE FORMULATIONS

UPM uses the Xcelodose® precision powder micro-dosing system from Capsugel to obtain accurate and reproducible dosing down to as little as 100 micrograms of powder and can be used for dosing APIs alone, APIs blended with bulking agents and APIs in formulations.

The Xcelodose® system is particularly useful for preparing capsules containing just microgram quantities of API for use in stability studies. It also requires minimal formulation development. Simplifying these activities and minimizing the

amount of API required reduces both cost and the time it takes to get into the clinic.

It is therefore an appealing option for many start-up companies concerned about consumption of their expensive APIs during early phase testing, while allowing them to get their product into human subjects as quickly as possible.

OFFLINE SERIALIZATION

In the United States, serialization requirements were established in the Drug Quality and Security Act (DQSA), which became law in November 2013. The law applies to manufacturers, repackagers, wholesale distributors, dispensers and third-party logistics providers.

Implementing an effective serialization solution is challenging. In addition to its cost, serialization impacts many different company operations and thus requires input from representatives of all affected groups. Labels must be redesigned, and large quantities of new data must be properly managed and shared with appropriate partners throughout the supply chain. Contract manufacturers have the added challenge of needing to serialize different drug substances and/or drug products for many different clients, each with its own understanding of serialization and related set of expectations.

When developing our serialization solution at UPM, we recognized the need to maintain a high level of security while implementing a flexible track-and-trace solution that allows for tailored customer service, combined with robust and reliable performance. We adopted an offline serialization strategy, with the equipment existing as its own workstation, to have the greatest flexibility in supporting our three packaging lines. Labels are preprinted in advance, electronically verified, and then applied to bottles or cartons. This approach allows us to troubleshoot problems without tying up a packaging line. As a result, we are able to maintain production efficiencies and maximize capacities. Importantly, we are capable of working with whichever serialization codes are used by our clients.

Currently UPM is preparing for the next level of serialization – aggregation – in which labeling, including printing, application and verification, will be required online.

TAKING CLIENTS TO COMMERCIALIZATION

UPM operates from our Bristol, Tennessee plant, previously owned by Pfizer. Here, we are well-positioned with a Solids Formulation R&D Facility, modern manufacturing suites, and a state-of-the-art, full-service analytical laboratory to support the production of solid and semi-solid products at batch sizes from 100 g to 1000 kg. Two high-speed packaging lines with serialization capabilities enable basic packaging for solid dose products. UPM also has a separate 250,000-ft² warehouse and provides warehousing and distribution services.

We have had numerous projects advance from the proof-of-concept stage to commercial production, and the bulk of our clients are now involved in later-stage development projects. We are therefore focused on enhancing services for these clients, including supporting scale-up and the production of registration batches, and are serving as a second supplier for several marketed products. Early stage support will continue to be provided for legacy clients and promising new projects.

At present, we have the capability to produce 700 million capsule units and 3.5 billion tablet units per year, with 50% of this capacity spoken for by 2021. We therefore have the capacity to onboard new business without creating any conflicts with our existing client projects. UPM's experienced group of technical services scientists have an extensive background in scale-up, technology transfer, process development and validation and can support client products into commercial manufacturing.

We regularly receive requests for work in all of our commercial capabilities: tablets, capsules, semisolids, immediate-release, sustained-release, controlled substances, potent compounds, and drug and device combinations. We can support orphan drugs 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 projects and clinical supplies. As a full-service CDMO, UPM has the capability to succeed in all of these categories of work. P

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Joseph Szczesiul serves as Director of Technical Services in UPM's Manufacturing department. He has over 30 years experience as a manager and scientist in formulation, process development, technology transfer and manufacturing support, with expertise in a variety of tablet and capsule modified release technologies.

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Social Networking and Information Exchange at China Pharma Week

Taking place concurrently with the internationally esteemed trade show CPhI China, China Pharma Week is a full five days of events geared toward expanding the network and knowledge of all visitors and attendees. China Pharma Week serves as the ultimate bolster to CPhI China, offering guests even more insight into the industry, including the opportunity to develop connections and learn about key themes.

Held for the third time this year from June 17–21 in Shanghai, China Pharma Week will cover themes central to the industry, including Leadership, Business, Networking, Recognition, Knowledge, and Innovation in the pharmaceutical industry.

CREATING A CUSTOMIZED PROGRAM

Attendees can create their own experience throughout the week by attending conferences that address their personal interests. Chinese and foreign pharmaceutical regulations and new policies will be covered extensively throughout the week and across conferences. Other notable topics include an analysis of key export markets and a discussion on overseas market development.

FACILITATING INDUSTRY NETWORKING

China Pharma Week is organized to be a catalyst for negotiation and to foster cooperation and partnership. With over 20 conferences and events over a total of five days, the possibilities for new business are extraordinary.

SPECIFIC HIGHLIGHTS OF CHINA PHARMA WEEK WILL INCLUDE THE FOLLOWING EVENTS AND HAPPENINGS:

The 10th China–World CEO Summit
For the key "Leadership" event under the theme, executives from some of the most respected organizations in the industry will share firsthand experience and practical advice for success, focusing on the impacts of policy in the market environment.

CPhI Networking Dinner (Invitation Only)
This invitation-only event will feature prominent guests from across the industry, including government officials, exhibitors, and experts both from China and internationally.

International Agencies Updates and Q&A
Representatives from the NMPA, FDA, EDQM, WHO, and drug regulators as well as pharmacopoeia commissions of various countries will be speaking on recent changes in drug regulatory policies and regulations. This open-forum Q&A is intended to help attendees improve their product registration applications and quality system construction and to demonstrate that Chinese pharma regulations are on par with international standards.

2019 CPhI / Rx-360 China Supply Chain Security Conference
The 2019 CPhI China Supply Chain Security Conference will be hosted in conjunction with Rx-360, an international pharmaceutical supply chain consortium featuring speakers representing some of the most recognized companies in the industry.

2019 Award for Top 100 Internationalized Companies
To raise the international recognition of Chinese pharmaceutical enterprises, the China Chamber of Commerce for Import & Export of Medicines & Health Products (CCCMHPIE) will hold the 4th edition of the Award for Top 100 Internationalized Companies. Winners will be selected based on product export, international registration, overseas M&A, and international cooperation, and will be chosen by the public, CPhI overseas visitors, and expert judges.

2019 Natural Extracts & Products Cocktail Party (Innovation Award & Networking)
This event will feature new product launches and promote trade development in an informal networking atmosphere.

The 9th CPhI Buyers Sourcing Event
Attendees of the 9th annual CPhI Buyers Sourcing Event can expect a specialized procurement matchmaking team to recommend quality suppliers based on member qualifications, buying leads and productivity, using databases in combination with the exhibition and the B2B website. The goal of the event is to bring buyers and sellers closer together via one-on-one and face-to-face meetings to speed up procurement time and increase efficiency.

Innovation Gallery & Tour
The Innovation Gallery & Tour will feature the latest packaging solutions, simulated cleanrooms, clean equipment, and fine projects, and showcase the quality plant extract suppliers and quality products jointly certified by CCCMHPIE, National Science Foundation (NSF), United States Pharmacopeial Convention (USP), SGS, and Intertek.

Plant Visit
The guests of the Plant Visit will witness manufacturing technology and gain an in-depth understanding of China's manufacturing culture. P

CPHI & P-MEC CHINA 2019
is sponsored by UBM EMEA, CCCMHPIE and UBM Sinoexpo and will be held:

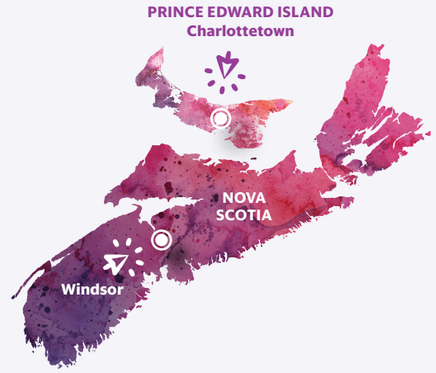
JUNE 18–20 2019
at SNIEC in Shanghai, China.

Visit the exhibition website **www.cphi-china.cn/en** to register for China Pharma Week and CPhI China online and be a part of the ultimate industry event for all pharmaceutical practitioners!

COME HOME TO BIOVECTRA

BioVectra is a Canadian contract development and manufacturing organization with nearly 50 years of experience supporting global pharmaceutical and biotech companies in their quest to produce medicines that improve and extend patient lives.

As an innovative and reliable, science-based company with a strong regulatory track record, we have embarked on a five-year, $144.6 million (CAD) expansion project to enhance our capabilities in both Charlottetown, Prince Edward Island and Windsor, Nova Scotia. **Over that period, we will be adding 150 highly skilled, full-time employees and are now seeking talented people interested in working at our exciting, growing company located in beautiful Atlantic Canada.**



“Thanks to innovations in life sciences, Canadians are living longer, healthier lives than ever before. Canadian companies like BioVectra are creating new jobs and establishing themselves as global leaders in producing lifesaving treatments for serious illnesses that affect millions of people around the world. ***Today, we are not only investing in an innovative Canadian business, but also in Canadians and the future prosperity of our country.***

The Rt. Hon. Justin Trudeau, Prime Minister of Canada, announcing the Canadian government’s Strategic Innovation Fund contribution to **BioVectra’s expansion project.**

PART 1

Company Overview

BioVectra is a vibrant company guided by the principles of performance, transparency, empowerment and accountability. Operating out of four cGMP facilities in Atlantic Canada, we provide services to our client base, which includes most of the top 20 biopharmaceutical companies in the world.

Our core competencies include both microbial fermentation and synthetic chemistry. With our scaled manufacturing setup, we are positioned to support projects throughout the entire life cycle of a product, from early development and clinical stages all the way to commercial manufacturing. Our active pharmaceutical ingredients have been used in therapeutics for the treatment of cancer, kidney disease, cardiovascular disease, autoimmune disease, multiple sclerosis and many other serious diseases.

BIOVECTRA’S VISION AND MISSION

As a developer and manufacturer of pharmaceutical products that improve health, BioVectra’s vision is to be a responsive, quality-oriented drug substance development and manufacturing partner for companies developing specialized therapeutics. We make ongoing selected and qualified investments to continue to serve our clients and grow alongside them.

We achieve these goals by serving as seamless extensions of our clients' businesses and an integral partner in their growth. Quality and safety are our top priorities. Providing our employees with a positive work environment and opportunities for career advancement is fundamental to our success.

FERMENTATION AND MUCH MORE

BioVectra has developed full-service capabilities for cGMP custom API manufacturing in both synthetic chemistry and microbial/fungal fermentation. A suite of ancillary analytical, process development, regulatory, packaging and labeling capabilities complements these services.

By offering both fermentation and chemical modification services, our clients can simplify their supply chains and streamline their development processes, reducing cost and time to market. For instance, BioVectra has helped clients reduce the number of synthetic steps for complex projects by as much as 75% using fermentation to produce complex intermediates or APIs. We have worked on over 100 chemical API projects, including complex multi-step syntheses, asymmetric chiral introductions, natural products, analogues and inorganics.

BioVectra also has the specialized facilities and equipment necessary to ensure containment of processes for the production of highly potent APIs (HPAPIs) with occupational exposure limit (OEL) levels of < 20 ng/m^3. We have manufactured more than 10 HPAPIs in the last decade up to 5-kg batch sizes. Key aspects of our approach to these projects are comprehensive potent handling training for our scientists and manufacturing staff and extensive environmental monitoring.

In addition to microbial fermentation for the production of smaller molecules, BioVectra has established expertise in the manufacture of biologic substances, with scalable cGMP operations from 30 L to 17,000 L. These projects are implemented at our new dedicated state-of-the-art facility in Windsor, Nova Scotia, which is equipped for bioprocessing with a range of biosafety level one (BSL-1) expression systems. Other niche capabilities offered include controlled substances, PEGylation reagents and biomass extraction and purification.

BioVectra also offers a range of catalog products, including bioprocessing, diagnostic, molecular biology and MPEG reagents, for a unique combination of capabilities. We are a highly diversified CDMO positioned to serve as a single development and manufacturing partner for pharmaceutical companies producing novel therapies that require expertise in the processing of both small and large molecules. In addition, these services are available at R&D to commercial scales, allowing customers to avoid the time and cost associated with technology transfer from one service provider to the next.

CUSTOMER FOCUS

BioVectra's tailored and personalized approach to process development and scale-up helps our clients reduce the time it takes to move from one development phase to the next. Success is achieved through the joint effort of BioVectra and customer R&D, manufacturing, quality and procurement experts.

As a mid-sized company, we are also very nimble. We react quickly to changes in project or market needs. Clients of BioVectra also benefit from our high level of employee retention. The same people that work on an initial process development project apply their experience, expertise and process knowledge all the way to commercialization and beyond.

INVESTING IN CLIENT SUCCESS

We also make significant investments to ensure the success of client projects. In fact, BioVectra first became involved in fermentation at the request of a client over 15 years ago. Since then, we have repeatedly expanded capacity and capabilities to support the commercialization of client products. We are committed to engineering and designing plants specifically for clients that drive efficiency and value as they achieve commercial success.

BioVectra also invests in infrastructure upgrades and enhancement of core competencies on a continual basis. In fact, the recent addition of a further 30,000 L of fermentation capacity at our API manufacturing facility in Nova Scotia makes BioVectra the CDMO with the most extensive ranges of fermentation and downstream purification capabilities in North America.

BIOVECTRA'S CULTURE

Since 1970, BioVectra has been committed to exceptional service with a solutions-driven approach. Our culture is built on the shared corporate values of teamwork, respect, professionalism, quality and care. We are a dynamic team of dedicated professionals united by common goals, shared values and an entrepreneurial spirit. We work together and apply our diverse knowledge to solve our customers' problems and challenges.

BioVectra maintains a quality-focused culture to ensure the highest priority is placed on the safety, effectiveness and reliability of our products.

PART 2

Passion

Meet BioVectra's People

Pape O. Sine

Buyer, Charlottetown, P.E.I.

Pape O. Sine, a Senegal native who has worked as a buyer for BioVectra since August of 2016, injects passion into everything, especially his work and education.

"It is well beyond what I expected," Sine said of his time so far with the company. "I was looking for a company that would let me really dive into what I wanted to do in my career and enhance my skills. I really appreciate the company culture, where there is such a diverse workforce and teamwork is really promoted."

Sine moved to Canada in 2008 to enroll in the University of Moncton in New Brunswick, where he graduated as the valedictorian of his Business Administration class. He then moved to Prince Edward Island (P.E.I.) in search of more opportunity before joining the team at BioVectra.

"This company has people working here from all over the world and I really appreciated that, as I felt I was not the only one from away," Sine said. "If you started naming all the countries, it would be unbelievable."

In his role as a buyer, Sine purchases raw materials and consumables for the company from distributors all over the world. In spite of being so globally connected, he is happiest when he sets down the phone and has the time to bask in the Atlantic Canada lifestyle he has grown to love. Living in downtown Charlottetown, Sine often takes his bicycle to work, enjoying the Confederation trail system through the city.

Sine has also been able to further his own education since taking his position. In addition to his full-time job at BioVectra, Sine is enrolled at the University of Prince Edward Island (U.P.E.I.) in Charlottetown, where he attends classes every second Friday and Saturday in pursuit of a Master of Business Administration degree.

"BioVectra has been very supportive of me doing this to further my career," Sine said. "It is a great work-life balance. When I wanted to do it, I asked my supervisor and told him for me I think it is the right time. I felt I was in a company that I was comfortable enough to do both, and BioVectra has proved me right. I still remember the day I got accepted; my coworkers and supervisor surprised me with a cake. There are a lot of opportunities to grow your career here."

> ***Our culture is built on the shared corporate values of teamwork, respect, professionalism, quality and care.*** *We are a dynamic team of dedicated professionals united by common goals, shared values and an entrepreneurial spirit.*

Krista Affleck

Director, Analytical Support and Development, Charlottetown, P.E.I.

Experience

Sine, though easily transitioning into BioVectra's company culture in such a short period of time, is a relative newcomer to the organization. Krista Affleck, on the other hand, has gone the distance with the company, having actually joined BioVectra's forerunner, Diagnostic Chemicals Ltd., over 15 years ago.

A recent college graduate with a young child to provide for, Affleck was looking for employment that would allow her to build a life and family without leaving her home province. After completing her U.P.E.I. studies at the company, she decided it was an exact fit for her and transitioned to a full-time position. In the years since, Affleck has grown her family more than she imagined and even met her current husband, Ankur Deshpande, at the company – the two now have two children.

Krista has held seven different positions in the company since her first day, starting out in Quality Control and then moving on to the Analytical department, where she has been for 10 years. She currently serves as Director, Analytical Support and Development at the Hillstrom facility in Charlottetown, one of three in the provincial capital. It should be noted that BioVectra is also opening a new operation in Windsor, Nova Scotia.

"There is opportunity to move up once you demonstrate your ability to take on more responsibility," Affleck said. "Now we're growing so much and so fast that the people who started out here entry level and now have experience are often the ones who are moving up to manager. Out of the vice presidents, I think half of them moved up through the company, so there are great examples there. There are lots of people who have advanced that way."

> ***There is opportunity to move up*** *once you demonstrate your ability to take on more responsibility.*

Growth

Kathleen Cullen is no stranger to the advancement opportunities afforded by BioVectra, which were a main factor in her decision to permanently settle in her native Charlottetown and join the company as a chemical engineer.

"I like that I am able to work on P.E.I.," Cullen said. "My family is all here – so that is huge – and it's great to get a job in my field at home. A lot of my classmates are working in Fort McMurray." While growing herself, Cullen has watched BioVectra nearly double in size, from 150 employees to over 300 – in only three-and-a-half years. In spite of the large size, BioVectra has managed to retain the small company charm that originally attracted her.

"Any time we have social events or anything, it is really great. If I meet people from other departments, people are really welcoming and want to let you know what they do."

Kathleen Cullen

Chemical Engineer, Charlottetown, P.E.I.

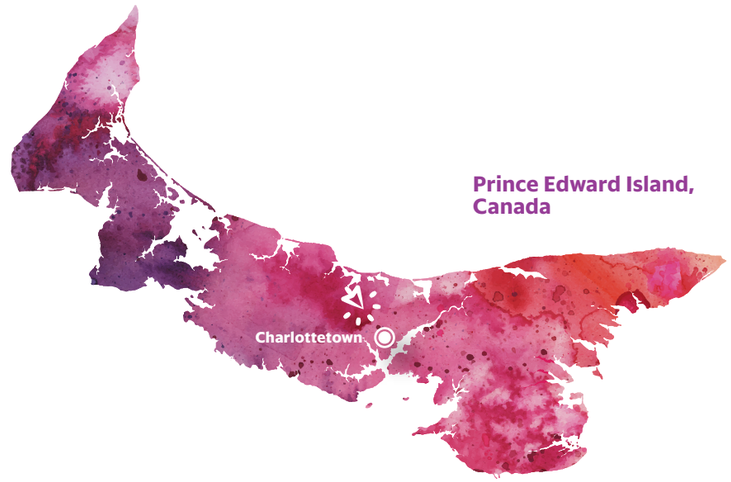
> *In recent years, the ever-growing bioscience sector has become a key pillar of the economic foundation of Prince Edward Island.* ***BioVectra is a key player, being the largest employer within the bioscience community, working within a collaborative bioscience business ecosystem.***

Being a member of the BioVectra team has also altered Cullen's outlook on both work and life. She is especially drawn to the fact that the company will let you train and learn different skill sets apart from the ones you had when you were originally hired. "Since I have started here, I have seen such growth in myself both professionally and personally. If you show initiative in anything or willingness to learn new skills, they are very supportive of that."

To Cullen, a move to the BioVectra team is definitely a solid choice, where you can enjoy a global company without sacrificing the East Coast lifestyle.

"Come to BioVectra if you're interested in a fast-paced environment that is always changing but is really innovative and cutting edge," Cullen said. "I feel like this is a company that has strong growth in its future; we're not just doing projects that have been hanging around for a couple of years."

PART 3A



Prince Edward Island – The Garden Province

Prince Edward Island (P.E.I.) is the smallest of Canada's 10 provinces. It is a red-colored sandstone island in the Gulf of St. Lawrence, measuring just 224 kilometers (km) long by 6 km at its narrowest to 64 km at its widest. P.E.I. boasts 800 km of beaches. It is one of four Canadian provinces that borders the Atlantic Ocean and is arguably one of the country's most beautiful places to live. P.E.I. is a convenient 200 km north of Halifax, Nova Scotia and 600 km east of Québec City.

The capital and largest city in P.E.I. is Charlottetown, boasting ~65,000 of the island's 160,000 inhabitants. The coastal and pastoral beauty of P.E.I. is the initial attraction, but people choose to stay because of the small-town feeling, non-existent rush hours, short commutes to work, low crime rate and quality of education.

In recent years, the ever-growing bioscience sector has become a key pillar of the economic foundation of P.E.I. BioVectra is a key player, being the largest employer within the bioscience community, working within a collaborative bioscience business ecosystem.

HOUSING, EDUCATION AND HEALTHCARE ON P.E.I.

The average price of a house on P.E.I. is around $200,000 (CAD), making it one of the most affordable places to live in the country.

> ***Our clients develop important, life-saving medicines for people around the globe.***
> *This exciting expansion project is designed to help propel us toward being a top-tier player in the biologics field, where many therapies are advancing rapidly and changing the way healthcare is delivered.*
>
> Heather Delage, General Manager, Windsor

The Prince Edward Island school system provides free education from Early Childhood Education programs through the end of high school. A comprehensive program of apprenticeships and training also exists to help people entering skilled trades after secondary school. P.E.I. is home to the University of Prince Edward Island, which includes Holland College, a publicly funded community college with 11 campuses throughout the province, and the world-renowned Atlantic Veterinary College.

Most basic health services in Canada are offered at no direct cost. The Medical Care Plan of Prince Edward Island ensures that all medically necessary physician services and surgical–dental services are provided to all citizens and permanent residents.

P.E.I. CULTURE AND QUALITY OF LIFE

P.E.I. is famous for its stunning beaches, pastoral landscapes and cozy towns. It has a vibrant, distinct and welcoming culture that served as the inspiration for Lucy Maud Montgomery's famous novel *Anne of Green Gables*. It also has an excellent reputation for safety and a friendly "know-your-neighbor" environment.

A wealth of outdoor activities are accessible across the island, including golf courses, scenic walking, skiing and biking trails, hunting/fishing areas and archeological digs. There are also historical villages, museums and art and music festivals to enjoy. Delightful farm-to-table cuisine and fresh seafood also contribute to a fulfilling and relaxing lifestyle!

Overall, P.E.I. provides a way to enjoy small-town life with all the conveniences of the modern world.

> ***BioVectra expects to create 150 full-time jobs over five years, including 40 in Charlottetown and 110 in Windsor.***

PART 3B

Nova Scotia – Canada's Ocean Playground

Nova Scotia is also one of Canada's four Atlantic provinces, but it has a population of nearly one million. The capital Halifax, with 400,000 people, is the largest city in the province and one of Canada's major seaports. Nova Scotia is full of some of the most beautiful small towns and heritage sites and breathtaking national and provincial parks, as well as the Bay of Fundy – one of Canada's seven natural wonders.

BioVectra's biologics manufacturing facility is located in Windsor, which is 66 km northwest of Halifax. The town has approximately 3,500 residents and claims to be the birthplace of ice hockey. There are six post-secondary institutions within a 45-minute drive of Windsor.

Outside of Halifax, Nova Scotia has strong forestry, mining and specialized agricultural industries. The province is also experiencing growth in the oil and gas sector, with extensive exploration of offshore reserves. In addition, the beauty of Nova Scotia attracts nearly two million visitors each year.

HOUSING, EDUCATION AND HEALTHCARE IN NOVA SCOTIA

Nova Scotia has affordable housing, with the average price of a house in the Halifax area just $281,000 (CAD) – about half the cost for a similarly sized home in Canada's other major cities. Free bilingual schooling (English and French) is available from kindergarten through grade 12. Several universities, technical/professional colleges and apprenticeship programs are located in the province.

NOVA SCOTIA CULTURE AND QUALITY OF LIFE

Nova Scotians are friendly and welcoming, with a culture generated by the fusion of many different groups that have settled in the province over time.

Whether you prefer sandy beaches and coastal cliffs or the culture and energy of city life, you're never far from either in Nova Scotia – or more than 30 minutes from the ocean. There is always something to do, regardless of the season, with skiing and skating in the winter, hiking, golf and surfing in the summer and theater, music festivals and museums all year round. You can also enjoy the world-renowned seafood, which is a livable luxury for residents.

PART 4

Expansion Project Creates New Opportunities

In March 2019, BioVectra announced a five-year, $144.6 million (CAD) expansion project to further develop its biopharmaceutical contract development and manufacturing capabilities at both the Windsor, Nova Scotia and Charlottetown, Prince Edward Island sites.

In Charlottetown, the project will expand the manufacturing capacity of the site's current active pharmaceutical ingredient (API) operations using microbial fermentation. In Windsor, BioVectra will expand its capabilities for producing biologic drugs, including the construction of a new facility dedicated to mammalian cell culture.

"Our clients develop important, life-saving medicines for people around the globe," noted Heather Delage, General Manager of the Windsor site. "This exciting expansion project is designed to help propel us toward being a top-tier player in the biologics field, where many therapies are advancing rapidly and changing the way healthcare is delivered."

BioVectra expects to create 150 full-time jobs over five years, including 40 in Charlottetown and 110 in Windsor. These include highly skilled positions across technical and manufacturing operations, including R&D, process engineering, analytical chemistry and technology transfer.

We invite you to visit our website for a current list of career opportunities
www.biovectra.com/careers

APPLYING ENZYMATIC SYNTHESIS FOR CHIRAL MOLECULES

→ BY **JULIETTE MARTIN, Ph.D.,** AND **SERGIO KREIMERMAN, Ph.D.,** SEQENS

Advances in our understanding of enzymatic transformations and the increased availability of enzymes engineered for use in fine chemical synthesis is making biocatalysis attractive for the production of chiral pharmaceutical intermediates and APIs. SEQENS is leveraging its expertise in chemo- and biocatalysis to identify cost-effective routes to increasingly complex small molecule drug substances with chiral centers.

THE IMPORTANCE OF CHIRALITY

Chirality is a fundamental property of organic molecules that contain asymmetric carbon atoms with four distinct binding groups, which can exist as paired stereoisomers – known as enantiomers – that form mirror images of one another. These enantiomers are often referred to as right- and left-handed. They not only rotate polarized light in opposite directions, they exhibit very different interactions with other chiral molecules.

Both the biologically active molecules targeted by small molecule drugs and their constituent building blocks (nucleic acids, amino acids) are chiral. Overwhelmingly, biological molecules exhibit strict homochirality – natural amino acids are left-handed, while DNA and sugars are right-handed.

Small molecule active pharmaceutical ingredients are also typically chiral, and classical production methods result in mixtures of paired enantiomers. Given that target molecules are homochiral, the two enantiomeric forms of a chiral API could exhibit different pharmacokinetic and pharmacodynamic behaviors – and different efficacies and toxicities. It is also possible for one enantiomer to be bioactive and the other not, or, in the most extreme cases, for one enantiomer to provide a therapeutic effect while the other is highly toxic. In some cases, the members of an enantiomer pair have been found to be effective in the treatment of very different diseases.

Regulatory agencies do not require the development of chiral drugs as single enantiomers. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), however, require pharmaceutical companies to comprehensively evaluate the properties of each enantiomer individually as well as the racemic (50:50) mixture of a chiral API.

NEW WAY OF THINKING

Small molecule drug candidates in the pipeline today are becoming more complex. It is common for an API under development today to have multiple chiral centers. The increasing complexity has driven the need for new approaches to obtaining chirally pure enantiomers. When pharmaceutical chemists first began developing routes for the preparation of single enantiomers of chiral APIs, they largely relied on separation technologies. The API was synthesized as a racemic mixture, and then the desired enantiomer was separated from the undesired one.

This approach has several disadvantages. It is often difficult to separate two enantiomers from one another. In many cases, the desired isomer remains contaminated with the undesired molecule. Even if an effective method is developed, the remaining enantiomer – often a very expensive material – becomes a waste product. As a result, this approach involves a significant waste of time and resources and is therefore very costly.

To avoid these problems, chemists began seeking methods for the selective production of single enantiomers of chiral molecules – and, to do so, they turned to catalysis. Catalysts mediate complex transformations but do not take part in them. Specially designed catalysts can mediate asymmetric transformations that result in the formation of several bonds and chiral centers, all in one step.

As an example, compared with kinetic resolutions of racemic mixtures, enzymatic desymmetrizations of *meso* compounds allow the synthesis of chiral derivatives with a 100% theoretical yield.

SEQENS has developed the asymmetric mono hydrolysis of the corresponding prochiral diester. After ammonolysis of the remaining ester, the corresponding amide was finally involved in a Hofmann rearrangement to afford R-baclofen (Fig. 1A).

After screening Protéus's enzyme portfolio, a hit was identified allowing the transformation of the prochiral diester with very high enanselectivity (> 99% ee). Moreover, the kinetic and thermodynamic analysis was further addressed for shedding insights into the desymmetrization process. The full R-baclofen process was then scaled-up at SEQENS's R&D center based in Porcheville.

FIGURE 1A:

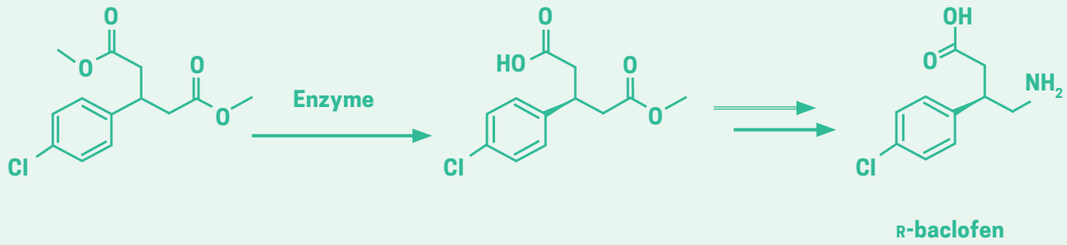
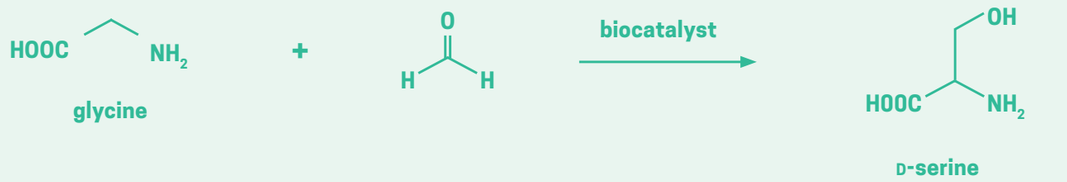


FIGURE 1B:



CONSISTENT WITH THE HOMOCHIRALITY OF BIOMOLECULES, THE **REACTIONS CATALYZED BY ENZYMES GENERALLY EXHIBIT HIGH STEREO- AND REGIOSELECTIVITIES, GENERATING PRODUCTS HIGHLY ENRICHED FOR SINGLE ENANTIOMERS.**

Furthermore, SEQENS has developed an enzymatic process for manufacturing D-serine product on a multiton scale; both productivity and high enantioselectivity were achieved (Fig. 1B). Protéus by SEQENS has developed its own enzyme library, with more than 300 enzymes available off-the-shelf.

BIOCATALYSIS VS. CHEMOCATALYSIS

Synthetic chemists have the choice of using chemo- or biocatalysts. Chemocatalysts typically are transition-metal complexes with complicated structures designed to bind in specific ways to specific substrates to achieve a desired and highly selective transformation. While most are designed to perform homogenous catalysis in solution, heterogeneous catalysts are also available. Often, there are several choices of chemocatalysts for mediating a certain type of reaction.

Like chemocatalysts, biocatalysts are designed to perform highly selective and specific chemistry, but can be composed of engineered enzymes. They have the advantage of being heavy metal free, and thus do not require the removal of metal impurities after completion of a reaction. Consistent with the homochirality of biomolecules, the reactions catalyzed by enzymes generally exhibit high stereo- and regioselectivities, generating products highly enriched for single enantiomers. Additionally, biocatalysts are highly efficient, allowing catalysis to be performed under mild reaction conditions, with reduced energy consumption and greenhouse gas emissions in comparison to chemical catalysis. Enzymatic reactions are also generally performed in water rather than organic solvents.

WHILE IN SOME CASES THESE OFF-THE-SHELF ENZYMES PROVIDE THE REQUIRED LEVEL OF PERFORMANCE IN TERMS OF YIELD AND SELECTIVITY FOR THE DESIRED ISOMER, **IT IS OFTEN THE CASE THAT SOME OPTIMIZATION IS NECESSARY FOR A SPECIFIC TRANSFORMATION.**

In addition to being used to replace chemocatalysts in straightforward asymmetric reactions, biocatalysis can sometimes be used to complete chiral transformations with significantly fewer steps. Typically, for molecules with more than one of the same type of functional group, chemocatalysts often do not selectively interact with just one of those groups. The others must first be protected, and then, after the asymmetric transformation is completed, be deprotected – potentially adding multiple steps to a synthetic route. In many cases, enzymes have the capability to selectively convert one of many similar functional groups in a molecule, reducing the overall process steps, time and cost.

There are also cases where enzymes are able to achieve transformations that cannot be performed effectively – or at all – using classical chemical methods or chemocatalysts. In many cases, biocatalysts can mediate complex transformations that generate complex intermediates or APIs with multiple chiral centers. Here, biocatalysis affords access to novel structures and can potentially have significant impacts on manufacturing time and cost.

In general, chemocatalysis and biocatalysis are complementary. Having expertise in both methodologies increases the likelihood of identifying the shortest, most efficient and cost-effective route to complex pharmaceutical compounds. The choice of catalytic technique will depend on the target molecule, the availability of different catalysts at industrial scale, the ability to develop appropriate analytical methods and, of course, cost. It is also important to remember that, in some cases, the same intermediate may not be used in a classical chemical synthesis route, as would be required for biocatalysis due to the different selectivities of certain enzymatic reactions.

GROWING NUMBER OF CHOICES

Building a comprehensive toolbox of biocatalysts is now possible due to significant advances in enzyme engineering technologies. Until recently, the number of enzymes suitable for use in the pharmaceutical industry (and available at industrial scale) was limited. In addition, the engineering of enzymes tailored to achieve a specific chiral transformation with high yield and selectivity was a lengthy process. Today, however, many different biocatalysts are available off-the shelf, and the development of customized enzymes can be achieved rapidly.

In the late 1980s, most enzymes used in the pharmaceutical industry at industrial scale were hydrolases, and most commonly lipases. These enzymes mediated the selective hydrolysis of esters. Since the 2000s, however, many additional types of biocatalysis have become available for pharmaceutical manufacturing, including nitrilases, transaminases, acyltransferases, epoxide hydrolases, ketoreductases and iminereductases, among others. The armentarium of commercially available enzymes continues to expand almost on a daily basis.

This growing array of enzyme choices allows route development chemists to consider multiple synthetic strategies and identify the best route possible. Evaluation of technical and cost considerations for the multitude of chemo- and biocatalysts available for achieving complex, yet highly stereoselective transformations helps determine the most appropriate methods for each step in an overall synthesis.

ENGINEERING SOLUTIONS

While in some cases these off-the-shelf enzymes provide the required level of performance in terms of yield and selectivity for the desired isomer, it is often the case that some optimization is necessary for a specific transformation. Given the numerous advances in rapid genome sequencing, site-specific mutagenesis, directed evolution, computational tools and other techniques, it is now possible to rapidly and efficiently engineer robust enzymes with tailored biocatalytic activity.

The key question becomes one of lead time. If an off-the-shelf enzyme is suitable, then lead times are no different than those for purchasing other key raw materials. If an enzyme must be engineered, the lead time will be longer; once the engineering is completed, the enzyme must be produced – typically via fermentation – and downstream processed. Procedures and analytical methods must be developed to ensure that residues linked to enzyme production are purged from the catalyst.

AT SEQENS, WE ARE IDEALLY POSITIONED TO BRING TOGETHER EXTENSIVE EXPERTISE IN ENZYMATIC TECHNOLOGIES AND PHARMACEUTICAL ROUTE DEVELOPMENT. **WE HAVE EXPERIENCE DEVELOPING OPTIMIZED ENZYMES FOR SPECIFIC TRANSFORMATIONS AND CAN EVEN PRODUCE IMMOBILIZED BIOCATALYSTS IF APPROPRIATE.**

INTEGRATED KNOW-HOW IN ASYMMETRIC SYNTHESIS

SEQENS was formed in December 2018 when Novacap took over Uetikon, PCAS, including Protéus and PCI Synthesis. With 24 manufacturing plants and three R&D centers in Europe, North America and Asia, we are an integrated global leader in pharmaceutical synthesis and specialty ingredients.

Our greatest expertise lies in developing and producing highly complex molecules using a unique skillset and a very broad continuum of technologies that encompasses both chemo- and biocatalysis. At SEQENS, we are ideally positioned to bring together extensive expertise in enzymatic technologies and synthetic route development. We have experience developing optimized enzymes for specific transformations and can even produce immobilized biocatalysts if appropriate.

As a one-stop shop, we provide support to clients from the lab and exploratory stages through route design, process development and scale-up to clinical manufacturing and commercial production for all types of APIs, including complex chiral molecules. We can produce intermediates in our non-GMP facilities and clinical and commercial materials at our GMP sites using our integrated capabilities for asymmetric synthesis and processing.

The ability to produce raw materials, intermediates and APIs within one company ensures that we develop the most cost-competitive synthetic strategies for chiral APIs, which may not be possible if raw materials and intermediates are purchased from external sources. Our in-house catalyst teams at both our non-GMP and GMP sites collaborate to identify the best synthetic routes and develop processes that are practical for implementation at commercial scale.

In addition, with respect to biocatalysis, which is still a newer technology in the pharma industry, our process development, engineering, production, analytical and regulatory groups collaborate and share their knowledge and understanding to rapidly and efficiently develop optimized, compliant manufacturing processes. The experience we have gained over the last several years, working on many different projects, gives us a real competitive advantage and directly benefits our customers. P

ABOUT THE AUTHORS

Juliette Martin, Ph.D.
General Manager of Protéus, SEQENS

After completing her Ph.D. in organic synthesis at the University of Caen (France), **Juliette** conducted an industrial postdoctoral fellowship in asymmetric chemocatalysis at Zeneca Life Science Molecules in the UK. In 1999, she joined Avecia (UK) as R&D Team Manager focusing on New Technology Platforms involving chemo- and biocatalysis. In 2006, she joined SEQENS once the new joint venture was created with the biotech company Protéus (France). In 2009, she became R&D Manager focusing on some key technologies in process development. She then became Head of Biocatalysis for Pharma Synthesis. In 2012, she was appointed General Manager of Protéus.

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Following a bachelor's of science from Universidad de la República in Montevideo, **Sergio** went to Japan, where he obtained a master's and Ph.D. degree from Osaka University in organic chemistry, followed by a Master's of Business from IAE – Université Pantheon Sorbonne in Paris. After working on lanoline with Lanco, medicinal chemistry at the Curie Institute and scientific databases at Becker, he joined SEQENS in 2007. At SEQENS CDMO, Sergio is manager in the Proprietary APIs Business Line, being responsible for the Pharma Development Portfolio. He has overseen the development and successful commercial launch of several APIs from the lab to the plant.

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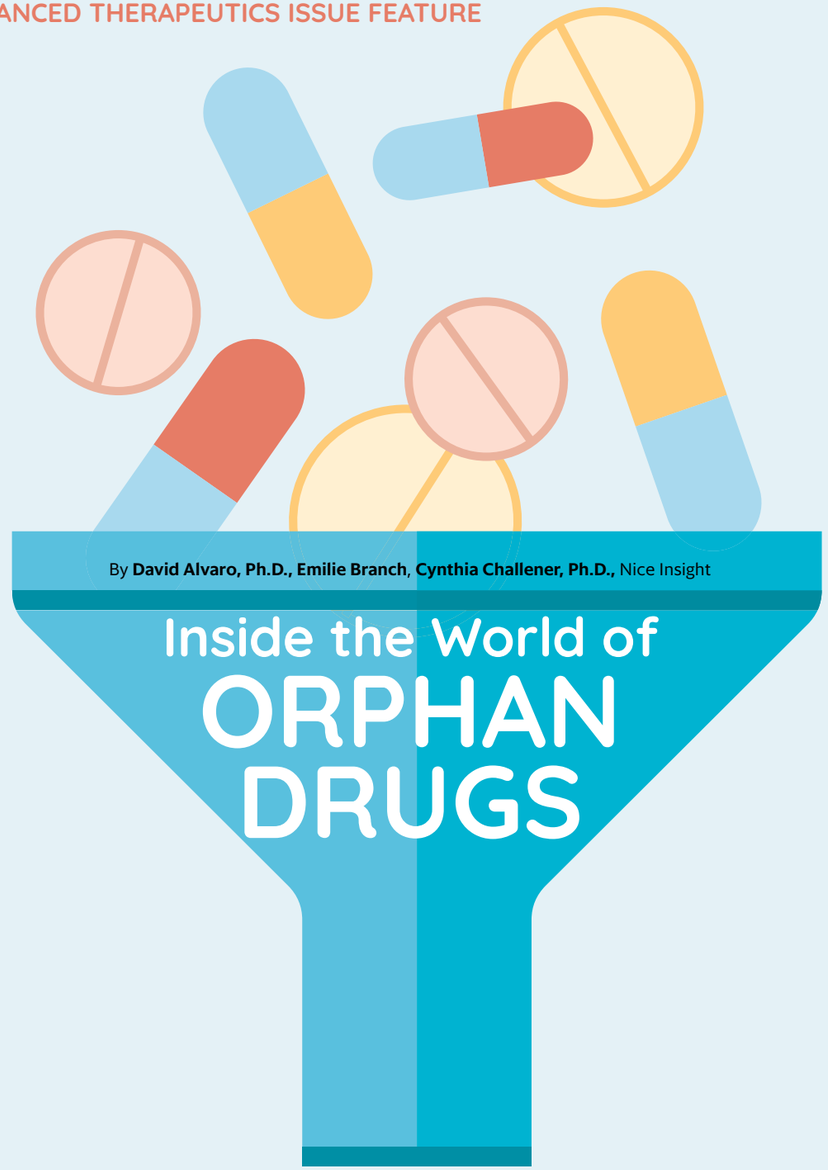

By **David Alvaro, Ph.D., Emilie Branch, Cynthia Challener, Ph.D.,** Nice Insight

Inside the World of ORPHAN DRUGS

PART 1

An Expanding Orphan Drug Market

Since the passage of the Orphan Drug Act in 1983, the number of approvals for rare disease indications and orphan drugs has increased dramatically. The approval rate has been further accelerated since the implementation of the Food and Drug Administration's (FDA) orphan drug modernization plan.

Increasing Approval Rate

Orphan drugs are intended to treat diseases that affect a limited number of people (<200,000 in the United States). There are currently 7,000–8,000 rare diseases known today, many of which affect children.

Before passage of the Orphan Drug Act (ODA) in 1983, which provides financial incentives in the form of tax breaks and patent exclusivity, only a few orphan drugs had been approved in the United States to treat rare diseases – just 34 from 1967 to 1983.[1] By mid-2018, nearly 7,400 orphan drug designation requests were submitted to the FDA, and, as of August 2018, a total of 503 unique orphan drugs had been approved for 731 different orphan indications. Of those approved drugs, 78% had orphan-only indications.

Approval of orphan designations and orphan drugs has accelerated in the United States over the last 2.5 years due to the implementation of the FDA's orphan drug modernization plan, which is intended to eliminate the backlog of existing designation requests and ensure timely review of new applications.[2] The greatest number of new orphan drug designations and approvals since passage of the ODA were granted by the FDA in 2017 and 2018,[1] and 2019 appears to be on a similar track.

In 2017 alone, 429 unique drug candidates were awarded orphan drug designations, up from 320 in 2016 – a 43% increase.[2] Eighty new orphan indications were approved by the agency that year.[1] Furthermore, in 2014, 2015, 2016 and 2017, 41%, 47%, 45% and 40% of new molecular entities (NMEs), respectively, approved by the FDA's Center for Drug Evaluation and Research (CDER) were orphan drugs.[3] When all drugs approved by the FDA in 2017 and 2018 are considered, the percentage of orphan drugs is actually even higher, at 50% or more.[3] This is occurring despite the reduction of the Orphan Drug Tax Credit from 50% of applicable clinical costs to 25% in 2017.[1]

A similar situation is occurring in Europe. Orphan drug approvals by the European Medicine Agency (EMA) more than doubled from eight in 2017 to 17 in 2018, accounting for nearly 29% and 38% of all new drug approvals, respectively.[4] Notably, the accumulated number of orphan drug designations granted by the FDA is more than that issued by the EMA and nearly 10 times greater than the number granted by Japan's Ministry of Health, Labor and Welfare.[2]

Expanding Market

Given the increasing rate of approvals, it is not surprising that the value of the global market for orphan drugs is expected to expand at a healthy rate. Evaluate Pharma predicts that worldwide sales for orphan drugs will increase at a compound annual growth rate (CAGR) of 11.3% from 2018 to 2024, approximately double the rate at which the non-orphan drug market will expand.[2] By 2024, the value of the global orphan drug market is predicted to reach $262 billion, with orphan drugs accounting for 20% of total global prescription drug sales.

Furthermore, by 2024, drug candidates currently in the R&D pipeline that have orphan drug designations are expected to account for slightly more than one-third of all sales generated by all pipeline products between 2018 and 2024.[2] Evaluate Pharma also predicts that 40% of the top 20 candidate orphan drugs could be blockbusters.

Many Therapeutic Classes

Oncology is by far the top therapy area today, and it is expected to remain so going forward. Beyond cancer drugs, the focus is primarily on treatments for blood and central nervous system disorders.[2]

Pediatric indications appeared in approximately one-third of orphan drug approvals between 2000 and 2017, including treatments for inherited blood disorders and metabolic disorders, rare cancers, infectious diseases and auto-inflammatory diseases and disorders, as well as antidotes and medical countermeasures.[5]

In 2017, novel orphan drugs were approved by the FDA to treat patients with lysosomal storage disorders, neuromuscular diseases, such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS), and hemophilia A (the first non-blood product). A new antisense oligonucleotide drug and an effective gene therapy were also approved that year.[1]

In 2018, several orphan drugs were approved for the treatment of rare genetic diseases, including the first small interfering ribonucleic acid (siRNA) therapy and the first RNA-targeting therapeutic designed to reduce the production of human transthyretin (TTR) protein for the

Even though many gene therapies target rare diseases, there are questions about how the FDA characterizes gene therapy products for purposes of orphan drug exclusivity.

treatment of different types of polyneuropathy. The first monoclonal antibody was approved for treatment of types I and II hereditary angioedema, as was the first oral medication (an alternative to enzyme therapy) for the treatment of adults with Fabry disease.[6]

Considerations for Gene Therapies

The first two gene therapies were approved by the FDA in 2017, and numerous candidates are rapidly progressing through clinical trials. Even though many gene therapies target rare diseases, there are questions about how the FDA characterizes gene therapy products for purposes of orphan drug exclusivity.[7]

Specifically, the question relates to whether the FDA considers the transgene component of a gene therapy by itself or the combination of the transgene and the virus or viral vector used to deliver it. The agency's definition must be known in order to determine whether another drug product is the same or different from a gene therapy that has been granted orphan drug designation and thus has patent exclusivity.

Recent comments by the FDA's Office of Orphan Products Development (OOPD) suggest that the agency considers a gene therapy to be the combination of the transgene plus the delivery vehicle for purposes of determining the sameness of different drug products.[7] Under this approach, two gene therapies with the same transgene but different viral vectors would be different products, while those with the same transgenes and only slight differences in the vectors (serotypes or promoter regions) may be considered the same drugs. P

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PART 2

Managing the Risks Associated with Orphan Drug Development and Manufacturing

Orphan drugs present numerous development and manufacturing challenges. Clinical trials can be difficult to set up due to the limited number of possible participants and their disparate locations. Production of novel small APIs and drug products create process design challenges. Manufacture of high-value, low-volume products also requires special considerations.

Technical Challenges

Rare diseases that affect limited patient populations and have not been extensively studied can pose significant research and development challenges for companies looking to identify new drugs to treat them.

In a recent Tufts Center for the Study of Drug Development survey,[1] rare drug developers indicated that they must overcome many different types of challenges owing to the lack of knowledge about disease mechanisms. In addition to an incomplete understanding of the biology underlying these diseases, researchers often do not have information about their natural history and are uncertain how to translate what information has been gathered into useful knowledge for drug development. In addition, they may have to choose between multiple potential disease pathways and establish endpoints and outcome measures without sufficient knowledge or access to biomarkers and animal models.[2] Rare diseases can also present differently in men and women and in children and adults.

Long Development Times

The Tufts study also found that, for orphan drugs approved by the FDA between 1999 and 2012, it took 18% longer on average to go from first patent filing to product launch than it did for all new drugs.[2] A separate analysis of FDA data from 2015 to 2017 revealed

Rare diseases that affect limited patient populations and have not been extensively studied can pose significant research and development challenges for companies looking to identify new drugs to treat them.

that an orphan drug designation does not contribute to accelerated approvals.[3]

Another study found that it can take 10 or more years – and sometimes more than 20 – from receipt of orphan drug designation to marketing approval, with four to eight years the most common timeframe.[4] From 2010 to 2017, the average time from orphan designation to FDA approval was 5.3 years, and the likelihood of FDA approval for an orphan indication was 0.25.[5]

Unique Development Approaches Required

In addition to often limited knowledge, another key factor contributing to the longer development times associated with orphan drugs is the difficulty in establishing clinical trials for very small patient populations. It takes time to recruit patients, and those that do participate are often highly geographically dispersed, so managing the trials can be complex.[6]

Modeling and simulation can help address many of these issues by enabling quantification of drug–disease trial and exposure–response models, providing insight into biomarkers and endpoints and facilitating dose selection and identification of pediatric treatment options. Both are also encouraged by regulators.[7]

Movement away from the traditional requirements for clinical trials is also necessary. Potential patient pools are too small to conduct large randomized controlled trials, let alone two or more pivotal confirmatory studies.[6] A common trial design for international multi-center trials would allow regulatory approval in multiple countries. Approvals based on less comprehensive but sufficient supporting evidence would also enable orphan drugs to reach patients more quickly. While such decisions can be made under specific but infrequent circumstances today, adoption of a clear pathway for orphan drugs that considers the risk/benefit balance in combination with requirements for appropriate postmarketing studies would be a more practical approach.

In a 2017 draft guidance for pediatric orphan drug development, the FDA outlined a new approach involving controlled, multi-arm, multi-company clinical trials, which would allow several products to be tested in a more time-efficient manner and reduce the number of patients needed to receive a placebo.[8]

Manufacturing Hurdles

Orphan drugs are in many cases formulated at high concentrations and administered to limited patient populations, leading to the need, even for commercial products, to manufacture much smaller quantities than have been traditionally required. The drug substances are also often highly complex, requiring novel and sophisticated synthetic routes and production methods (e.g., low temperatures or high pressures), including new types of equipment that can be implemented under GMP conditions.[9] Similarly, flexibility in manufacturing scale is essential for the production of sterile biologic drugs (typically injectables).

The high value and limited quantity of these materials (drug substance and drug product) also pose challenges for analytical method development and validation. Quality-by-design (QbD) and design of experiment (DoE) approaches are increasingly implemented to help ensure the development of robust processes and methods.[9]

The Role of CDMOs

Contract development and manufacturing organizations (CDMOs) have key roles to play in overcoming the manufacturing challenges posed by small-volume orphan drugs.

CDMOs that have adopted QbD and DoE approaches and have established expertise in continuous manufacturing, particularly using modular systems that can be readily replicated, are best suited to support orphan drug projects. They provide lower costs of production and enable in-country manufacturing at multiple locations, leading to more cost-effective and secure supply chains.[10]

CDMOs are also ideal partners for small and emerging pharma companies that are focused on niche, targeted therapies. These firms have limited resources and benefit from tailored, customized support offered by CDMOs with integrated services including process and formulation development, validation, analytical method development, regulatory compliance support and manufacturing activities.[11] Outsourcing partners with the right complements of technical capabilities and experience can accelerate drug development and reduce costs for their clients.

Large pharma companies developing orphan drugs can also benefit from strategic partnerships with smaller CDMOs that are flexible and have experience with both small- and large-volume manufacturing.[12] These CDMOs are adept at designing cost-effective routes to drug substances and formulated products, as well as managing multiple small-volume projects simultaneously, including candidates with accelerated approval designations. They are flexible enough to scale with projects as they move through the development cycle and are capable of producing larger volumes if necessary. P

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PART 3

Navigating the Road to Successful Orphan Drug Commercialization and Launch

Some drug candidates with strong potential to treat rare diseases may not be suitable for commercialization. The development and approval process may be too lengthy and expensive. Establishing a geographically dispersed and highly complex supply chain may not be feasible, and implementing the required postmarketing clinical studies may be very difficult. Pharmaceutical companies are taking a variety of approaches to overcome these challenges.

Drug Repurposing

One such approach to reducing the challenges of orphan drug development is drug repurposing (DRPx). Approximately one-fifth of approved orphan drugs are repurposed existing drug products.[1] For these drugs, development costs and times are significantly reduced (1/20th and ½ compared with NCEs, respectively). The risk of failure is also lower, because the safety profiles of repurposed drugs have already been approved, and the manufacturing processes intellectual property strategies are already established.

Patient-Centric Packaging

Medication adherence continues to be a key issue for the pharmaceutical industry and regulatory agencies. Even for the newest orphan drugs designed to treat rare diseases for which no medications have been previously available, inconvenient or difficult-to-use products may lead to patient noncompliance.

Since orphan drugs generally target much smaller patient populations, it is essential to take into consideration the specific needs and characteristics of the targeted group. Pediatric patients often have very different requirements than adults, and elderly patients have their own preferences. Patient needs with respect to the delivery technology and packaging design should be considered from the earliest stages of a development project, with revisions made throughout clinical trial phases based on actual patient experiences.[2]

Supply Chain Solutions

Although the total number of potential patients is relatively small, orphan drugs must often be delivered to more different locations around the world than non-orphan drugs, including highly remote sites. When orphan drugs are developed as personalized medicines, the complexities are multiplied. Ensuring that the right dose reaches the right patient at the right time and under the right conditions (e.g., temperature control) can be challenging.

If patients cannot receive new medications designed to treat their rare diseases, regardless of how effective the drugs may be, there is no value in commercializing them. Fortunately, these issues can and have been overcome.

Advanced and precise planning is a priority when developing supply chain solutions for rare disease treatments.[3] Five factors should be addressed when planning for an orphan drug supply chain: the number of patients, where they will be treated, any special handling requirements, the expected inventory management needs and the design of the ordering process.[4]

Five factors should be addressed when planning for an orphan drug supply chain: the number of patients, where they will be treated, any special handling requirements, the expected inventory management needs and the design of the ordering process.

Consideration of patient needs from the beginning is important, as is understanding the properties of the drug product and how they may impact labeling and shipping requirements (e.g., packaging materials and design, temperature control, time sensitivity) and customs documentation.[3] Insurance coverage and financial questions for patients must be addressed. It is also essential to understand the impact of increasing patient numbers on manufacturing and distribution needs. Distributors may also need to collect clinical data to support the manufacturer's requirements for demonstration of treatment effectiveness.

Further value can be added by providing patient and provider education programs that cover the unique characteristics of the drug, any specific requirements for administration and any available prescribing tips.[4] Provision of financial assistance and assistance with reimbursement efforts is also a recommended component for any orphan drug distribution program. Drugmakers can provide value for themselves through the implementation of a system for the collection of transactional and other data that allows for analysis of trends in purchasing, inventory, product returns and other factors.

A comprehensive risk assessment must be performed to ensure that the commercial viability of a rare disease treatment is balanced with the feasibility, cost and effort required to establish an effective supply chain.[3]

The Role of Commercialization Partners

Often, outsourcing partners that can provide real-time insight into patient and provider needs and key market issues, such as preferred patient treatment experiences and adherence behaviors, can have a large impact on the success of an orphan drug commercialization effort.[5] For instance, they can provide information on the typical comorbidities suffered by patients with specific rare diseases that affect their needs and preferences for obtaining and taking their medications, as well as the potential for undesirable drug interactions. For many rare diseases, a hub model supported by a case manager is an effective approach to addressing these issues and others, such as reimbursement authorization and affordability.

An effective commercialization partner can also ensure that the right IT systems are in place to collect and analyze the most valuable data to demonstrate the health and economic benefits of their orphan drugs once they reach the market.[5]

Successful Orphan Drug Launches

McKinsey has identified four strategic pillars of successful orphan drug launches: a commitment to the rare disease community, use of innovative methods for patient identification, use of a tactical approach to patient access and extensive support for patients and caregivers as they navigate the healthcare system.[6] For each drug and each rare disease, however, the solution will be unique. The launch team — which must be cross-functional and operate in a highly collaborative manner — needs to integrate all insights gained to develop a launch strategy optimized to support the specific patient population. P

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SUPPORTING AAV AND LENTIVIRAL **VECTOR DEVELOPMENT AND COMMERCIALIZATION**

→ BY **JAMES BROWNI, Ph.D.,** ALDEVRON

Plasmids are essential for the development of viral vectors used to manufacture novel gene therapies and viral vaccines. Aldevron is supporting the innovation of drug developers in this space by providing standardized royalty-free, bulk AAV helper and lentiviral packaging plasmids for research and GMP production.

IMPORTANCE OF PLASMIDS

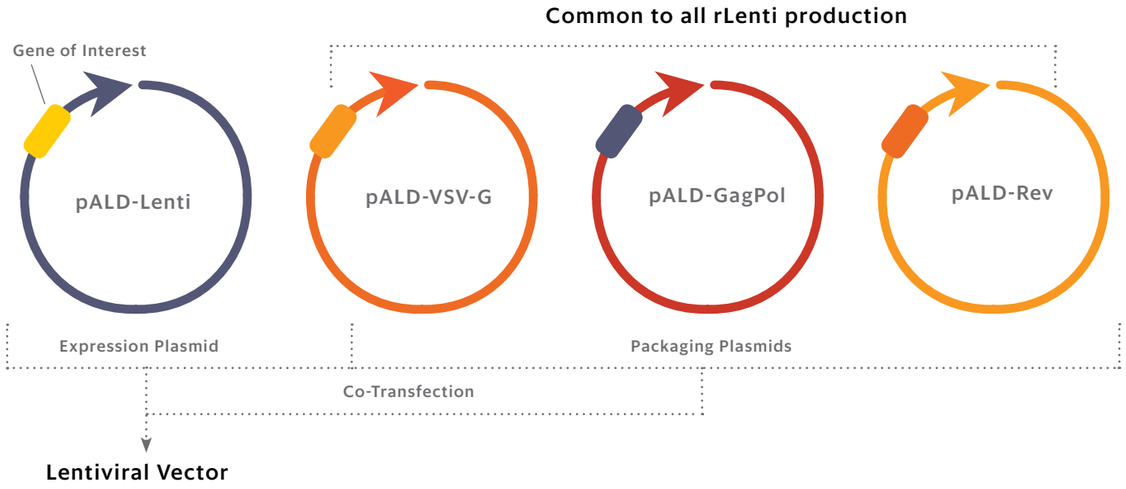
Plasmids are circular DNA molecules found mainly in bacteria, but also in yeast and plants, that replicate independently from the host's chromosomal DNA and enable bacteria to transfer genetic information from one to another via the process of horizontal gene transfer. They may also serve other functions, such as imparting antibiotic resistance.

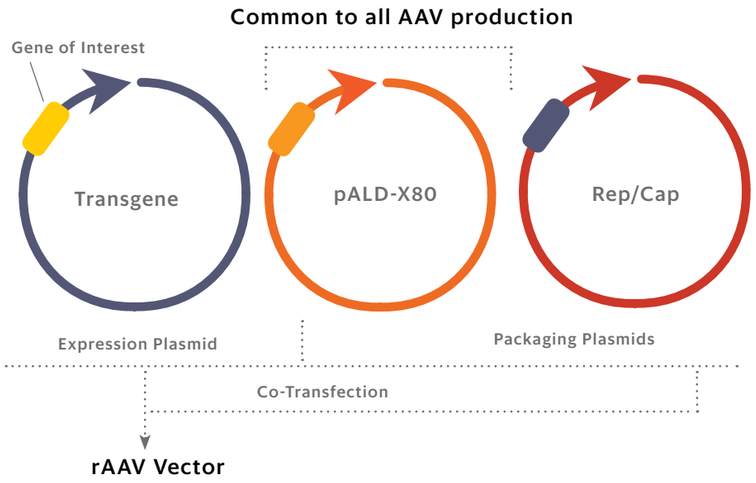
Natural plasmids contain an origin of replication, which controls the host range and copy number of the plasmid and allows initiation of replication. They also generally have at least one other gene that facilitates bacterial survival. Engineered plasmids are designed to introduce foreign DNA into other cells – typically mammalian cells during biopharmaceutical manufacturing. This process is referred to as plasmid transfection.

Like natural plasmids, engineered plasmids (also referred to as vectors or constructs) with specifically inserted genes have an origin of replication and a selection marker (e.g., antibiotic resistance to allow for the selection of plasmid-containing bacteria) and cloning site(s). Expression plasmids also have promoter regions that determine which cell types the gene is expressed in and the amount of recombinant protein produced.

Once the desired vector has been created, it is transformed into bacterial cells that are then selectively grown on antibiotic plates. The type of plasmid – cloning, expression, gene knockdown, reporter, viral and genome engineering – dictates the end-use application, including the production of viral vectors for gene therapies and viral vaccines.

FIGURE 1: Plasmids Used in Viral Vector Production





TRIPLE-TRANSFECTION PROCESS

There are several methods for manufacturing viral vectors. One popular technique involves the use of an insect cell/baculovirus expression system. Another system, which relies on a set of engineered herpes simplex viruses (HSVs) and a mammalian cell line, also has advantages, but is patent-protected and must be licensed. A producer cell method involves integration of all necessary genes into the genome of the cell, which allows for very stable expression but is highly complex and is generally only selected when one needs to manufacture a large quantity of a specific viral vector.

The most common plasmid transfection approach used for adenovirus (AV) and adeno-associated virus (AAV) vector production is transfection in mammalian cell lines, typically HEK293 cells. Multiple different plasmids are required in this method. For AAV, the *cis*-plasmid contains the gene of interest flanked by inverted terminal repeats (ITRs), which allow the genome to infect cells and then express the gene of interest. The *trans*-plasmid (also known as the Rep-Cap plasmid) contains the Rep and Cap AAV genes, which are not sandwiched between the two ITRs. The third plasmid – called the helper plasmid – contains the E4, E2a and VA genes for AAV (or AV), with the cell itself providing the AV E1A gene. As a result, no co-infection with adenovirus is required.

The *cis*-plasmid is unique for each recombinant AAV vector to be produced, as it contains the specific transgene of interest. The *trans*-plasmid containing the Rep and Cap genes is specific to the serotype of AAV being used. Different serotypes elicit a distinct immune response and also can have different tissue tropisms. The helper plasmid, however, is always the same regardless of the transgene and serotype.

In some cases, the *trans*-plasmid and helper plasmid have been combined into one larger plasmid, allowing for a two-plasmid system. This approach has some advantages, most notably a higher transfection rate, since only two plasmids need to enter the cell rather than three. There are potential cost savings to this method as well, but the combined plasmid is very large and more complex to produce. This approach tends to be limited to projects that involve only certain serotypes.

BULK AAV HELPER PLASMID

As a leading contract manufacturer of plasmids, Aldevron has extensive experience producing the three types of plasmids at research to commercial scale. Because the helper plasmid is the same for all triple-transfection projects, it is produced on a regular basis. Part of Aldevron's growth strategy is to advance the field by becoming a full-service company and adding value for clients through various product offerings. Production of bulk helper plasmid as a standard, off-the-shelf product for research, clinical trial material production and commercial manufacturing is an ideal offering for Aldevron.

Our first focus was on the AAV therapy space. Two types of helper plasmids are used in AAV vector production: AAV AdΔF6 and AAV pXX6-80. There are various forms of each available that have various optimizations to perform better during transformation and viral vector production.

Aldevron collaborated with Asklepios Biopharmaceutical, Inc. (AskBio), a gene therapy company, to make its helper plasmid available as an off-the-shelf product. AskBio's pXX6-80 plasmid has been used in recombinant AAV (rAAV) production since 1998[1] and has been safely used in viral vectors administered to humans. In addition, Aldevron has produced all of AskBio's clinical GMP material and is familiar with the production of this helper plasmid. Furthermore, both companies are dedicated to advancing gene therapy with enabling technologies that get treatments to patients as quickly as possible.

Our pALD-X80 standardized helper plasmid relies on kanamycin resistance rather than ampicillin resistance, which is commonly found in older helper plasmids. Many people have allergic reactions to ampicillin, and histamine responses can occur even with ampicillin reduced to very low levels. As a result, regulatory agencies are demanding that viral vector manufacturers avoid ampicillin resistance.

Another crucial element of this product offering is the agreement that no royalty fees would be passed on to Aldevron's customers; they only pay for the pALD-X80 product itself. Given the intellectual property minefield in the gene therapy space, this approach helps dramatically simplify the use of the off-the-shelf material. Aldevron also makes small quantities of pALD-X80 available for free to academic and pharmaceutical industry researchers investigating its use for viral vector production.

STANDARDIZED LENTIVIRAL PACKAGING PLASMIDS

In the production of lentiviral vectors, the number and types of plasmids used differ, but the overall manufacturing process is similar. The process is based on a less-rugged, enveloped HIV virus, and four plasmids are involved: a plasmid containing the gene(s) of interest and three packaging plasmids. In this case, however, there are no serotypes, so the same three packaging plasmids are used for every project.

Aldevron has obtained rights to manufacture the set of plasmids developed by Oxford Genetics through a recent collaboration. These plasmids (pALD-Rev, pALD-VSV-G, pALD-GagPol and pALD-LentiEGFP) have been optimized to produce high-titer, high-infectivity lentivirus. Optimization includes minimization of vector backbones, reduced homology with HIV/VSV and inter-cassette homology. In addition, lentiviral vectors produced with pALD Lenti packaging plasmids transfect cells at a higher rate than commercially available kits, with infectious titers in the range of 5 x 10^7/mL.

Once a client provides Aldevron with the gene of interest, it is cloned into the lentivirus expression plasmid (pALD-LentiEGFP) for custom production, replacing the EGFP sequence. The three packaging plasmids are available off the shelf. Aldevron's production scale and experience with custom manufacturing of lentiviral expression plasmids, combined with the in-stock packaging plasmids, provide clients with a complete set of products and services for their programs.

As with the AAV helper plasmid, the pALD lentivirus products are available royalty-free, and limited quantities of research material are provided free of charge. The products are currently available for research applications, with material suitable for the production of clinical trial materials ready for purchase in the summer of 2019.

MANY BENEFITS FOR VECTOR MANUFACTURERS

AAV and LV manufacturing have traditionally required unique custom batches of helper and packaging plasmids, respectively. It can take months for the production of these custom clinical and commercial plasmids. In addition, manufacturing capacity is currently limited, and wait times before projects can be initiated can be three months or longer.

AS A LEADING CONTRACT MANUFACTURER OF PLASMIDS, ALDEVRON HAS EXTENSIVE EXPERIENCE PRODUCING THE THREE TYPES OF PLASMIDS AT RESEARCH TO COMMERCIAL SCALE.

Aldevron's off-the-shelf AAV and LV plasmids are, on the other hand, immediately and universally available with acceptable plasmid elements (i.e., kanamycin resistance). As a result, the timeline for production of AAV and LV vectors can be significantly reduced, accelerating project timelines and lowering cost. Cost is also reduced because these products do not carry any pass-through fees after purchase.

As importantly, because Aldevron provides a reliable supply of consistent, high-quality plasmids and has demonstrated performance producing lentiviral and AAV vectors used in clinical trials, we facilitate supply chain risk reduction for our biopharma partners that are developing novel, life-changing therapies.

Customers also benefit from access to three quality grades of standardized plasmids for use in research applications, the production of clinical trial materials and commercial GMP manufacturing. Clients have the option of choosing the quality grade that fits their needs and stage of development with the assurance that the royalty-free product will be available when it is needed.

STRAIGHTFORWARD MANUFACTURING PROCESS

The bulk AAV and LV vectors from Aldevron are produced in *Escherichia coli* bacteria. First, the bacteria are subjected to a

process that makes them competent (able to survive transient poration to allow the plasmids to enter), so they will be more accepting of the plasmid DNA. The bacteria are then transformed with the plasmid DNA. Exposure to antibiotic kills the bacteria that do not contain the plasmid.

The remaining bacteria are grown and then lysed to release the plasmids. This step is challenging at large scale with large volumes, and Aldevron's process development team has invested significant time and effort to develop large-scale processes that are highly efficient. The lysate is subjected to multiple filtration, chromatographic and buffer-exchange modalities before final formulation in the appropriate buffer to the desired concentration.

This process can be performed at very small to large scales. Currently, Aldevron can grow bacteria to a volume of 300 liters in a single-use fermentor, which can contain as much as 100 g of DNA. Recently, Aldevron has expanded their fermentation capacity to 1,000 L and will produce its first 1,000-L batch in the fall of 2019.

Product characterization includes measurement of the supercoiling density and sequencing, among other analyses. The level of impurities (e.g., endotoxins, residual host-cell proteins, DNA and RNA, dimerized plasmids) is also monitored. The basic attributes are dictated by the fact that these plasmids are used as raw materials for the production of viral vectors and are not intended for therapeutic applications that involve direct injection into humans.

MULTIPLE GRADES FIT FOR PURPOSE

The off-the-shelf plasmids from Aldevron are offered in three grades: research, GMP-Source™ and GMP.

Research-grade material is manufactured in a large, separate, open laboratory, in which multiple projects are performed simultaneously. The goal is to produce material rapidly at low cost and with high quality to enable effective research programs. Although the quality is high, it is not sufficient for use in humans because there is a small probability of contamination, even if at levels lower than can be detected. In addition, non-qualified assays are performed in a QC lab for these research materials.

GMP material is produced in a new facility designed specifically for plasmid manufacturing – the largest plasmid manufacturing facility in the world. Multiple independent air-handling systems enable production of multiple lots simultaneously, with no two lots sharing the same HVAC. Extensive environmental monitoring and rigorous cleaning and changeover procedures help ensure the quality of the products. This material is produced in compliance with current Good Manufacturing Practices and is of sufficient quality to be injected directly into humans.

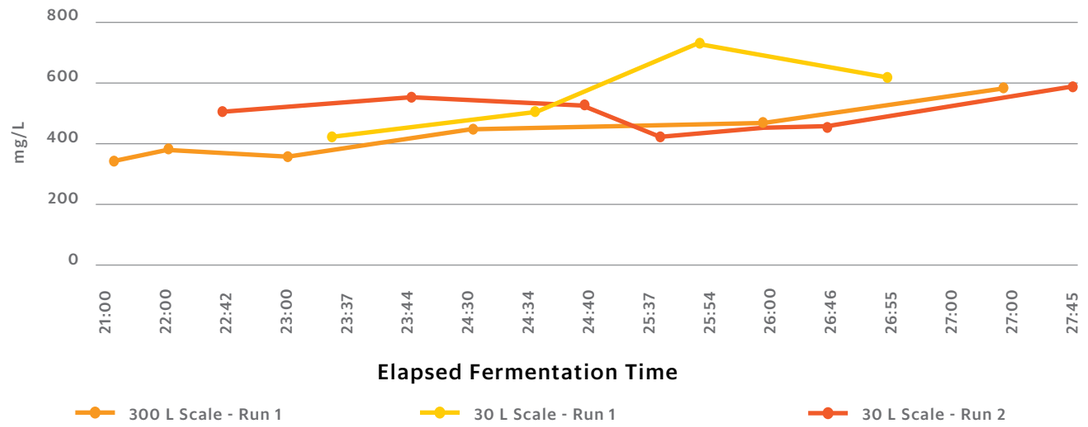
ALDEVRON OFFERS A SERIES OF INTEGRATED SCIENCE PLATFORMS FOR THE PROVISION OF NUCLEIC ACID, PROTEIN AND ANTIBODY SERVICES.

GMP-Source™ material is manufactured in the same facility as our GMP products in separate suites that also have their own air-handling systems. The same raw materials are used for both GMP and GMP-Source materials, and all of the same qualified assays are used for both types of products and performed in a dedicated lab. The same quality system, which supports corrective actions and trending, is also used for both GMP and GMP-Source products. GMP-Source suites are not ISO classified, there is no environmental monitoring and the GMP-Source quality assurance review is limited to critical procedures. This quality level provides plasmids appropriate for use in viral vector production at a reduced cost and with a faster timeline without sacrificing any safety or efficacy in the final viral vector product. By offering this interim quality grade, we are helping viral vector manufacturers implement phase-appropriate GMP-compliant solutions.

FIGURE 2: Comparison of GMP-Source and GMP Plasmid Grades

	GMP-Source ™	cGMP
Aldevron retains process control	✓	
Controlled, non-classified suites	✓	
QA sampling review of documentation	✓	
Manufacturing summary report	✓	
Segregation	✓	✓
Documentation	✓	✓
Traceability	✓	✓
Vendor Management	✓	✓
CAPA	✓	✓
Master Batch records dictate process		✓
ISO-classified suites & EM		✓
QA review of all documentation		✓
Change control		✓
Validation		✓

FIGURE 3: Efficient Large-Scale Plasmid Manufacturing



ADVANCING THE FIELD

At Aldevron, we are driven to make a meaningful difference. We want to make real contributions to the lives of others by providing the basis for breakthroughs that improve human health and promote positive change throughout the world.

As a CDMO, Aldevron offers a series of integrated science platforms for the provision of nucleic acid, protein and antibody services. By supplying our customers what they need, when they need it, with expert support at every stage of development and production, we help them open up their laboratories for ground breaking science and breakthrough discoveries.

We are constantly looking to innovate and advance our technologies, products and services through partnerships with those who share our goal of advancing science in our field. We attach great importance to the close, collaborative relationships that allow us and our partners to concentrate on our core efforts. This means giving organizations of all sizes access to affordable, high-quality products and services to advance their work.

We are also committed to bringing groups together to accelerate the process of drug and treatment discovery. In some cases, that requires changing traditional mindsets. With respect to our off-the-shelf plasmids for AAV and LV production, that means recognizing that some aspects of gene therapy and viral vaccine manufacturing do not need to be customized. Helper AAV and packaging LV plasmids do not require unique specifications that add complexity and cost.

The off-the-shelf products Aldevron produces have specifications that are appropriate for viral vector manufacturing and are consistent with those applied to the production of viral vectors that have been administered to patients. Gene therapy development is highly complex, but identifying components that can be safely standardized allows innovation efforts to target other aspects that cannot be standardized. As the gene therapy field continues to grow and mature, we fully expect more players in the industry to realize – and leverage – the benefits offered by our off-the-shelf plasmids. P

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James Brown has over 25 years of biotechnology industry experience and has spent the last decade in gene and cell therapy. In 2015, he joined Aldevron, where he heads the product management team, which expands existing product features and develops new products. His responsibilities include developing and implementing strategies for expanding Aldevron's DNA, mRNA, antibody, and protein products and production services. Dr. Brown holds a Ph.D. in chemistry from Stanford University and a B.S. in chemistry from Butler University.

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Catalent Pharma Solutions

Oral Solid Dose Manufacturing for Customers Now and into the Future

Despite all of the advances made in the biologics space, the majority of drugs on the market are formulated as small molecule APIs and administered orally. Catalent is continually investing to support the evolving needs of drug developers for state-of-the-art OSD formulation and manufacturing solutions.

Listening to Customers

In the past, any contract development and manufacturing organization (CDMO) with an excellent reputation was highly sought after and attracted good projects – the same does not hold true today. The market is increasingly competitive, and sponsor firms are more frequently looking to establish strategic partnerships with CDMOs for specific needs.

Catalent recognizes that the needs of drugmakers in the 21st century are very different from those of a few decades ago – and that they continue to evolve. We are listening to our customers and responding by implementing continuous improvement projects, adding relevant capacity and expanding our technical capabilities. By doing so, we add more services, provide more value as a long-term partner and drive costs down in development and manufacturing processes.

Winchester Facility Investments

In order to grow, it is often necessary to reinvent yourself. During the last five years, Catalent has invested over $105 million to ensure that our Winchester, Kentucky site is equipped to meet future demand. In addition to continuous improvement initiatives, we have completed compliance-related projects and added fluid-bed drying and encapsulation capacity. The facility also now includes a bottling line and has the ability to support pediatric formulations in stick-packs.

Capsule-banding technology was also installed at the site to support the move of prescription drugs to over-the-counter products, including the ability to band capsules as small as size 5. In response to increasing demand for next-generation controlled-release formulations based on osmotic release, we have also upgraded our laser tablet drilling system.

On April 30, 2019, Catalent announced it is to add commercial spray drying (SD) capability at the Winchester site. In total, we will be investing approximately $40 million over the next 12–18 months to increase patient-centric dose form capabilities, including expanding roller compaction capacity and adding a commercial spray dryer.

Controlled Substances Expertise

The Catalent Winchester facility has been offering controlled substance manufacturing services for over 20 years. Our impeccable record is the result of extensive investments in the process training, procedures and security systems required to account for every tablet and capsule and every last gram of API.

OSD Solutions

Catalent is always looking for new technologies and approaches that will provide real value for our customers. In addition to traditional development and manufacturing solutions, we offer scientific, regulatory and clinical supply consulting services that help us serve as a comprehensive partner.

Specifically, for OSD customers with poorly soluble APIs (which account for up to 70% of pipeline candidates), our OptiMelt® hot-melt extrusion (HME) solution is an integrated offering that provides clients with a finished product – including bottling if desired. With our OptiForm® Solution Suite, Catalent provides a feasibility assessment of four technologies (lipid formulation in softgel capsules, HME, spray-dried dispersion or micronization) for improving solubility and bioavailability, all within 12 weeks. Because we offer all four solutions, Catalent has no incentive to choose one over the other; this agnostic approach will find the best fit for a customer's API and can trim a year and sometimes more off the development cycle.

Integrated Offering

Catalent provides integrated services that support small, emerging and virtual companies, as well as large pharma firms. Our integrated, nimble network with end-to-end services supports smaller companies looking to partner or be acquired. For traditional pharma companies, in addition to aligning our supply chain management systems, we can serve as a strategic partner with all the same capabilities – plus additional specialized technologies – and simultaneously manage multiple products in their portfolios.

Focused on the Future

Catalent continually evaluates ongoing trends in the OSD marketplace. With the addition of patient-centric solutions, we support the development efforts of our customers, including for poorly soluble APIs and orphan drugs.

In addition, with expertise in both oral solid dosage forms and biologics, Catalent is ideally positioned to help advance the development of oral novel delivery solutions for biomolecules. From orally disintegrating tablet technologies to intramuscular delivery solutions, Catalent has the integrated and evolving capacities required to solve the future challenges that will arise in the OSD field. P

Ron Connolly
Executive Vice President, Business Development, Alliances and Regulatory
Frontida BioPharm, Inc.

Taking Extra Care with Formulation

A major challenge when taking drug candidates from clinical studies to market is finding robust product formulations that can be used from early stage studies through product commercialization. Early stage clinical studies frequently use Active Pharmaceutical Ingredient powders or oral suspensions that may have limitations in stability or bioavailability, necessitating potentially time-consuming, costly reformulations as doses are established during later development trials.

Frontida Biopharm was formed in 2016 with the acquisition of three Sun Pharma facilities in Philadelphia, Pennsylvania and Aurora, Illinois to provide co-development and commercialization services to pharmaceutical partners. These three cGMP sites cover 335,000 square feet, with an annual capacity of 3 billion capsules and tablets. Our services include determining optimal stable product formulations for drug candidates, as well as providing manufacturing, packaging and logistical support for commercialized products.

Cost-Saving Proprietary Product Formulations

We have two specialized product formulation platform offerings. The AdaptDose™ flexible dose technology platform allows us to combine 2–3 populations of mini-tablets, beadlets, liquids or granules into a single capsule. Each type of mini-tablet or beadlet contains a single compound, allowing the quantities of each compound to be weight-adjusted independently in the capsule. One application of this technology is for formulations required for adaptive clinical studies and clinical dose escalations, where the formulation can be adjusted easily by changing mini-tablet/beadlet quantities in the capsules while the clinical study is in progress. Since the formulation is modular, there are no additional costs for formulation development efforts or stability studies, thereby reducing project time and costs by about 30%.

AdaptDose™ is also useful for extended-release (ER) formulations. Mini-tablets and beadlets can be coated with various pH-sensitive polymeric or enteric coatings that allow different biological release rates. Coatings can be designed to dissolve portions of the formulation populations at specific pH values in the gastrointestinal tract and thus be released in a staggered fashion as the formulation particles travel from stomach to small intestine to colon.

Frontida's DuraGran® process is a patented technology for producing controlled release or taste-masked beadlets or granules. The DuraGran® process utilizes high shear granulation, fluid bed drying and continuous milling and classification to create granules of a desired particle size distribution range that can be coated and compressed into tablets or filled into capsules. The process can handle hundreds to thousands of kilograms of DuraGran® material. Compared with spheronization and extrusion, this technology may enable reduced production costs, energy requirements and in-process monitoring with an efficient transition from lab to commercial scale.

Frontida's Collaborative Approach

Frontida has a very strong R&D focus, with an R&D team of more than 40 scientists, 70% of whom have Ph.D.s or Master's degrees in their area of expertise. The team has extensive industrial, pharmaceutical and academic experience. We also have a technology bridging group of engineers who work with the R&D team and production areas to ensure that formulations work on a commercial scale. These teams collaborate with scientific thought leaders at sponsor companies to set and accomplish scientific and business goals. This approach brings value to commercial projects by establishing strong science from the beginning and building that into processes. A significant advantage is that these collaborations can result in patentable outcomes that can strengthen and extend a client's product positions in the market.

Frontida is interested in forming partnerships ranging from fee-for-service for quality work for larger pharmaceutical companies, to helping smaller companies find funding and partnering with them for win–win outcomes. The management team has extensive experience with a broad range of pharmaceutical and biotech companies, including many U.S. and Chinese firms who have brought products to these markets.

Integrated Development, Manufacturing and Packaging

Frontida currently manufactures 20–25 products for a range of clients, with the opportunity to grow to about 3 billion tablets and capsules per year. These are supplied as finished products and sent directly to client distribution centers, with full bottle packaging, serialization and labeling services. We can also provide packaging-only services, analytical services and method validation to support clients as required. The expertise developed over our team's many years in the market provides a seamless, efficient process for product development and commercialization. P

Carole Grassi
Vice President, Marketing and Communication
SGD Pharma

Implementing Ready-to-Use Glass Vials for Flexible Aseptic Filling

As the first commercial ready-to-use (RTU) molded glass vial system that reduces costs while simultaneously improving quality, the new Sterinity platform is an efficient solution to the challenges associated with aseptic filling.

Parenteral Delivery on the Rise

Parenterally delivered drugs have gained in popularity over the last several years. According to IQVIA MIDAS, in 2018, parenterals accounted for 32% (by volume) of the global drug market.[1] The parenteral packaging market is projected to grow at a robust compound annual growth rate of 11.4% between 2018 and 2024.[2] Parenteral delivery of drugs is often preferred because it allows absorption directly into the body at the site of delivery. Parenteral administration is the route typically associated with biological drugs, but it can also be used for small molecule drug products, especially those that present solubility issues, and for the delivery of nutrition and vitamins.

Addressing the Challenges of Aseptic Fill and Finish with RTU

The increased demand for personalized medicines and biologics drugs and the consequent flexibility in manufacturing capacity has led to a growing demand for RTU systems. While washing, depyrogenizing and sterilizing glass primary packaging are non-core activities for a pharma company, which should focus on drug development, a need for fill/finish solutions that can ensure sterility without significant investment or operational demands has emerged. In RTU systems, packaging is pre-prepared so that the only step left in the process is to fill and finish the container, which eliminates the majority of process challenges. While an RTU solution has largely been implemented for small-volume containers, another option for larger-volume containers (defined as those in the 20–500 mL range) is a crucial need in the market.

As industry leaders specialized in the manufacture of molded glass packaging, SGD Pharma has introduced the Sterinity platform – the first commercial solution for RTU molded vials – as a flexible solution for scale-up. Sterinity is a key differentiator because it allows for the commercial availability of RTU molded glass vials for the first time. The Sterinity platform leverages the well-established EZ Fill® system by Ompi, Stevanato Group (Padua, Italy) to extend the benefits of RTU across a range of applications.

Quality First

Our Sterinity platform focuses on quality and flexibility. We use Type I glass in production and are committed to bringing new solutions to the market by steadily expanding our portfolio to include even more products in a broad range of sizes. Over the next 1–2 years, we will be releasing an RTU system in partnership with Ompi with two central design options, one featuring a premium quality ISO design and one with an optimized EasyLyo product.

The SGD Pharma Expanded Portfolio

All of our ISO vials are made from a premium quality molded glass RTU option. The EasyLyo product relies on molded glass technology and has an aesthetic appeal, along with the chemical durability needed to store sensitive drug products (in a host of potentially extreme conditions) with minimized risk of breakage, leakage or quality issues. In addition to being stronger than traditional molded glass, the vials are also 30% lighter on average and are also optimized for heat transfer during lyophilization. The RTU solution has an ISO 20-mm neck finish, which is a model measurement for stoppering and securing the product and is also optimized for heat transfer during lyophilization.

SGD Pharma is currently adopting both nest-and-tub and tray secondary packaging presentations from Ompi EZ-Fill® to provide our clients with even more options. Our vials are packaged without glass-to-glass contact to ensure product integrity. Tray configuration is generally a preferred packaging solution for a dedicated line, while a nest-and-tub configuration can support multiple filling technologies to process vials, cartridges and syringes in a single solution.

The Sterinity Solution

Sterinity offers a selection of secondary packaging configurations, and boasts a diverse glass vial portfolio that meets all industry standards and customer requirements. As the need for flexible filling increases, companies will be seeking a cost-effective quality solution to streamline production and increase the speed of changeover. As the first commercial solution for RTU molded glass, SGD Pharma's Sterinity platform is a viable answer to this pressing issue. P

Sterinity offers a selection of secondary packaging configurations, and boasts a diverse glass vial portfolio that meets all industry standards and customer requirements.

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Ori Gutwerg
Vice President, Head of U.S. Generic Rx
Taro Pharmaceutical Industries, Ltd.

Being at the Right Place at the Right Time

Always remember that your goal is to ensure your customers (the patients) know that your product has the highest quality, is always available when they need it and reduces their cost of healthcare.

An Innovative Company Culture

For me, the position of Vice President, Head of U.S. Generic Rx at Taro Pharmaceutical Industries is the ideal place in the current landscape of the U.S. generics market.

Since 1988, when Taro entered the U.S. marketplace, they were laser-focused on differentiation and complexity, becoming one of the few generic companies focused on semisolids. Since its inception, Taro has fostered a culture of seeking challenges, going after difficult-to-develop dose forms, and initiating costly and high-risk biostudies, approaches that are more fundamental than ever for success in today's large and competitive market. Joining a superb company like Taro, with an appropriately bold and innovative sensibility, was the most obvious next step for me.

Since 1988, when Taro entered the U.S. marketplace, they were laser-focused on differentiation and complexity, becoming one of the few generic companies focused on semisolids.

Today's generic drug market is very demanding. There are a lot of excellent pharma companies in the marketplace, and, as a result, we are seeing more and more ANDA approvals and very significant price competition.

A Recipe for Success

In my view, a successful generic drug company is one that delivers on the following key practices:

- be a leader in your dose form space with a large portfolio of products,
- make sure you are cost competitive and seek every possible advantage and efficiency to remain so,
- have a strong product development team that will identify the right candidates and get FDA approvals in the first wave,
- ensure that you provide consistent and impeccable quality, and
- ensure that you always maintain ample flexibility to ramp up supply on short notice.

Taro has always followed these fundamental guidelines. With a key focus on extended topicals including unique delivery platforms, semisolids and complex oral solids, we currently have 204 approved ANDAs and 27 more that are awaiting FDA approval. Taro has invested year-over-year in semisolids and other niche products with high clinical and regulatory barriers to entry, technically complex manufacturing and opportunity for API synthesis.

With 58 drug master files (DMFs) currently submitted to the FDA, we aim to ensure that our key products are vertically integrated. We have taken the initiative to find dual sourcing for our key finished dosage forms. We are continuously assessing all aspects of our operations to identify opportunities to improve and find new efficiencies in our manufacturing operations and the underlying supply chain.

Committed to Quality, Innovation and Efficiency

All of our sites that supply products to Taro undergo rigorous inspections by all agencies. We have a strong track record of audits that resulted in no observations, and we continue to invest in improvements to our QA capabilities. We feel that our quality commitment is sufficiently robust to set the bar for the whole industry.

We are in the process of implementing a new SAP ERP system that will improve our inventory management and supply efficiency. Our goal is not only to be able to supply our customers, but also to be able to respond to any market shortage or demand from customers for whom our product is not currently their primary drug.

Our capabilities are even further enhanced through our integration with Sun Pharma, the majority owner of Taro. We leverage support from Sun's India and U.S. operations, including strong financial backing and synergies between both businesses that come into play with various joint services that increase efficiencies while reducing redundancies and thus operating expenses.

Overall, Taro is committed to supporting any of our customers' needs, and we look forward to expanding our partnerships and establishing new ones to develop new complex products for which we lack certain capabilities in-house. In addition, we offer ourselves as a commercial platform to companies that seek to sell products in the United States and would like to piggyback on our strong customer relationships and flawless service levels. P

Mark Frigerio, Ph.D.
Director, Chemistry UK
Abzena

Juan Carlos Cordova, Ph.D.
Principal Scientist,
Bioconjugation, Abzena

Integrating ADC Manufacturing for the Future

Antibody–drug conjugates (ADCs) in development target many indications beyond cancer and consist of a multitude of different types of components. Integrated development and manufacturing capabilities are essential to bringing these promising yet complex therapeutics to market.

Moving Beyond Oncology

ADCs are constructs that allow the targeted delivery of a payload molecule – via its linkage – to an engineered antibody that binds to a specific cell type. The first wave of ADCs focused on oncology indications, because the relevant binding sites are more uniquely expressed on cancer cells, but there are tremendous opportunities in other disease areas for both traditional ADCs and their derivatives.

Conjugates are being developed to treat inflammation, pain, Alzheimer's, Parkinson's, diabetes and many other diseases and disorders. These new drug candidates may comprise antibodies or other protein components (e.g., Fc fragments, highly engineered protein carriers) conjugated to peptides, nucleic acids, other proteins, polysaccharides or immunomodulators. Their development is driven both by the identification of novel targets and advances in linker payload technologies.

Early Phase Challenges

Drivers of failure for existing ADCs in development involve payload shedding before delivery at the target site and non-specific antibody binding, typically through Fcγ receptors. Abzena works to understand the target, the desired expression levels, the sensitivity to different payload mechanisms, mechanistic interactions – and other key information – using bioanalytical assays to ensure that the right conjugation approach is incoporated from the start.

Development and Manufacturing Hurdles

Because ADCs consist of three distinct components (antibody, payload and linker), their development and manufacture require expertise in biologic production, small molecule synthesis and conjugation technology. While cell line engineering and antibody production are more straightforward, payload preparation may involve 12–25 complex synthetic organic reactions, often needing to establish and maintain multiple chiral centers. Cytotoxic payloads require specialized equipment and facilities to ensure protection of workers and the environment. The conjugation step must be robust and reproducible, generating the product with a consistent payload: antibody ratio. In addition, no single platform approach can be applied – multiple conjugation technologies and approaches, and purification methods are used that often must be tailored to the specific ADC.

Importance of Analytics

Successful ADC design and development is driven by access to a suite of robust analytical methods – *in vitro* cytotoxicity, characterization, serum stability, mechanistic and functional assays. Together, they underpin the successful design of developable and manufacturable ADCs. In-depth analytical evaluation of antibodies, linkers, payloads and their various combinations is crucial for effective lead candidate selection. Abzena also uses translational assays that correlate well with *in vivo* PK and efficacy to eliminate ADCs that lack desirable performance properties.

Integration Advantages

Although each of the three elements of an ADC requires its own manufacturing process and supporting validated analytical methods, their development and implementation must be coordinated. Having capabilities that span all three areas allows Abzena to bring expertise on the manufacturing side into the R&D and early process development stages for rapid process optimization. Our integrated approach, from gene to GMP, allows simultaneous work on various aspects of a project, significantly reducing the whitespace typically present in ADC development programs.

Global project management supported by site-specific project management teams ensures seamless project progression and avoidance of delays and costs associated with the transfer of technology from one company to another. Project teams are staffed with highly experienced personnel that support each project from the early stages to commercial production, adding value to each project throughout its lifetime. Experts involved in the development process also bring their knowledge and understanding to manufacturing campaigns. As a result, teams are able to troubleshoot process-related issues before moving to commercial production – and rapidly find solutions to any issues that arise during manufacturing.

Abzena is also positioned to support ADC production from lab to clinical scale, with a range of specialized equipment and facilities (such as high containment capabilities for cytotoxic payloads and solvent handling and processing for conjugation processes). Single-use systems are employed (where feasible) at manufacturing scale to eliminate the need for cleaning validation between projects. Much of our equipment is directly scalable, from process development to manufacturing, minimizing the change for unexpected issues during scale-up. P

Peter Pekos
Chief Executive Officer
Dalton Pharma Services

Quality and Experience Crucial for Sterility Assurance

The increasing complexity of drug substance and formulated drug products is affecting the entire supply chain. At the same time, expectations for quality assurance are climbing, and patients are demanding innovative drug delivery systems that provide convenience. CDMOs like Dalton Pharma Services with extensive experience in sterile manufacturing combined with a long track record of compliance and the use of closed process systems have a competitive edge.

Sterile Liquid and Powder Filling

Dalton Pharma Services is a cGMP contract service provider of integrated chemistry, drug development and manufacturing services, including expertise in cGMP API and solid and sterile finished dose manufacturing. With all services located in our single facility in Ontario, Canada, we have full control over all sterile processing – including aseptic manufacturing/sterile filtration and low bioburden filling followed by terminal sterilization with wet or dry heat or gamma irradiation – from start to finish.

Extensive Qualification and Validation

Extensive qualification and validation combined with strong microbiologic analysis capabilities and experienced and highly trained operators are essential for achieving successful sterile fill/finish operations. In addition to these capabilities, Dalton has a solid environmental monitoring program for both viable and nonviable particles. Operators are subjected to comprehensive gowning and aseptic process-operation qualification procedures. All cleanrooms are qualified and validated before use, as are all equipment and components that support sterile processing, cleaning agents (used for a minimal time at a minimal concentration) and microbiological methods.

Sterile Chemical Reactions

In addition to traditional sterile processing capabilities, Dalton has the unique ability to perform aseptic organic chemistry processes. This capability is made possible through the installation of a restricted-access barrier system (RABS) designed specifically to handle organic solvents. As a result, we can perform aseptic crystallizations and other transformations, including nanoparticle synthesis. We are able to convert non-sterile APIs into sterile APIs and then package them in bulk or into dosage units.

Sterile Liposomal Formulations

Liposomal formulations are increasingly common, because they can be used to enhance the solubility of poorly soluble APIs. Liposomes are also used in some formulations to protect sensitive APIs from other ingredients in the formulation and to enable delayed or targeted delivery of APIs. The size of liposomal particles varies significantly. Some are sufficiently small to pass through aseptic filters, while others are larger and cannot be filtered. Formulations containing these liposomes must be terminally sterilized, but sterilization in an autoclave often changes the percent liposomal encapsulation and/or the liposomal size distribution. These products must be produced via aseptic formulation, which is more complicated and requires specialized equipment and expertise.

Quality and Experience

Dalton places an emphasis on quality, reliability, speed and flexibility – all at one centralized location. We move projects seamlessly from inception to cGMP manufacturing, simplifying client supply chains and reducing timelines and cost.

Our commitment to quality and our comprehensive quality systems ensure that our facility is under excellent control at all times. An inspection conducted by the U.S. Food and Drug Administration in January 2019 resulted in zero 483 citations, confirming our high performance. These results were achieved despite the complex sterile processing projects that Dalton tackles on a regular basis, from sterile liposomal and nanoparticle formulations to sterile crystallizations.

With more than 30 years of experience in sterile liquid manufacturing and 17 years in sterile powder manufacturing, including aseptic filling and terminal sterilization of a wide variety of APIs and formulation types using many different types of equipment, Dalton has amassed significant knowledge that is applied to each new project.

Our dedicated and committed workforce brings together highly trained engineers and scientists from all over the world with international experience and different perspectives and viewpoints. This diversity ensures an open-minded approach to innovation and problem solving that adds real value for our clients.

This expertise is supported by our ongoing continuous improvement efforts and investments in our facility and equipment. A recent $10 million facility and capital expansion project included addition of a new automated sterile liquid filling system and analytical capabilities for elemental impurities. We will also soon expand our powder filling capacity with the addition of a high-throughput robotically controlled sterile powder filling line. P

POLPHARMA BIOLOGICS: BUILDING ON EARLY ACHIEVEMENTS

BY **GUENTER STEMPFER,** POLPHARMA BIOLOGICS

Polpharma Biologics is a fast-growing unit within Poland, developing and manufacturing new biopharmaceuticals as molecular entities (NMEs) or biosimilars, as well as delivering biopharmaceutical CDMO services. Established in 2013, Polpharma Biologics is already constructing its second manufacturing facility in Poland to provide customers with integrated support from cell-line development to the commercial-scale drug substance and drug product supply.

ATTRACTIVE BIOLOGICS MARKET

The global market for biopharmaceuticals is significant and growing at a healthy rate. Estimates for the worldwide revenue for biologics in 2018, including vaccines, range from $237 billion[1] to $275 billion, and the biologics market is expanding at a compound annual growth rate (CAGR) of approximately 8.5% to reach $340 billion in 2023[2] and nearly $390 billion in 2024.[3]

The Business Research Company estimates there are currently more than 1000 biologic drugs in development and predicts that the U.S. Food and Drug Administration's (FDA) focus on reducing time to market will lead to an increase in year-on-year growth of the biologics market from a recent 5.4% to 9.6%.[4] In addition, the number of biotech patents applied for every year has been growing at approximately 23% annually, and more than 1,500 biomolecules are currently undergoing clinical trials.[5] To date, the success rate for biologics in clinical trials has been over twice that of small molecule drug products. By 2022, biopharmaceuticals are expected to make up about half of the top-selling 100 products and about 30% of the prescription drug market.[6]

Furthermore, the global biosimilars market is expected to expand at a CAGR of 31.7% from $5.95 billion in 2018 to $23.63 billion by 2023.[7] Currently, there are over 800 biosimilars in the global pharmaceutical pipeline.[8]

Contributing factors to the growth of the biologics market include the approval of new products, expansions of indications for existing products, and increased demand stemming from the global growth of an aging population.[1]

NEED FOR INTEGRATED SERVICES

The rapid growth occurring in the biopharmaceutical industry is creating significant demand for outsourcing services. A large percentage of innovation in the industry is driven by emerging and smaller biotech firms with limited resources.[9,10] These companies often rely heavily on contract development and manufacturing organizations (CDMOs) that can provide integrated services across the entire development cycle from discovery to commercial launch. Even large biopharmaceutical companies are seeking the assistance of outsourcing partners with differentiated capabilities, including integrated services that enable accelerated timelines and reduced costs.

As such, the global biopharmaceuticals contract manufacturing market size is growing at an even more rapid rate than the biopharmaceutical market as a whole, with a $13.3 billion valuation in 2018 and projection to grow at a CAGR of 15.5% to reach $48.8 billion by 2027.[11]

POLPHARMA'S BIOLOGICS GROWTH STRATEGY

Polpharma Biologics was established in 2013 by Polpharma, a privately owned, Polish pharmaceutical company producing small molecule generics and active pharmaceutical ingredients (APIs) largely for the Eastern European market, in response to the clear demand for both biosimilars and integrated biopharmaceutical contract development and manufacturing services. As one of the largest pharmaceutical companies in Central and Eastern Europe, the company leveraged its more than 80 years of experience producing generics and over-the-counter medicines and GMP/regulatory compliance and quality assurance to serve the biologics market.

The first step in our strategy was to construct an 8,000-m^2 Biotechnology Center in Gdansk for the development and optimization of both upstream and downstream bioprocesses in support of projects from conception through R&D, and on to production of clinical trial materials – in accordance with cGMP guidelines. The Center is outfitted with state-of-the-art equipment and staffed with a diverse team of world-class veterans with years of experience at big pharma companies and extensive collaboration with regulatory agencies.

The comprehensive R&D platform and GMP production capabilities include 2 x 1000-L single-use bioreactors for cell culture of clinical and small-scale commercial batches, a 500-L bioreactor for microbial fermentation and a flexible fill/finish line for use with vials, prefilled syringes and lyophilized products (5 million units per year), which will be operational by mid-2020.

In addition to the CDMO services, Polpharma Biologics is developing biosimilars in-house up to the approval stage and then commercializing those biosimilars with the appropriate partners. This approach allows us to work on biosimilars that fit our capabilities without the need to focus on a single therapeutic area or justify sales in particular markets. Today, the company has five biosimilars in development.

We also offer contract development and manufacturing services based on our established competencies, and are interested in all types of deals – from fee-for-service to co-development, and beyond. The Biotechnology Center has the available capacity to support external client projects from development through clinical and small-scale commercial manufacturing and, starting in 2020, also large-scale manufacturing of drug substance and drug product out of our new site in Duchnice, near Warsaw.

INITIAL EXPANSION THROUGH ACQUISITION

One of the keys to successful biologic drug production is the identification of optimized cell lines that are capable of production at high yields. High-yielding cell lines allow the use of smaller-scale upstream and downstream processing equipment – which minimizes capital expenditures – and the potential to produce fewer batches per year – which then reduces operating costs.

Polpharma Biologics developed the capability to engineer optimized cell lines with the acquisition of Bioceros in 2016. Bioceros' well-established proprietary CHO BC® cell line development platform technology has been used for more than 25 years to generate high-yield production cell lines for both biosimilar and innovative proteins. The platform is complemented by a full range of cutting-edge high-throughput technologies to achieve the rapid generation of optimum, high-producing cell lines that meet specific quality attribute requirements.

A comprehensive toolbox for targeted modulation of posttranslational modifications (PTMs) facilitates the development of proteins with fingerprint biosimilarity, which can be readily analyzed using robust in-house bioassays. Bioceros also possesses a wide range of advanced analytical capabilities, including mass spectrometry, state-of-the-art chromatography systems for clarification and purification and the custom design and execution of bioassays.

THE USE OF COMPARABLE — AND, IN MANY CASES, IDENTICAL EQUIPMENT FOR RESEARCH, DEVELOPMENT AND PRODUCTION, COMBINED WITH THE COLLABORATION BETWEEN OUR MANUFACTURING AND DEVELOPMENT TEAMS — **INCLUDING THE SHARING OF ANALYTICAL AND BIOASSAY DEVELOPMENT DATA — FACILITATES SMOOTH AND FAST IN-HOUSE TRANSFER.**

With this suite of capabilities, it is typical for a client to have a locked-in "50-L process" ready for upscaling within 11 months.

LARGE-SCALE GMP MANUFACTURING FACILITY

Once the small-scale facility in Gdansk was completed, Polpharma turned its attention to establishing a large-scale commercial production plant. This facility is located in Duchnice, Poland, near Warsaw. The building has been completed, and the drug substance manufacturing line (2 x 2000-L bioreactors), including cleanrooms and utilities (as well as administrative offices), are currently under construction. Cleanrooms and utilities are also being installed for two additional production trains, allowing rapid expansion (within a few months) to 6 x 2000-L capacity as needed, without interrupting ongoing operations. Work will be completed in 2020, and technology transfer of the first product will take place in the third quarter of 2020. High-speed fill and finish lines have also been designed into the concept of this new site.

This facility will largely serve as a contract development and manufacturing site with mammalian and fill/finish technologies. Importantly, the technologies used for large-scale production are aligned with the technologies at all of our other facilities. The use of comparable – and, in many cases, identical equipment for research, development and production, combined with the collaboration between our manufacturing and development teams – including the sharing of analytical and bioassay development data – facilitates smooth and fast in-house transfer.

ONE-STOP SHOP

With our two facilities in Poland and cell line development capabilities at Bioceros, Polpharma Biologics is able to provide truly integrated contract development and manufacturing services for both branded and biosimilar projects. Our capabilities span the full range from cell line, process and analytical development to GMP manufacture of drug substance and drug product that meet international quality standards.

Our modular one-stop-shop approach enables flexibility in terms of work packages and scope. We are happy to collaborate on integrated, end-to-end projects, or just one aspect of the development cycle. We are also able to readily scale with projects as they move from development to the clinic and commercial launch. As importantly, we provide a comprehensive range of services tailored to each individual project.

COMMITTED TO SERVICE

CDMO services from Polpharma Biologics are tailor-made for customers from all over the world for biosimilars and innovative molecules, including next-generation biologics, such as newer antibody frameworks.

Polpharma Biologics is dedicated to functioning as a true service provider. At the highest levels of the company, our goal is to collaborate with clients in order to help them accelerate the development and commercialization of life-improving and life-saving medicines. The company is 100% committed to supporting clients through the development process, including investment (with appropriate agreements in place) in additional capacity in response to evolving project needs. P

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SPEEDING UP ADC DEVELOPMENT WITH THE RIGHT PARTNER ORGANIZATION

→ BY **COURTNEY MORGRET, Ph.D.,** ABBVIE CONTRACT MANUFACTURING

As antibody–drug conjugate (ADC) programs progress from the early to late stages of clinical development, and more of these therapies actually penetrate the market, there is a clear need to manufacture ADCs efficiently, cost-effectively and with an eye toward commercial production from the earliest stages of development. Accelerating ADC production is integral to supplying patients with these potentially life-saving therapies while also securing a competitive advantage within the market and guaranteeing shareholders a return on investment.

PARTNERING FOR ADC ADVANCEMENT

To successfully compete in the ADC space, a strategic approach for reducing time to market is key. Strategic process/analytical development and characterization, commercial manufacturing site selection, and manufacturing-scale process performance qualification (PPQ) are all part of expediting time to launch. Undergoing these activities sooner decreases the risk of unexpected issues arising later in development, which would impact chemistry, manufacturing and control (CMC) activities and be more expensive to correct further down the line.

To avoid any potential missteps in ADC production and speed time to commercialization, partnering with an expert contract development and manufacturing organization (CDMO) that has a history of successes is key for the advancement of an ADC program. The ideal CDMO candidate will demonstrate expertise in early phase process understanding and possess a team of experts with proven scientific and technical knowledge, as well as staff versed in operations and program management, and also be equipped to handle diverse regulatory requirements. Finding the right CDMO partner can mean the difference between a commercial-ready ADC program and one that is unable to move past the clinic.

ADC GROWTH AND MANUFACTURING CHALLENGES

Using specific antibodies for targeted cell death, ADCs offer a more advanced treatment for cancer than chemotherapy. This potential has not gone unnoticed in the market. ADC therapeutics are predicted to reach a value of nearly $10 billion by 2025.[1] The success of ADCs against tumors has helped spur the approval of five ADC drugs for oncology indications within the last decade.[2,3] Further potential indications for ADCs coupled with steroids for inflammatory diseases and antibiotics for the treatment of infectious diseases are also currently in development.[4,5]

ADCs offer tremendous potential as life-saving therapies for a number of indications, which means pushing them rapidly from the clinic to market is critical. However, the manufacture of ADCs presents a unique set of challenges. Moving an ADC program through a complex supply chain, in which several manufacturing facilities are tasked with producing the antibody, payload, linker, conjugate and final drug product can add substantial time, cost and difficulty to the process. ADCs must also be handled with extreme caution to prevent their contamination and the exposure of handlers to the potent compound. Partnering with a CDMO that is experienced in minimizing risk and assuring product quality can keep an ADC program on track throughout the life cycle.

A CDMO can help navigate a partner organization through regulatory hurdles and even accelerate approval. To get drugs to patients who are in critical need as quickly as possible, the FDA created the Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review programs, all of which can potentially be used for the advancement of ADCs. In order to qualify for these accelerated pathways, a CDMO must work to expedite a drug through each phase of the lifecycle, including process design (stage 1), process qualification (stage 2) and continued process verification (stage 3).

STRATEGIC SUPPLIER SELECTION

Manufacturing ADCs at the designated commercial site is another way to speed up development while allowing the multistage process characterization program to begin sooner, eliminating the need for late stage tech transfer and process-intensive comparability studies before regulatory submission. If a partner organization is able to manufacture multiple components of the ADC, product supply lead times are considerably reduced. Operating under an integrated system also creates flexibility. The selected supplier must demonstrate strong program management abilities, especially if multiple phases of the process are mediated by one organization.

A strategic supplier will also know to begin process characterization in phase I, instead of waiting for phase II. Applying process characterization, which is essential for process validation, to the process after phase I leads to earlier PPQ. For tight timelines, PPQ runs may be tiered to overlap with process characterization. Even though PPQ is typically performed after process characterization, an experienced CDMO will suggest a tiered approach in order to implement PPQ faster.

The process characterization step ensures that the process is robust enough to deliver a quality target product profile (QTPP) appropriate for commercial launch. In order to successfully carry this out, expertise in analytical method development and application is a priority. The supplier organization should have experience creating representative laboratory scale-down models (SDMs) in order to establish QTPP, which should be embedded in their process for both conjugation and purification, as well as small-volume liquid-handling robots for chromatography.

Analytical studies, including range-finding, process mapping, impurity spiking/clearance studies, resin/membrane cleaning/storage studies, resin/membrane aging studies, virus clearance validation studies and leachable/extractable analyses help define parameters and can be implemented at other stages of validation, including structural elucidation, extended characterization for comparability and QC release. An organization that conducts the proper analytical tests from the onset spares the sponsor organization costly changes or unpredictable issues further into the timeline.

Although crunched timelines may theoretically hinder process optimization before launch, robust comparability studies can work to support any pre- or postapproval changes. A reliable comparability package gives sponsors the tools to enhance process robustness, improve product yield, or reduce cycle time.

WORKING WITH A TRUSTWORTHY AND EXPERIENCED PARTNER

ADCs have the potential to impact the lives of millions of patients, but getting these programs from the clinic into the market creates challenges. A sponsor's decision to partner with a supplier organization is the single most important decision for a program. AbbVie Contract Manufacturing is equipped to handle the ADC life cycle from start to finish. We rely on comprehensive experience to provide partners with unparalleled expertise in delivering launch-ready ADCs that can support accelerated timelines, from analytical understanding, a well-defined process characterization strategy that enables PPQ, manufacturing expertise, process validation and comparability strategies, to regulatory submissions. P

IF A PARTNER ORGANIZATION IS ABLE TO MANUFACTURE MULTIPLE COMPONENTS OF THE ADC, **PRODUCT SUPPLY LEAD TIMES ARE CONSIDERABLY REDUCED.**

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PLANT-BASED PROTEIN EXPRESSION FOR RAPID, GREEN BIOPROCESSING

→ BY **TERENCE E. RYAN, Ph.D.,** iBIO, INC.

Mammalian cell culture is widely used for biologic drug substance production, but the high cost and long development times pose challenges to the implementation of this technology in many parts of the world. Traditional protein expression systems are also often not optimal for the novel biomolecules under development today; however, plant-based expression systems can overcome many of these shortcomings.

TWENTY-YEAR HISTORY

Therapeutic proteins have been produced in plant-based expression systems for more than 20 years. Human trials were first conducted in the late 1990s for an experimental cancer therapeutic and an antibody for the prevention of tooth decay. Since then, various antibodies, vaccines, enzyme therapies and other therapeutic proteins developed by iBio and other companies, such as Protalix BioTherapeutics, Medicago, Icon Genetics and Kentucky Bioprocessing, have reached clinical trials and, in some cases, achieved regulatory approval.

ADVANTAGES OF PLANT-BASED EXPRESSION

Despite the many advances made in recent years with mammalian cell culture upstream processing, important fundamental challenges remain with CHO-based systems, including long product and facility development timelines and high capital expenditure requirements for bioprocess trains and buildings. Even in instances where single-use systems (SUS) are deployed to reduce costs and timelines associated with stainless steel bioprocessing, there are significant unfavorable associated environmental impacts. Expression levels can also be low for the next-generation biologic drug substances in the pipeline. Some newer therapeutic proteins cannot be produced at all in existing mammalian, bacterial, fungal or insect cell systems.

Unlike traditional mammalian cell culture, plant-based transient protein expression systems typically do not require identification, isolation and development of optimal high-producing cell lines to enable large-scale production. There is also no need to invest in the large-scale production equipment or highly skilled labor required for commercial cell culture processes. Scale-up is simpler, too – all it requires is growing more plants rather than switching to larger bioreactors, which can impact processes and potentially cause delays and higher costs. Furthermore, since no animal-derived materials are used, there is no risk of contamination by adventitious viral agents or other undesired pathogens, and expensive aseptic liquid-handling process steps can be avoided.

It has also been shown that antibodies manufactured in plant-expression systems exhibit superior antibody-dependent cellular cytotoxicity (ADCC) compared with those produced in mammalian cells, such as Chinese hamster ovary (CHO) systems.[1] CHO and NS0 systems add in sugar residues (α-1,6-fucosylation), which results in down-regulation of ADCC. Plant-manufactured versions of palivizumab, an anti-respiratory syncytial virus (RSV) mAb, have been shown to have enhanced viral clearance compared to the original antibody, which is produced using mouse myeloma cells.

iBIO'S PLATFORM TECHNOLOGY

iBio employs *Nicotiana benthamiana*, a relative of the common tobacco plant, for its protein-expression platform. The system takes advantage of two gene expression components in the proprietary expression vectors. The first expression cassette is derived from a plasmid carried by *Agrobacterium tumifaciens* and allows for the efficient transfer of DNA to the nucleus of

USING NON-GMO PLANTS IN THE iBIO MANUFACTURING PLATFORM ELIMINATES **THE MONTHS OR YEARS NEEDED TO FIND A HIGH-PRODUCING STABLE CELL CLONE USING MAMMALIAN EXPRESSION SYSTEMS.**

GIVEN THE SPEED OF ITS PLANT BIOPROCESSING TECHNOLOGY, **iBIO CAN COMPLETE A FEASIBILITY STUDY FOR CLIENTS IN JUST WEEKS AND PROVIDE 100 MG OF PROTEIN FOR TESTING.**

plant cells and expression of downstream genes. The second expression component is derived from tobacco mosaic virus or other plant viruses and drives runaway expression of the desired protein product in the plant cell's cytoplasm. The plants grow rapidly and contain little nicotine. In addition, *N. benthamiana* supports replication of a wide range of viruses, which is advantageous when it is necessary to express multiple genes in the same cell.

The third-generation iBio platform uses unmodified green plants grown hydroponically in a vertical stack system under artificial lighting. After about five weeks of growth, the plants have generated sufficient biomass to enter the transient expression process. The plants are removed from the growth stacks in pallet-sized trays and inverted into a solution of *Agrobacterium* containing the appropriate expression vector. The racks of plants are then exposed to a mild vacuum, which draws gas from the plant leaves. Upon release of the vacuum, the plants replace the missing gas with the *Agrobacterium* solution, initiating the gene transfer process to first the nucleus and subsequently the cytoplasm of every leaf cell in the plant. Translation of these recombinant viral vector mRNAs can result in the accumulation of gram quantities of target protein in the plant leaves per kilogram of fresh plant tissue (up to 20–30% of total soluble protein) in less than a week.

The plant biomass is then harvested, homogenized, and clarified to produce an extract containing the protein of interest. Proteins are further purified as required using conventional separation and chromatography steps widely used in the biopharmaceutical industry.

This transient expression system is highly flexible and has been used for the expression of vaccine antigens (including virus-like particles), antibodies, fusion proteins, interferons and cytokines, growth factors, protease inhibitors, clotting factors, enzymes for replacement therapy (specifically alpha-galactosidase A) and other products that cannot be produced using conventional expression systems.

The iBio manufacturing facility in Bryant, Texas is also designed to be highly sustainable. All gray water from the manufacturing process is recycled, and the lights used for growing the plants are highly efficient, using spectrum-calibrated LEDs that generate only the wavelengths of light required by the plants.

Until the plants are infiltrated with agrobacteria containing a specific viral vector, they are considered raw materials. They are kept in a separate area of the facility and are rigorously assessed for quality before entering the manufacturing process. All process development, purification, fill/finish and analytical operations take place in portable PODs from G-CON, physically independent rooms with individual utilities allowing the simultaneous completion of multiple independent projects. It takes just one week to completely clean and sterilize the facility to prepare for a new campaign. Parallel processes can proceed simultaneously at different scales (R&D, pilot, full factory).

REAL ACCELERATION AND COST SAVINGS

Using non-GMO plants in the iBio manufacturing platform eliminates the months – or years – needed to find a high-producing stable cell clone required by mammalian expression systems. Process development can begin within 30 days of knowing the target gene's sequence. As a result, iBio's plant-based system offers rapid evaluation of protein expression and screening of candidate molecules at a very low cost.

Seamless scale-up is achieved by growing additional plants in numbers consistent with the scaling factor, with no concerns about scaling causing changes in protein structure or posttranslational modifications (PTMs), further accelerating process development. It is thus possible to reduce the time to IND filing by six months or more compared with CHO-based systems.

A techno-economic analysis of plant-based protein manufacturing was performed for the iBio Texas facility using a model developed by a group at UC Davis.[2] The existing iBio facility, which was built for $110 million in six months, could be built today for ~$120 million, while a typical CHO facility would cost $2 billion or more. As a result, the cost of goods (COGS) for a mAb produced by iBio is ~$120/gram including depreciation – a 50% reduction compared to published COGS values for mAbs produced using CHO systems.

END-TO-END SUPPORT

iBio's Texas facility has a current capacity of approximately 3,500 kg of biomass per week, which can be doubled to 7,000 kg of biomass per week by building out an additional grow room. Proteins can be produced at any scale: material obtained from one plant through lab and GMP-pilot scales to commercial quantities (350 kg of purified mAb per year, which can also be doubled). Given the speed of its plant bioprocessing technology, iBio can complete a feasibility study for clients in just weeks and provide 100 mg of protein for testing.

All equipment is in a constant state of readiness, fully commissioned and ready for scale-up cGMP activities as needed. All of the purification equipment, which is located in G-CON cleanrooms, has been sized to accommodate the doubling of protein expression capabilities.

In addition to cloning the necessary vectors, biomass production and protein extraction and purification, iBio also supports clients with buffer exchange, formulation and both automated and manual sterile fill and finish activities (hundreds to thousands of vials for early stage clinical trials and stability testing). Our sophisticated synthetic biology tools allow for the modification of DNA, protein sequences and protein structures to create patentable product candidates with improved function, stability, potency and other desirable characteristics.

Process development services include proprietary approaches to improved gene expression through codon optimization and significant know-how to eliminate protease activity and improve unit process yields. The use of a quality-by-design approach ensures the development of robust processes with high and reproducible product quality.

Experienced analytical staff provides method development and validation support as part of projects and on an *ad hoc* basis, with special capabilities in protein characterization using mass spectrometry. A partnership between iBio and regulatory consultant CBR International (which has 20 years of experience in plant-based protein manufacturing) ensures successful regulatory filing. For clients that wish to build and operate their own facilities, iBio will transfer the technology.

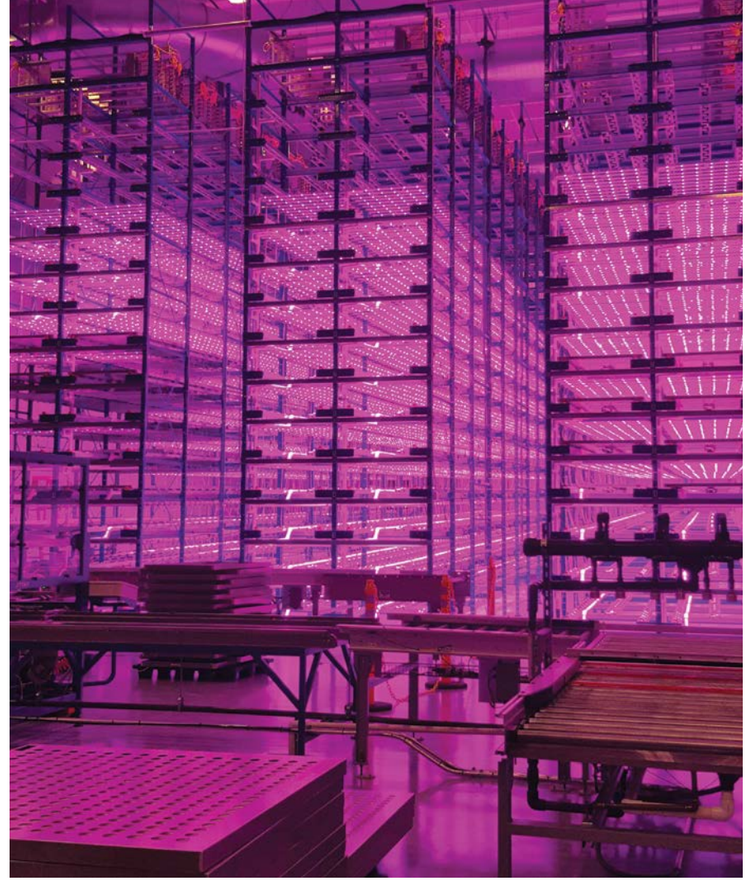
IMPORTANT COLLABORATIONS

iBio would like to support both early stage biotech and large pharma companies, as well as universities, spinouts and government agencies. The simplicity of the technology makes it well suited for implementation in areas of the world where capital and a highly skilled biopharmaceutical workforce are in short supply. The short development timeline also makes it attractive for the development of drugs and vaccines in response to pandemics.

iBio is particularly interested in supporting drug development activities in emerging markets. Bio-Manguinhos/Fiocruz, the technical/scientific unit of the Oswaldo Cruz Foundation (Fiocruz), is employing iBio's technology in a planned plant-based multipurpose biopharmaceutical and vaccine manufacturing facility in Brazil for the low-cost production of a novel yellow fever vaccine.

AzarGen Biotechnologies, an early stage pharma company in South Africa, is moving a biosimilar rituximab targeted for non-Hodgkin's lymphoma initially developed by iBio toward preclinical testing. The company rapidly evaluated several candidates, developed a process, conducted an early stage risk assessment and developed a regulatory path. It is ready to produce material for preclinical studies and the preparation of a pre-IND package for FDA. The plant-based expression technology provides the only economically viable platform for the production of this biosimilar in South Africa.

iBio is also working with the Chinese pharmaceutical company CC-Pharming Ltd. to develop products and manufacturing facilities for the Chinese biopharmaceutical market that leverage plant-based expression technology. The companies are starting with the development of a biobetter for rituximab, for which iBio will provide development and manufacturing services. The firms will also work together to design and construct a plant-based manufacturing facility in China and additional products will eventually be selected for development and sale in China. P



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LEVERAGING GMP-GRADE HUMAN SERUM ALBUMIN FOR PHARMACEUTICAL MANUFACTURING

→ BY **CARLOS ORTIZ,** GRIFOLS BIO SUPPLIES

Human serum albumin (HSA) has unique properties that make it attractive as a nutrient in cell culture media and as an excipient for lyophilized biologic drug formulations and when produced as nanoparticulates for drug delivery. The quality of HSA is crucial to its performance in manufacturing processes and the safety of any final drug products produced. Use of HSA prepared according to current good manufacturing practices (cGMP) from the outset of a project shortens time to the clinic and the market while helping to ensure product safety.

THE ALBUMIN MARKET

Albumin is the most abundant protein found in blood plasma, accounting for approximately 50% of blood protein. Two types of serum albumin are used in pharmaceutical and biotechnology applications: human serum albumin (HSA) and bovine serum albumin. A third more recent option is recombinant albumin, which is produced via fermentation in yeast or bacteria.

The global albumin market is projected to expand at a compound annual growth rate (CAGR) of 6.0% from $3.91 billion in 2017 to nearly $5.87 billion by the end of 2024.[1]

MANY PHARMACEUTICAL APPLICATIONS

Albumin in its various forms has traditionally been used for many different applications, including as a protein stabilization excipient in biologic drug formulations, particularly for those that are lyophilized, and as a nutrient in cell culture media formulations. More recently, it has been shown to be effective as both a nutrient and stabilizer during the culture, expansion, freezing, thawing and manipulation steps involved in the development of cell therapies. Albumin in nanoparticulate form is currently being explored as an effective drug delivery vehicle. In some cases, albumin has also been applied as a coating on implantable medical devices.

EXCIPIENT FOR BIOLOGIC DRUG FORMULATIONS

Serum-derived albumin is well known to stabilize the properties of proteins and other biologic drug substances. In the body, HSA is responsible for maintaining the oncotic pressure, plasma pH and the distribution of a variety of endogenous and exogenous ligands.[2-4] Albumin, in general, has a large number of sulfur binding sites that can interact with proteins in various ways, preventing aggregation and oxidation, reducing surface adsorption and improving solubility and batch-to-batch consistency. As a result, albumin can often replace multiple excipients, eliminating the need to spend extensive time and effort developing optimal compatible excipient combinations. This advantage has become increasingly important as the complexity of biologic drugs has increased with the introduction of next-generation treatments, such as antibody-drug conjugates, cell therapies and viral vaccines.[2]

CELL CULTURE MEDIA NUTRIENT

Albumin is added to cell culture media as a supplement to enhance the overall health of cells and to promote cell growth, productivity and viability.[5,6] In addition to providing nutrients (e.g., hormones, growth factors), it binds to toxins (e.g., copper) and free radicals, preventing them from harming cells. Albumin binds to excess proteins, thus acting as a buffer, and to hormones, growth peptides and other media ingredients, stabilizing them. For instance,

ALBUMIN IS THE MOST ABUNDANT PROTEIN FOUND IN BLOOD PLASMA, **ACCOUNTING FOR APPROXIMATELY 50% OF BLOOD PROTEIN.**

FOR MANY OF THE SAME REASONS THAT ALBUMIN SERVES AS A BENEFICIAL INGREDIENT IN CELL CULTURE MEDIA FORMULATIONS, **IT IS ALSO PROVING ADVANTAGEOUS FOR THE PRODUCTION AND HANDLING OF STEM CELL AND OTHER CELL THERAPIES, AS WELL AS VARIOUS REGENERATIVE MEDICINAL PRODUCTS.**

binding to fatty acids, amino acids, bilirubin and pyridoxal-5´-phosphate by albumin prevents their oxidation. The performance of the albumin as a media supplement depends on the quality and relative quantity of the specific ligands present, which is determined by the nutrition provided to the animal (human, bovine) source.

The use of natural HSA in cell culture media formulations has increased in recent years, owing to the shift away from animal-derived ingredients.

NEXT-GENERATION THERAPY PRODUCTION

For many of the same reasons that albumin serves as a beneficial ingredient in cell culture media formulations, it is also proving advantageous for the production and handling of stem cell and other cell therapies, as well as various regenerative medicinal products. Cell therapies often must be cryopreserved for storage and shipment. Consistent, reproducible media is required to protect these fragile biologic treatments, and HSA is often an important ingredient.[7] In fact, it is typically used from the beginning of cell therapy manufacturing processes to enhance consistency, quality and reproducibility. It has also been shown to improve vector transduction for adeno-associated viruses (AAVs).[8]

DRUG DELIVERY

Albumin has also been used as a drug delivery vehicle for various types of active pharmaceutical ingredients (APIs), including antibiotics and anti-inflammatories. It is attractive for this application because it is nontoxic, non-immunogenic, biocompatible and biodegradable[9] and has a long half-life of approximately 19 days, allowing drug concentrations to remain high over an extended period of time.[10]

Most often, albumin used for drug delivery applications is generated in nanoparticulate form using a variety of methods, such as desolvation, emulsification, thermal gelation, nano-spray drying, nab-technology and self-assembly.[10] Abraxane – a nanoparticle albumin–bound paclitaxel – is one such example.

Currently, many other opportunities for the application of nanoparticulate albumin in drug delivery are being explored.[10] Due to the extensive binding and complexing ability of albumin, nanoparticles of the protein can be loaded with chemotherapeutic drugs, pulmonary drugs, inhibitors, fluorescent dyes, contrast agents and other molecules, including other proteins and antibodies, to develop novel drugs – as well as highly targeted therapeutics and imaging agents. When conjugated with certain excipient-grade polymers, albumin nanoparticles can cross the blood–brain barrier and also achieve delivery of oligonucleotide drugs. Nanoparticles that are unstable in biological fluids can be stabilized using albumin to enable efficient drug delivery.

THE INTRODUCTION OF PLASTEM® FOR THE BIOPHARMACEUTICAL MARKET REFLECTS **GRIFOLS' FOCUS ON INNOVATION AND CONTINUED IMPROVEMENT ACROSS OUR ENTIRE PORTFOLIO.**

IMPORTANCE OF cGMP HSA

There are several methods for isolating human serum albumin from plasma. There are also various manufacturing processes for the production of recombinant HSA. Regardless of which method is used and which type of product is produced, it is essential that any HSA intended for pharmaceutical applications are pharmaceutical grade and manufactured in compliance with current good manufacturing practice (cGMP) requirements.

Using pharmaceutical-grade products from the beginning of development ensures a smooth regulatory pathway when entering the clinic and scaling to commercial production. Companies that initially use BSA or research-grade HSA (natural or recombinant) in their cell culture media or drug formulations will eventually have to replace those ingredients with pharmaceutical-grade material produced under cGMP conditions, which can significantly delay project timelines.

HSA FROM GRIFOLS BIO SUPPLIES

Grifols Bio Supplies, a division of Grifols Group, distributes high-quality biological materials for biotechnology research, clinical trials and the manufacture of pharmaceutical and diagnostic products. We have extensive experience manufacturing a number of different proteins for diagnostic applications and therapeutic uses.

Our human serum albumin meets the highest quality and safety standards expected for drug products, even if its intended use is as a pharmaceutical raw material. We also provide extensive regulatory support. Most recently, Grifols has developed a serum albumin with performance equivalent to fetal bovine serum for use as a supplement for mammalian cell culture, called Plastem®.

Plastem® is a GMP human plasma-derived protein supplement containing albumin that overcomes many issues associated with FBS. It has traceability because it comes from FDA-approved plasma centers. Plastem® also has reduced batch-to-batch variability because each batch is manufactured from thousands of donations. As importantly, it is cGMP pharmaceutical grade and xeno-free, containing no animal-derived materials.

The introduction of Plastem® for the biopharmaceutical market reflects Grifols' focus on innovation and continued improvement across our entire portfolio. We are committed to ongoing product development to support new advances in pharmaceutical manufacturing systems and processes. P

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Advanced Therapies: Landscape, the Road Forward, and M&A

Successful CAR-T treatments burst onto the immuno-oncology [IO] scene earlier this decade, and their compelling clinical data for blood cancers (overall remission rates above 50%) led to rapid regulatory approvals for *Yescarta* (Kite–Gilead) and *Kymriah* (Novartis) beginning in 2017. These approvals helped accelerate the growth of cell therapy clinical trials (now over 1,000 worldwide) and financings, which increased 73% to $13.3B in 2018.

However, first-generation IO cell therapies are of the "patient-specific," autologous variety, which require a logistically complex, two-week, costly manufacturing process that ultimately drives pricing to greater than $350,000 per patient. Additionally, there are identified safety risks, including neurotoxicity, the now controllable – but nevertheless violent – cytokine release syndrome. There are also concerns about the continued use of viral vectors to perform the genetic reprogramming of T cells. However, the future for advanced therapies is bright, with next-gen IO products in position to overcome those issues while expanding indications to solid tumors. Beyond oncology, cell therapies and 3D bioprinting techniques are in development with the potential to revolutionize fields from neurology to transplantation.

Cell-Based/Gene Therapy

The FDA estimates that, by 2025, there may be 10–20 new cell and gene therapies (C/GT) approved per year. Some of those will be in IO, where the switch from autologous treatments to lower cost "off-the-shelf" (allogeneic) products may be realized. Strategies to "go-allo" include the use of alternative cell types. Natural killer (NK) cells, macrophages and induced pluripotent stem cells (iPSCs) plus new gene-editing tools are facilitating the creation of creatively named "Armored CARs," "TaNKs," and other next-gen products, which have the potential for greater efficacy and lower costs. Additionally, new "non-viral" gene delivery methods (e.g., transposon systems, mRNA technologies and synthetic DNA nanocarriers) provide new capabilities while improving safety.

Meanwhile, outside the field of oncology, allogeneic mesenchymal stromal cell (MSC)-based therapies continue to make slower yet steady progress for indications ranging from Crohn's disease (EMA approval of TiGenix–Takeda's Alofisel in 2018) to multiple sclerosis, ischemic stroke and congestive heart failure (note Mesoblast's active 600-patient phase III trial). CRISPR and other gene-editing tools hold significant promise for MSC use in inflammatory disease indications, too. Some innovators even seek to use those tools to modify MSCs to turn them into "drug delivery systems," given the cells' innate ability to "home" to sites of immune dysfunction.

The development of iPSC-based cell therapies is yet another promising category. The field was catalyzed by Bayer/Versant Ventures' enormous $225M Series A investment that created BlueRock Therapeutics in 2016. Leading with a dopaminergic neuron product, BlueRock hopes to address critical unmet clinical needs in Parkinson's disease, among others.

Biofabrication – the Next Big Thing in Biologics?

With 20 people dying in the United States each day waiting for an organ transplant, the need for alternatives to organ donations grows unabated. Fortunately, technologies are continuing to emerge that combine bioinks (cells), biopapers (scaffolds), bioprinters and other materials to create biofabricated tissues. This will be a challenging task, no doubt, but a number of companies already have active development programs underway, including Biostage's work on a lab-produced esophagus, Orgenesis' liver constructs, and United Therapeutics' endeavor to build the *XenoLung*.

The Future of Biologics M&A Activity

The past appears to be the prologue for advanced therapies. Like monoclonal antibody deals in the late 2000s, cell therapy deals are ramping in the back half of this decade, recently punctuated by BMS' $74B pickup of Celgene. The heat is on in biologics manufacturing M&A, too. Danaher grabbed GE's BioProcess business for $21B to pair with their Pall Life Science holding. Meanwhile, a couple of CDMOs made grabs for viral vector capability and capacity. Thermo Fisher shelled out $1.7B for Brammer Bio, and Catalent paid $1.2B for Paragon Bioservices, within weeks of one another. It is remarkable that Paragon had only just held the grand opening of its new viral vector facility four days before its deal with Catalent was announced.

It's hard to imagine the field getting any hotter over the coming years. However, with therapeutic proteins far from "mature," cell and gene therapies just entering the growth stage of their life cycle and the field of biofabrication hardly even out of the gate, there's almost certainly much more to come. So, hold on to your hat: there is plenty of activity in advanced therapies, bioprocess systems and biologics CDMOs in the forecast. P

Eric Mattson
Principal
Excellere Partners

Running a CDMO Business is Hard – So Now Let's Talk about Value Creation

Many years ago, early in my tenure running a private equity (PE)-backed business, two nurses in my contact center got into a fight (literally a fistfight) over one's objection to the other's apparent disregard for our dress code. A few months later (unrelated to the fight), a disgruntled boyfriend threatened to blow up our facility. What does this have to do with *value creation* in CDMOs? Nothing, really, except that it underscores the unique and varied challenges in running a business, which are all incremental to your customers, competitors, suppliers, regulators and others, who are constantly throwing you curveballs.

Then, all of a sudden you have these new PE owners, and they want to talk to you about "value creation." It's like, "Sure, I'll get to that right after I diffuse the bomb in the parking lot." As a former operator, I can appreciate the apparent absurdity in the additional ask to engage in value creation, but I can also attest to the merit of successfully executing a valuation creation plan.

First, it's important to understand one's definition of "value creation." Admittedly, within private equity, it has become a bit of a cliché. That's not because value creation isn't important or valid, but rather it's a result of bad actors in PE – those who don't really understand the nuance of truly partnering with their management teams to achieve value creation together – who place the entire burden on their operating company. Within Excellere, we have a systemic value creation process that focuses on two core philosophical elements: (1) establishing the vital few and (2) the foundation before growth.

Vital Few

Within virtually every pharma CDMO business we have encountered, there seem to be two or three key value detractors. They're not always the same, but generally they include some combination of the following: customer concentration, lack of management depth, inconsistent and/or non-recurring revenue, heavy capital expenditure requirements, lack of institutionalized business development, unreliable API supply, etc. When executing a value creation plan, we believe it's imperative to not try and "boil the ocean." Accomplishing the most critical two or three things well is far more effective than diluting your efforts across the entire to-do list. Once one is accomplished, you can then move down the list sequentially.

Foundation Before Growth

You would never add another story onto your house without first being certain that the foundation could support it. In a similar fashion, we would never propose a major growth initiative without first having the corporate foundation in place to absorb the expansion. For example, do you have key managers who have experience executing and integrating acquisitions? Are your information systems delivering real-time business insights? Is your regulatory and compliance team equipped to support new lines of business or operate in foreign countries? Are your key suppliers capable of handling the growth? Are you able to focus on strategy and not get bogged down with the "brush fires"? Whatever they are, you must shore up your foundational weaknesses before embarking on transformational growth – which is what PE wants.

Most CDMO businesses have tremendous value creation upside — just be certain that all stakeholders are aligned with how to achieve the results.

As a leader in your business, it's important for you to know that we're considering making an investment largely because we believe that there's additional value that can be derived.

Value creation should be about a shared vision of growth, and it is certainly as much art as it is science. Here at Excellere, we're unwavering in our discipline around value creation. As a leader in your business, it's important for you to know that we're considering making an investment largely because we believe that there's additional value that can be derived. We also believe that you and/or your management team have the passion to execute the plan, which for us means focusing on those few key initiatives that have the potential to move the needle, and committing to a strong foundation. Most CDMO businesses have tremendous value creation upside – just be certain that all stakeholders are aligned with how to achieve the results. P

Haig Armaghanian
Founder and CEO
Haig Barrett, Inc.

Cancer's New Foes— Novel Oncology Approaches in the Battle Against Cancer

The healthcare burden of cancer is increasing worldwide. There were an estimated 18 million new cancer cases in 2018,[1] a 28% annual increase from 2012. Alarmingly, by 2030, annual diagnoses are expected to increase another 31% to 23.6 million new cases per year.

The Cancer Burden

Contemplating both the ominous increase in cancer rates and its biological drivers, reviewing the oncology landscape becomes akin to studying the military strategies of Attila the Hun. The story is one of deception, traitorous conversion, brute force and surrender. Cancer cells' number-one priority is to survive, thrive and expand their territory.

Until recently, the medical community's primary strategy to battle cancer was to reduce or eliminate cancer cells or cancerous masses by surgery, radiation, cell-killing chemotherapy or a combination of the three. Because of an incredible array of scientific, biological, medical and therapeutic advancements, there is now a diverse set of treatment approaches – many still in various stages of development.

An Expanding Arsenal

The expanding set of treatment options include more efficacious and less toxic chemotherapies, targeted therapies, hormone therapies, stem cell transplants, increasingly sophisticated biomarkers, immunotherapies, therapeutics utilizing cancer's metabolic behaviors and a growing understanding of ways to deliver on the promise of precision medicine.

Immunotherapy, currently the darling of the oncology world, is an approach that uses or retrains the patient's own immune system to fight cancer. The age of immunotherapies was ushered in by the approval of ipilimumab, a melanoma treatment, in 2011. As of March 2019, 13 new cancer immunotherapies have been approved and are becoming the standard course of care for a growing number of cancers. In fact, according to a *Nature* survey published in November 2018, from September 2017 to September 2018, there was a 67% increase in the number of active agents in the global immuno-oncology pipeline (2,031 agents in 2017 versus 3,394 in 2018).[2]

Until recently, the FDA has approved therapeutics in alignment with the area of the body where the cancer in question originated (e.g., lung cancer or ovarian cancer). However, this is changing, presenting some fascinating opportunities for a possible new paradigm in the development of cancer drugs that are tissue agnostic. The agency has now approved two treatments based on a common biomarker across different types of tumors rather than body location.[3]

Maybe putting cancer cells to "sleep" while avoiding the potentially dangerous side effects of most oncology treatments will work. Associate Professors Tim Thomas and Anne Voss from the Walter and Eliza Hall Institute, Professor Jonathan Baell from the Monash Institute of Pharmaceutical Sciences and Dr. Brendon Monahan from Cancers Therapeutics CRC are leading research to determine whether inhibiting KAT6A and KAT6B could be an effective and less risky approach to treating cancers. Rather than focusing on damaging cancer cell DNA (which also damages the DNA of healthy cells) as chemotherapy and radiation strive to do, this approach targets KAT6A and KAT6B proteins, both of which are known to play important roles in fueling cancer growth. With these genes in a state of permanent sleep, several cancers should simply stop progressing.[4]

Yet another approach takes advantage of the unique metabolic characteristics of cancer cells. Several emerging methods strive to change or suppress cancer's metabolism to stop it in its tracks. However, the development team at Vybyl Biopharma is taking advantage of cancer's metabolic behaviors to target drug delivery. The Vybyl team knew that RAS-driven cancers are "hungry" for the fatty acids contained within human serum albumin (HSA). They are developing a small molecule drug conjugate that hitchhikes by uniquely mimicking fatty acids on key HSA and lipid nutrient acquisition pathways central to tumor growth to deliver highly toxic yet highly effective solid-tumor chemotherapies like paclitaxel in a targeted manner. This avoids many of the consequences of untargeted chemotherapy administration.

A Revised Outlook

It was not long ago that surgical removal, radiation and untargeted chemotherapies were the only weapons within the medical community's cancer-fighting arsenal. Today, the rapid development of novel oncology solutions shows no signs of slowing down, and the battle to fight cancer will continue with increasingly effective weapons. P

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The Value of Experience and Strategic Thinking

In the pharmaceutical industry, larger pharmaceutical companies that have a tactical mindset and no longer value the experience of long-term industry personnel are on the verge of being supplanted by strategically operated, small and medium-sized firms that do.

Complex Industry

The pharmaceutical industry is highly complex, and it is only becoming more so with each passing year. For pharmaceutical companies to be successful in this challenging environment, people in leadership positions must be competent in all aspects of the business: pharmaceutical, regulatory, healthcare, legal and financial.

Inexperienced Leadership Creates Risk

Placing inexperienced people in management and executive roles creates significant risk for the company and the pharmaceutical industry overall.

While it may seem like an exaggeration, the human brain is not fully developed until approximately age 30. Partially because of this, those most likely to have strong decision-making abilities and more advanced skills tend to be older. After receiving a university degree, it takes most people at least 10–15 years of experience in the pharmaceutical industry to truly be in a position to accept a managerial role.

Recent graduates may be able to speak the current business language, but they lack an implicit knowledge of the industry. Individuals that come from other sectors may have work experience, but that will not necessarily translate into an understanding of the complex workings of pharma. Younger managers are also more likely to seek to implement seemingly "new" ideas that have already been explored in the past, leading to cyclicity that can hinder long-term business success.

Experienced Leadership Brings Value

People that have worked in the pharmaceutical industry for many years learn the five disciplines important for effective leadership naturally, through their involvement in various projects and roles. They understand the potential impact of medical intervention on the human body, the expected manufacturing and regulatory compliance hurdles, patent and reimbursement challenges and the financial incentives behind each new drug under development.

Experienced leaders recognize that management roles are teaching roles just as much as they are decision-making positions. They have extensive knowledge about what occurs at each level of the company and how the diverse operations work together and are able to pass that information on to the people that report to them, as they move from one level to the next.

These experienced people are ideally suited to serve as department heads and site heads and in executive management positions. They recognize the importance of bringing young talent and new perspectives into the organization and are committed to helping those that want to learn become steadily more experienced.

Tactical Thinking Hurts in the Long Run

Public companies have a responsibility to their shareholders, who generally expect to see immediate returns. They are incentivized to achieve short-term gains, and company thinking is fundamentally tactical. This mindset trickles down to all aspects of company operations, including the placement of inexperienced, younger people with lower salaries in leadership positions. Goals are established on a 5-year timeframe, but even when they are achieved, it is done at the cost of the future; many of these firms find themselves struggling just 5–10 years later.

Privately owned companies do not have to operate in this type of environment. Strategic thinking is, in fact, often encouraged. In the pharmaceutical industry, where it takes 10–15 years to get a molecule from discovery to market, long-term thinking is essential. These companies recognize the value of experienced management and seek out industry experts to ensure ongoing success.

Small and medium-sized pharma companies, many of which are privately owned, have become the innovation engine of the pharmaceutical industry.

Bright Future for Small and Medium-Sized Private Pharma Companies

Currently, many of the largest pharmaceutical firms are struggling with regulatory compliance and legal and finance issues, in part because they no longer have the necessary level of experience in leadership positions. While not all big pharma firms have gone this route, it has definitely presented itself as a trend.

Meanwhile, small and medium-sized pharma companies, many of which are privately owned, have become the innovation engine of the pharmaceutical industry. They recognize the value of experienced leadership and have attracted top experts in the industry, in some cases enticing them away from big companies that no longer seem to value experience. P

Following the **Tobacco Road**

BY **NIGEL WALKER,** NICE INSIGHT

The U.S. Food and Drug Administration has imposed slow and steady restrictions on the sale and use of tobacco over the last 60+ years. That smoking is harmful to human health was first acknowledged in the medical community in 1954, when Richard Doll and A. Bradford Hill confirmed the link between lung cancer and smoking in findings published in a study in the British Medical Journal.

In the years following, actions have been taken to dissuade tobacco use, including adding warning labels to cigarette packaging, banning smoking in public places and funding federal campaigns urging smokers to quit. Tobacco use is now regarded as a health risk, and the connection between poor health and tobacco use is considered uncontroversial.

In spite of opposition, regulatory or otherwise, the tobacco industry is still relying on minors to become the next generation of smokers. Tobacco companies have a well-documented history of targeting young people and, before restrictions were placed on advertising, used billboards to communicate that smoking was "cool" and an "adult" thing to do.

My Personal Journey Against Tobacco Marketing

I moved to New York City in 1992 for a college exchange program at the Fashion Institute of Technology, from the village of Studham in the United Kingdom (2019 population: 1,128). While in the United States, I was taken aback by how minors were targeted by tobacco companies – from ubiquitous outdoor billboard ads to sponsorships of sporting events and concerts and promotions like Camel Cash and Marlboro Miles, which overwhelmingly appealed to teenagers. As a further example of this marketing, Virginia Slims sponsored a women's tennis championship, held annually at Madison Square Garden, in order to appeal to teenage girls.

I was not used to seeing such bold, repetitious messaging encouraging such an unhealthy activity, specifically in youths, and found it alarming. I felt so strongly about this that I decided it would be the subject of my dissertation.

To conduct my dissertation research firsthand, I planned to take a road trip across America and personally observe the extent of the signage that I knew was out there. The obvious first step of this journey would be to rent the vehicle that would take me across country, but, much to my chagrin, only those aged 25 and older were able to rent a car in the United States. I had just turned 21 and four weeks, so that marked the end of that.

Going on the Road to BIO After 25 Years

Of course, I never gave up on my dream of driving across the country. The temporary roadblock, in which I was denied the right to drive over the American open road, would be officially lifted in 2017, about 25 years later. So it was in 2017 that I again decided to drive (along with seven select staff) across the country in a chrome-wrapped Lamborghini Aventador Roadster SV, as well as an RV. The trip, which we dubbed the Road to BIO, started in Cambridge, Massachusetts and ended at the BIO International Convention in San Diego, California. Over 12 days and 100 hours of driving, we logged over 6,000 miles, crossed 19 state lines and visited and interviewed 15 clients. We were thrilled to be able to release a film documenting this journey as the first release from Nice Passion, a non-commercial venture focused on making short films, each highlighting a unique passion of an individual juxtaposed with their daily work in life sciences (www.nicepassion.com).

E-Cigarettes: Echoes of the Past

Throughout the Road to BIO, taken 25 years later, the signage targeting minors on behalf of the tobacco industry was noticeably absent compared with the roads in 1992, the year I wrote my dissertation. In 1998, lawsuits entered by the attorneys general of 46 states against the four largest tobacco companies (Phillip Morris Inc., R.J. Reynolds, Brown & Williamson and Lorillard) to recoup Medicaid expenses for tobacco-related healthcare costs resulted in the Tobacco Master Settlement Agreement. In addition to agreeing to annual payments in perpetuity to cover the states' healthcare expenses, the tobacco companies agreed to restrict their advertising, sponsorship and lobbying activities, particularly those that could be construed as targeting minors. Specifically, the Agreement called for an end to tobacco advertisements on outdoor billboards and transit vehicles as well as any marketing associated with sports and other public events. These restrictions were formally codified into law with the 2010 passage of the Family Smoking Prevention and Tobacco Control Act.

Unfortunately, tobacco companies are still targeting minors, if not in the same obvious way – and the FDA is still fighting, steadily imposing new regulations. The recent explosion of popularity of e-cigarettes and vaporizers has created a new front in the battle between tobacco companies and regulators that closely resembles the conflict of a generation past. By 2014, e-cigarettes had surpassed combustible cigarettes as the tobacco product of choice among American middle and high school students, with more than two million teens using these products in 2017.

E-cigarettes pose a new and specific threat to young people that threatens the gains made over the years by anti-smoking campaigns. The most famous of these e-cigarette products – the JUUL – contains as much nicotine within a single "pod" as a pack of regular cigarettes and may expose users to toxic chemicals with the potential to cause serious health effects. The marketing of these products takes advantage of the public perception of the health risks of smoking to position e-cigarettes as a healthier alternative, obscuring the real

Around the same time that I attempted my trip to document youth-targeting advertising, more than 100,000 children **from over 700 city schools fought back by submitting entries for the first annual New York City Smoke-Free Ad Contest,** examples of which are shown here.

health risks of these products, as well as the dangers of creating new nicotine addicts who will inevitably transition into smokers of conventional cigarettes.

When they first brought them to market, manufacturers of these products were able to exploit loopholes in the laws that explicitly targeted combustible cigarettes to market them in ways that had long been prohibited. Suddenly, we saw the return of the dreaded billboards and cross-promotional campaigns. If anything, the companies peddling e-cigarettes found even more egregious means of targeting youths than in the past, creating products with fruity flavors – crème brulee, mango, bubble gum – designed to appeal to young users, sold in packaging designed to mimic either juice boxes and candy (and even packaged with lollipops and other sweets) or the streamlined look of Apple and other trendy tech products.

However, the FDA, under the leadership of outgoing Commissioner Scott Gottlieb, has identified the use of these products by teenagers as a major public health issue and has enacted and proposed policies to close these loopholes. The agency has already cracked down on youth-targeted packaging and promotions and has succeeded in restricting sales of flavored e-cigarettes (except for tobacco, menthol and mint) in stores. Additionally, the FDA has expanded its successful youth tobacco prevention campaign, "The Real Cost," to educate teens about the real risks of vaping and to reverse public perception that e-cigarettes are a harmless alternative. There is still considerable work to be done to combat the current epidemic of teen e-cigarette use, but it is becoming clear that regulatory efforts will follow the successful precedent of the original effort against youth smoking.

Full Circle

Although that aborted road trip didn't appear hugely significant at the time, I have been struck since by its continued relevance. The intersection between marketing and healthcare was a unique consideration for me in 1992, but it ended up being the focus of my career, and I joined an advocacy group in New York that publicized the marketing of cigarette advertising to minors, which I was part of for three years.

I also never lost that yearning for a great American road trip, although it did take me 25 years to make it happen. And, while I redirected my attention to other issues and concerns, I continued to follow the regulatory and educational efforts to fight smoking among young people and exulted in its successes, only, distressingly, to see echoes of the same issues appear again in recent years. However, I do feel confident that we have collectively learned the lesson from decades past and that we will be able to quash teen vaping as effectively, and more quickly, than we reduced teen smoking. P

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Mr. Walker is the founder and managing director of That's Nice LLC, a research-driven marketing agency with 20 years dedicated to life sciences. Nigel harnesses the strategic capabilities of Nice Insight, the research arm of That's Nice, to help companies communicate science-based visions to grow their businesses. Mr. Walker earned a bachelor's degree in graphic design with honors from London College.

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A Maturing Gene and Cell Therapy Market Drives Interest in Acquisitions

As the cell and gene therapy market matures, companies are looking to gain a stronger foothold by acquiring innovators rather than collaborating with them.

From Collaborations to M&A

Although only a handful of cell and gene therapies have received regulatory approvals, study results are highly promising. Large pharma and biotech companies alike have identified cell and gene therapy as a market worthy of significant investment. Until recently, the market has been dominated by collaborations between big pharma and smaller firms that focus on the development of novel cell and gene therapies. These partnerships seek to leverage proprietary technologies to target specific disease states.

However, the nature of transactions has changed drastically as the cell and gene therapy markets mature. Although investment in the market has increased exponentially, there is a shift from collaboration to acquisition. Large drug companies are increasingly interested in establishing a firmer foothold rather than collaborating with smaller firms to reduce risk. These companies are not managing their exposure to cell and gene therapies as rigorously now that the market has become more established. While co-development deals will continue to form, big pharma is electing to acquire at increasing frequency. Of course, these types of acquisitions – regardless of size – must provide quantifiable value for shareholders. The value will continue to be realized as acquired therapies advance clinically; however, market growth projections have helped buyers justify valuations and appease shareholders. Value within this space has been heavily driven by market growth projections to this point.

Another consideration that continues to accelerate acquisitions within this space is the competitive nature of today's pharma companies. The transactions are not happening within a vacuum, and industry players are very conscious of their competitors' actions. Companies are motivated to respond to the actions of rival firms. As a result, a number of cascading acquisitions have occurred in the cell and gene therapy space. These acquisitions will continue to apply pressure on major companies absent from the market and will likely translate into increased M&A activity going forward.

Competitive Acquisitions

Cell and gene therapy continues to be an exciting space for investors. Transactions within the last 18 months alone show a trend toward increased acquisition. Notably, the market has seen deals between Brammer Bio and Thermo Fisher Scientific ($1.7 billion), Spark Therapeutics and Roche ($4.3 billion) and AveXis and Novartis ($8.7 billion) – each motivated by different factors.

The addition of Brammer Bio to Thermo Fisher is expected to be accretive in the first year. Thermo Fisher acquired a leading CDMO and stands to benefit from strong growth projections and increased R&D investment in cell and gene therapy. Operational synergies highlight further long-term benefits to this deal.

As drug development companies, Roche and Spark Therapeutics stand to benefit from increased strength in R&D. Through the acquisition, Roche gained access to Spark's expertise in the development and manufacturing of therapies for a variety of genetic diseases and secured a product portfolio that includes the first FDA-approved gene therapy and several candidates in development.

Meanwhile, Novartis acquired AveXis to bolster its market position. Novartis owns one of the first FDA-approved cell therapies, Kymriah. The company also addressed development and manufacturing shortfalls with the acquisition of Cell*for*Cure, the French CDMO that will begin manufacturing Kymriah for Novartis in mid-2019. The AveXis deal provides Novartis with expertise in gene therapy and a robust pipeline of candidates.

While some companies have yet to take the leap into the cell and gene therapy market, preliminary clinical data indicate that this field has high promise for patients and high investment for major pharma and biotech companies. As long as shareholder value can continue to be identified, this investment will materialize in more acquisitions sooner rather than later.

Sosna & Co.: Our Network. Your Growth.

Sosna & Co. provides business development services to clients in the pharmaceutical and biotech industries. We pride ourselves on our ability to stay ahead of change, leverage technological advances and pass on insights, which are all crucial capabilities in the rapidly evolving cell and gene therapy space.

Our global network and industry relationships allow our clients to make impactful connections to address their unique business needs. We support both early stage emerging biotech and big pharma firms in their search for partnering, licensing and acquisition opportunities. Our goal at Sosna & Co. is to serve as an extension of our clients' executive team, providing services that leverage our business development expertise to create growth for our partners. P

DRIVING INNOVATION TO SUPPORT STRATEGIC CLIENT PARTNERSHIPS

→ BY **FEDERICO POLLANO,** RENTSCHLER BIOPHARMA SE

Patients have been benefiting from the innovative nature of the pharmaceutical industry for over a century. With an increased reliance on outsourcing, contract development and manufacturing organizations focused on bringing cutting-edge solutions to the market have a distinct competitive advantage, and Rentschler Biopharma has been at the forefront of biologic development and manufacturing for over 40 years. Innovation remains central to all our activities and enables us to provide optimum support for our strategic client partners, from concept to market and ultimately to patients.

MODULAR ONE-STOP SHOP

Rentschler Biopharma's value chain comprises the whole process from gene to vial and from concept to market. As a full-service provider, our partners have one primary contact, sign only one contract and deal with just one quality system for all phases of the development cycle. As a solution provider, we help clients transition a project from genetic engineering all the way through fill and finish. Projects are supported by analytical method development and validation, formulation development and the elaboration of optimal global regulatory approval strategies from clinical studies to market approval.

CLIENT-FIRST MINDSET

As a mid-sized, family-owned contract development and manufacturing organization (CDMO), Rentschler Biopharma has the ability to make decisions based on the long-term value we can provide to our clients. We have a client-first mindset and "live our clients' products." We appreciate the challenges our clients face and value every client and project, regardless of size.

We seek to partner with our clients to develop effective solutions for their complex products and processes. We are the ideal partner for both biotech and pharma companies in need of support for projects with challenging requirements, such as designer biologics.

Rentschler Biopharma works with large biopharma companies that appreciate our long track record and reputation for reliability and trustworthiness. We also complement smaller and mid-sized firms seeking a sustainable and reliable CDMO for process development and manufacturing that will satisfy future licensing partners.

Our client partners benefit from Rentschler Biopharma's continual investment in high-end technologies (i.e., advanced analytical and process development capabilities) that increase efficiency and productivity to reduce time to the clinic and the market. We also offer more than just capacity and product output; we serve as a consultant, advising our clients and advocating for solutions that provide the best products for patients.

THE ACQUISITION OF THE FACILITY ANSWERS OUR U.S. CLIENTS' STRONG REQUEST TO BRING OUR INNOVATION AND TECHNOLOGY **TO THEIR DOORSTEP AND UNDERSCORES OUR DEEP COMMITMENT TO MEETING THEIR UNIQUE MARKET NEEDS.**

LONG HISTORY OF INNOVATION

Innovation is deeply embedded in Rentschler Biopharma's culture. We are a biopharma pioneer committed to the development and application of advanced technologies and innovation leadership. We think strategically and invest in innovation for the long-term success of both the company and our biopharma partners. We think globally, yet focus exclusively on our partners' current projects and future needs.

Rentschler Biopharma has been producing biopharmaceuticals via mammalian cell culture since 1974 and working with recombinant cell lines since 1979. The first market approval for a natural interferon, and one of the first for a recombinant interferon, were awarded to Rentschler Biopharma in 1983 and 1989, respectively. Rentschler Biopharma also pioneered the use of disposable technology for bioprocessing and was the first company to install a 1000-L single-use bioreactor.

In 2012, Rentschler Biopharma won the Facility of the Year Award (FOYA) sponsored by the International Society for Pharmaceutical Engineering (ISPE), INTERPHEX, and *Pharmaceutical Processing* in the category Equipment Innovation, in recognition of our flexible, multiproduct manufacturing facility designed to minimize manufacturing costs and product cycle times.

In 1997, Rentschler Biopharma became one of the first CDMOs focusing on biologics. Since then, we have been a 100% dedicated CDMO committed to providing development, manufacturing and consulting support to our client partners.

Since 1997, Rentschler Biopharma has produced 90 different therapeutic proteins under cGMP conditions, including monoclonal and multispecific antibodies, fusion proteins and challenging recombinant proteins. Overall, we have worked with approximately 280 molecules in manufacturing and/or aseptic filling, with 23 of them reaching the market, 42 at phase III, 183 at phase I and 29 at the preclinical stage.

These development and manufacturing efforts have included the preparation of 80 complete dossiers for regulatory submission, including 25 for submission of market approval. Our facility in Laupheim, Germany has undergone 46 authority audits (EMA, U.S. FDA, Health Canada and various other country agencies) since 2000 and is subjected to approximately 40 client audits per year.

BUILDING STRATEGIC PARTNERSHIPS

Since 1997, Rentschler Biopharma has worked with approximately 140 different partners, including small and medium-sized biotech firms as well as 18 of the top 20 biopharma companies. Over one-third of our clients have been partners for more than five years, and about half work with Rentschler Biopharma on more than one project.

Our goal is to establish collaborative, long-term, win–win strategic relationships with our clients. With our flexibility, commitment to innovation and room to expand capacities and capabilities, we are ideally positioned to support clients from early phase development to commercial launch and beyond. We work closely with our partners to help them plan, build and implement long-term strategies for their candidate pipelines, including complex and next-generation biologic molecules for the treatment of severe and orphan diseases.

DRIVING INNOVATION THROUGH STRATEGIC ALLIANCES

In order to complement our offering along the entire biopharmaceutical value chain, we seek out strategic alliances with other organizations that have best-in-class capabilities. Their offerings are integrated seamlessly into Rentschler Biopharma's business processes, allowing our clients

access to a single service provider. Rentschler Biopharma manages the entire process, ensuring that all parts of the project are aligned. As a result, clients not only benefit from outstanding services, but their time to market is also reduced significantly.

Our alliance partners also continue to have their own business interactions and further develop their knowledge and offerings, which often benefit Rentschler Biopharma as well. With this approach, these alliances extend the high level of services that Rentschler Biopharma can offer while driving further innovation within the company.

Rentschler Biopharma currently has two important strategic alliances. Leukocare AG is the exclusive formulation developer for Rentschler Biopharma, offering its patented SPS® Formulation Technology for protein stabilization. Rentschler Fill Solutions provides access to a brand new, state-of-the-art fill/finish facility for the production of clinical and commercial biologic drug products, including liquid and lyophilized formulations.

Rentschler Biopharma will be expanding its strategic alliances going forward.

OPENING DOORS TO INNOVATION WITH A NEW U.S. SITE

In response to requests from North American client partners to bring our expertise, full-service CDMO offerings and passion for performance and innovation closer to them, Rentschler Biopharma acquired a state-of-the-art facility strategically located in the Boston metro area.

The fully FDA-audited facility with a consistently favorable inspection history (FDA, EMA, Health Canada) currently supplies a recombinant hemophilia A product for Shire/Takeda. In the future, it will be qualified as a multi-product production site to accommodate the growing biologics market. It has flexible cleanroom capacity with capability to expand within the current footprint and site.

The facility currently has capability to provide process development support. A 500-L bioreactor and downstream processing train will be operational in mid-2020, and additional single-use bioreactors up to 2000-L will be added shortly thereafter. We will, therefore, be able to support partner projects from early stage development through clinical and commercial production. An integration management team comprising experts from both Laupheim and Milford, Massachusetts ensures that the administration, quality, technical operations and other systems are aligned across both sites.

The Milford facility not only increases Rentschler Biopharma's flexibility and manufacturing capacity, but is also located in close proximity to many biotech startups, large pharmaceutical companies, incubator sites, world-class universities and biotech-focused research institutions. As a result, we will be able to strengthen our important U.S. partnerships and forge new ones, further elevate our technological capabilities and tap into the region's wide pool of expert talent.

Indeed, we expect the Milford facility to become a driver for innovation, both in manufacturing and partnerships. One further advantage of the site is access to a building dedicated to the exploration of new technologies and innovative products and separate from ongoing partner projects.

INNOVATING FOR THE FUTURE

To head up our innovation efforts going forward, Rentschler Biopharma recently hired Dr. Jesús Zurdo, previously Senior Director of Strategic Innovation at Lonza Pharma & Biotech, as Senior Vice President of Process Science and Innovation. Jesús will provide scientific leadership for development and manufacturing services from cell line development through to final product manufacturing. He will also be responsible for managing key strategic collaborations so that Rentschler Biopharma remains at the forefront of innovation and technology.

A new dedicated training facility enables Rentschler Biopharma to provide both initial training and retraining of internal staff and partner representatives in GMP operations, working under aseptic conditions, quality awareness and much more. The new facility will also serve as a site for the testing of new equipment, technologies and standards.

In addition, we continue to develop our Strategy 2025 initiative to ensure investment in innovation that can be directly translated into long-term client value. The strategy focuses on two types of innovation. The first involves innovations within cell culture to enhance our core business, including technologies that not only improve efficiency and productivity but also enhance interactions with clients and partners and enable them to participate more in the development process. The second addresses innovative therapy areas that rely on technologies other than mammalian cell culture. With input from external consultants, client partners, academicians and patients, we are considering all options before selecting the right business models to successfully take Rentschler Biopharma and our partners forward. In the future, we will provide full-service beyond recombinant proteins to support whatever our clients have in their pipelines. P

ABOUT THE AUTHOR

Federico Pollano
Senior Vice President Business Development, Rentschler Biopharma SE

Federico Pollano is Senior Vice President at Rentschler Biopharma, located in Laupheim, Germany. He has nearly 30 years of experience in pharmaceuticals and biopharmaceuticals, mainly in senior and executive positions at the following companies: Polpharma Biologics, Richter-Helm BioTec, Helm, BioGeneriX, Glaxo Wellcome and Zambon. Pollano studied biology at Bielefeld University in Germany, and at the German Primate Center, Göttingen, Germany.

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Passion for Performance

Rentschler Biopharma

A world-class biopharmaceutical CDMO

- Experts in cell culture bioprocess development and manufacturing
- Family-owned company, thinking globally and focused exclusively on our client projects
- Biopharma pioneer with commitment to advanced technology and innovation leadership
- Extensive track record and 40 years of experience

New U.S. Biopharma Site Milford, MA

Our partners:
one contact – one contract – one quality

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DESIGNING A CUSTOMER-CENTRIC CDMO

BY **PATRICIO E. MASSERA,** AGC BIOLOGICS

As biologic drug substances and their manufacturing processes become more complex, and smaller biotechs play a greater role in drug development, outsourcing to contract service providers is also growing. Successful biopharmaceutical CDMOs must offer advanced technologies and flexibility that enable highly efficient, lower-cost production of high-quality products across the entire development cycle to support clients located around the world.

RAPIDLY EXPANDING BIOPHARMA MARKET

Growth of the global biologics market has been fairly steady over the last 15 years, expanding on average at a very healthy rate of approximately 12% per year. Revenues have increased by 6250%, and today biologic drugs account for approximately one-quarter of the total biopharmaceutical market.[1] In both 2002 and 2017, biopharmaceuticals accounted for 35% of the new drug approvals issued by the U.S. Food and Drug Administration (FDA), and throughout the period the percentage varied only slightly up or down.[2] Today, of the top selling drugs worldwide, seven of the first 10 and 12 of the first 20 are biologic therapies. Seven of those top 12 biopharmaceuticals were based on mAbs.[3]

The value of the global biopharmaceutical market, including monoclonal antibodies (mAbs), recombinant growth factors, purified proteins, recombinant proteins, recombinant hormones, vaccines and synthetic immunomodulators, was estimated to be slightly more than $237 billion in 2018 and may reach nearly $389 billion in 2024.[4] A different analysis assessed the market at $186 billion in 2017 and projected growth to $526 billion by 2025.[5]

Biosimilars, while initially growing more slowly than expected, may be experiencing a resurgence of interest that could drive even greater growth in the overall biopharmaceutical market.[6] A greater number of biosimilars is expected to be approved going forward while much of the ongoing litigation slowing the introduction to the market of many biosimilars will be resolved. In addition, the FDA is implementing initiatives designed to increase biosimilar uptake. The global market for biosimilars is estimated to be expanding at a compound annual growth rate (CAGR) of 31.7% from $4.49 billion in 2017 to $23.63 billion by 2023.[7]

In the next few years, breakthroughs in immunotherapies, and gene and cell therapies will bring more novel, diversified biologics into the market and contribute to significant growth. Gene and gene-modified cell therapies were approved for the first time by the FDA in 2017. According to the Pharmaceutical Research and Manufacturers of America, in the United States alone, nearly 300 cell and gene therapies were in development for a broad range of diseases in 2018.[8]

SHIFT IN FOCUS FROM BLOCKBUSTERS TO NICHE THERAPIES

Expansion of the biologic drug market has been occurring simultaneously with a shift in focus of the overall pharmaceutical industry away from blockbusters to niche therapies that treat rare diseases. This shift has in large part been driven by legislation passed in several countries encouraging and incentivizing drug manufacturers to develop treatments for the thousands of rare diseases that currently have no cures.

Estimates for the value of the global market for orphan drugs vary, with the market expanding at CAGRs of 6.8% to 12.1% to $169[9] to $209[10] billion by 2022 and $318.5 billion by the end of 2025.[11] It is predicted that orphan drugs will account for 21.4% of global prescription sales in 2022, excluding generics (up from 6% in 2000).[10] Biologic drugs have the greatest market share, owing to their ability to precisely target disease pathways.[12]

GROWING ROLE FOR BIOLOGICS CDMOs

While initially many biopharmaceutical manufacturers preferred to maintain control of all of their development and manufacturing efforts, as the market – and the complexity of branded biologics and biosimilars – has grown, the interest in outsourcing manufacturing for established products has also increased. The growing importance of emerging and small biotech firms is also driving the growth in the outsourcing sector, as these companies do not have the in-house resources or capabilities and prefer to rely on third-party experts.

The decision to outsource is often made by the needs to expedite research and development, shorten the time to market, gain access to novel technologies and regulatory expertise, increase flexibility and minimize risks, all at a competitive cost. The use of CDMOs can also help drugmakers address potential capacity constraints.

More recently, biopharmaceutical innovators have begun to engage with their contract manufacturers much earlier in the development cycle, given the growing preference for using quality-by-design (QbD) and the desire to better understand products and processes. Full-service contract development and manufacturing organizations (CDMOs) offer a comprehensive set of services from early development to commercial manufacturing in an integrated process.

THE DECISION TO OUTSOURCE IS OFTEN MADE BY THE NEEDS TO EXPEDITE RESEARCH AND DEVELOPMENT, SHORTEN THE TIME TO MARKET, GAIN ACCESS TO NOVEL TECHNOLOGIES **AND REGULATORY EXPERTISE, INCREASE FLEXIBILITY AND MINIMIZE RISKS, ALL AT A COMPETITIVE COST.**

CHARACTERISTICS OF A SUCCESSFUL CDMO

Compared with the synthetic chemical processes used for the production of small molecule APIs, the biopharmaceutical manufacturing process is more complex and costlier to develop, operate and maintain. Successfully developing biologics requires a combination of state-of-the-art facilities and a broad array of technological and operational expertise.

Biopharmaceutical CDMOs must be agile in adopting technological advances in order to lead process innovation and operational efficiency, including single-use technologies and continuous bioprocessing solutions. They must also implement proprietary technology platforms consistently across development phases and global networks of manufacturing facilities to reduce project costs and

BIOPHARMACEUTICAL CDMOS MUST BE AGILE IN ADOPTING TECHNOLOGICAL ADVANCES **IN ORDER TO LEAD PROCESS INNOVATION AND OPERATIONAL EFFICIENCY, INCLUDING SINGLE-USE TECHNOLOGIES AND CONTINUOUS BIOPROCESSING SOLUTIONS.**

timelines. In addition, as the industry shifts away from large-scale to smaller-scale production of niche and targeted therapies (e.g., personalized medicines and orphan drugs), flexibility in operational capabilities, production scales and multiple-product operations are essential for CDMOs.

DESIGNING A CUSTOMER-CENTRIC CDMO

Owing to the nature of process development, results are not always exactly as expected. To ensure the success of a given molecule, we encourage an open communication framework with our customers. To build the trust necessary to overcome these challenges, a customer-centric CDMO concept is essential, in which every employee treats the product and processes as their own, where communication flows between the customers and the core team and all customers and employees have easy access to top management in order to make timely decisions.

AGC Biologics was formed with all of these requirements in mind. Integration of the capabilities of AGC Bioscience, Biomeva GmbH and CMC Biologics generated a CDMO with deep industry expertise in both mammalian cell culture and microbial fermentation methods for the scale-up and cGMP manufacture of protein-based therapeutics, from preclinical to commercial production.

AGC Biologics is a customer-centric CDMO that employs technical acumen and innovation to develop and manufacture complex biologic clinical material and provide secure global clinical and commercial supply for mammalian- and microbial-based therapeutics. We have manufacturing facilities at a variety of scales for mammalian cell culture and microbial fermentation in Berkeley, California and Bothell, Washington, as well as in Heidelberg, Germany, Copenhagen, Denmark and Chiba, Japan.

We have implemented the same systems, technologies and management practices across all of our sites, integrating nine different business areas, including operations, quality, IT and our supply chain. Our people are also encouraged to share best practices with different sites and to work at multiple locations so they can learn from one another. As a result, transfer and scale-up of projects as they move from early to late-phase or expand to meet demand in new geographies can occur seamlessly within our global network.

AGC Biologics also has an ambitious strategic growth plan that includes significant investment in our various production facilities. We expanded our site in Copenhagen, Denmark to support demands from current and potential new customers developing orphan drugs and niche products. The expansion includes addition of a proprietary Single-Use Bioreactor (SUB) 6Pack™ suite, consisting of six 2,000-L production bioreactors and a 2,000-L seed train to enable more flexible, innovative and customized cGMP production capabilities at scales from 2,000-L to 12,000-L within a single run. Capabilities for harvesting, purification, buffer and media production to support the processing of different therapeutic proteins, including high antibody titer processes, were also added.

AGC Biologics is now in the process of adding to our microbial manufacturing capabilities in Chiba, Japan a new state-of-the-art mammalian cell-culture process development and manufacturing facility – the first facility of its kind in Japan. Expected to be operational in Q3 2019, the new facility will include 500-L and 2,000-L single-use bioreactors suited for the production of monoclonal antibodies (mAbs), fusion proteins and other therapeutic proteins.

In March 2018, we announced the addition of a 2,000-L single-use bioreactor (SUB) as part of a production expansion project at our Berkeley, California facility. In July 2018, we opened our new global headquarters in Bothell, Washington, which houses Process Development labs and Corporate Administrative offices, as well as provides expansion space for additional manufacturing capacity. The new headquarters enables us to further integrate the development, manufacturing and commercial functions at our global headquarters and reinforce the effectiveness of our extensive global network.

We also plan to install 2x 6Pack™ (12 additional 2,000-L single-use animal cell bioreactors) at our Bothell site and establish a new CDMO facility for microbial cells, an offering that was previously only available in Europe and Japan. This expansion will triple AGC's biopharmaceutical production capacity in the United States while also ensuring seamless operation of microbial and animal cell-based biopharmaceutical CDMO activities across the Japan, Europe, and U.S. regions. The total investment for this expansion is estimated at about $75 million, with full-scale operations slated from July 2020.

Collectively, our global network of facilities provides us with well-aligned development, manufacturing, and quality/compliance systems and procedures and is capable of providing seamless tech transfers and scale-up, geographical expansion and out-licensing, and security of clinical and commercial supply of mammalian- and microbial-based therapeutics.

Additional expansion in the United States is planned for the near future. AGC Biologics has also been actively investigating M&A opportunities in the cell and gene therapy space, which we expect to be a key growth area for the company going forward.

DEEP EXPERTISE AND FLEXIBILITY

AGC Biologics has deployed unique technologies that enable acceleration of development timelines, getting customer projects from the DNA stage to IND filing in less than 14 months.

Our proprietary CHEF1® mammalian expression system is a robust and scalable expression platform that enables the development of cell lines in a 12- to 14-week period. The system is well recognized by regulatory authorities, with four approved products on the market and many more in clinical trials that have been developed using CHEF1® technology.

We have also developed expertise in continuous cell culture – or perfusion – processing. High cell densities can be achieved and operated for extended periods, resulting in higher volumetric productivity than traditional fed-batch manufacturing. The product is harvested continuously, enabling continuous downstream purification at a small scale, making continuous bioprocessing more capital-equipment efficient. We are also exploring continuous chromatography for enhanced downstream processing capabilities.

Overall, AGC Biologics has manufactured more than 200 biological projects, from preclinical studies through commercial approvals, including rare-disease treatments and personalized medicines, more traditional antibodies and products with accelerated approval pathways. Within our portfolio, we are currently working on getting 12 late-phase products to market within the next three years.

One major trend in the industry that we are closely following is the growth in niche products that target rare or orphan diseases. These drugs tend to be the kinds of complex molecules that we specialize in working with, so we are well positioned to support clients working in this space.

We are interested in working with companies that are looking for a CDMO that will collaborate closely and serve as an extension of their own operations. We can support projects from cell line development to commercial launch and market growth. With our flexible capacity that grows as needed, advanced technologies including continuous manufacturing and our ability to work on accelerated pathways, as well as a customer-centric culture that fosters a warm and positive collaborative experience, AGC Biologics makes it possible for our customers to get their high-quality treatments to patients as quickly as possible. P

OVERALL, AGC BIOLOGICS HAS MANUFACTURED MORE THAN 200 BIOLOGICAL PROJECTS, FROM PRECLINICAL STUDIES THROUGH COMMERCIAL APPROVALS, **INCLUDING RARE-DISEASE TREATMENTS AND PERSONALIZED MEDICINES, MORE TRADITIONAL ANTIBODIES AND PRODUCTS WITH ACCELERATED APPROVAL PATHWAYS.**

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Patricio joined AGC Biologics (previously CMC Biologics) in August 2012 as General Manager and Managing Director of the CMC Biologics A/S based in Copenhagen. He then served as Chief Operating Officer for over two years before the board appointed him to the role of CEO in May of 2019. During his 20-year career, Patricio has held several key executive positions at MSD AH, Intervet/Schering-Plough, Biogenesis-Bagó and other Biotech companies in Spain, Brazil and Argentina developing, manufacturing and controlling biotechnological products and vaccines for human and animal health. Patricio holds a biochemist degree from the University of Buenos Aires and a Master's of Business Administration from UCEMA.

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MANUFACTURING TECHNOLOGY

What advances in manufacturing technology are most enabling the scale-up and commercialization of next-generation therapies?

I see the biggest impacts enabling scale-up and commercialization of next-generation therapies in the near term as small tweaks on existing platforms: items like incremental advances in closure of single-use systems enabling a completely closed cell therapy process, improvements in plastics creating more robust integrity at cryogenic temperatures, or working out nuances of adapting isolator technology to operations requiring a high level of dexterity and high turnover. **Automated robotic systems have great potential but are still not having the impact of simpler automated devices** that combine peristaltic pumps and pinch valves. The next-generation antibodies (e.g., Fabs, bispecifics) could be made with the same process trains as mAbs, but continuous processing will enable them to reach commercialization with less capital investment.

Erich Bozenhardt,
Lead Process Engineer and BioProcess Specialist, IPS

Next-generation processing is quickly gaining traction in the industry because of the significant impact it will have on bringing therapies to patients. This manufacturing evolution will intensify the manufacturing process from multiple unit operations to a continuous flow-through process.

At MilliporeSigma, we start process intensification by updating and upgrading outdated unit operations, then connecting these processes to run in a continuous flow-through fashion and ultimately reaching what we call "contiGuous" manufacturing — that is, a process that is continuous, connected and digitally enabled with all the suitable software and automation, run as an orchestrated production train. However, while continuous processing is the future of drug manufacturing, customers face challenges today in terms of speed to market, facility flexibility or cost of goods. We've designed the BioContinuum™ Platform to feature next-generation technologies that provide incremental process benefits now, with a mind to the "contiGuous" process of the future. The platform will revolutionize drug manufacturing by setting the standard for improvements in process efficiency, simplified plant operations and consistency in manufacturing. We predict that by 2020, approximately 20 percent of today's molecular pipeline will be manufactured using elements of next-generation bioprocessing, or "contiGuous" manufacturing.

Andrew Bulpin,
Head of Process Solutions at MilliporeSigma

It is important to discuss two key areas in manufacturing science that are developing in the pharmaceutical industry. The first is not necessarily scale-up, but rather streamlining manufacturing by pushing pharmaceutical manufacturing into the 21st century.

For example, continuous manufacturing processes utilizing engineering techniques long used by other industries. Unlike what was once exclusively a batch process, with a multitude of limitations (inefficiencies, higher costs, higher risks of failed batches), drugs may now be produced in continuous manufacturing lines, coupled with precise monitoring through technologies like PAT (process analytical technology). It is important to note that a paradigm shift in manufacturing technology such as this will require manufacturers and suppliers to work side-by-side to design safe and effective processes.

Next, instead of scale-up, next-generation therapies are likely to be scaled down, as a result of the personalization of medicine. We are not far off from walking into a local pharmacy and having a precise dosage form tailored to an individual patient, whether it is a 100-kg adult or a 2-year-old child. One such example would be the use of a 3D printer, mixing APIs and excipients as liquids, solids or melts to form exact dosage forms essentially on demand.

Dr. Frank Romanski ,
Global Technical Marketing Manager, Pharma Solutions, BASF Corporation

Manufacturing across many industries, including pharma, is evolving into more digital, automated environments. As this occurs, the use of artificial intelligence (AI) to optimize the manufacturing environment, including better predictive tools for instrument performance and maintenance, could provide pharma with significant efficiency gains in productivity and is a compelling technological advancement in manufacturing.

AI could also be deployed to optimize complex manufacturing lines, including biologics where process monitoring and feedback will determine the final product quality characteristics and can ultimately provide faster scale-up. Additionally, adoption of the Internet of Things (IoT) into manufacturing will also provide the industry with tighter, real-time controls, accelerating scale-up and release testing for small molecule and biologics manufacturing.

Tiffani A. Manolis,
Senior Director, Pharma Strategic Program, Agilent Technologies Inc.

A large number of next-generation therapies are personalized drugs and formulations, which target smaller patient groups. Consequently, they are typically produced in small batches, which requires manufacturers to turn toward flexible manufacturing operations. This is where ready-to-use (RTU) containers come into play, and more specifically, standardized platform solutions. By working closely with pharma companies, machine manufacturers, and elastomer component suppliers, we introduced our iQ™ platform, which standardizes the tub format of RTU syringes, vials and cartridges to allow the different containers to run on the same filling line. Due to the standardization, fewer change parts are necessary when switching from one container to another, enabling pharma companies to fill various drug/container configurations on the same line with minimized changeover times. This enables the short time to scale-up and commercialization of these drugs.

Anil Busimi,
Senior Global Product Manager for iQ Platform at SCHOTT

Q: What advances in manufacturing technology are most enabling **the scale-up and commercialization of next-generation therapies?**

In the past few years, antisense oligonucleotides (ASO) have become a trendsetting class of marketed drugs. The best known ASO is nusinersen/Spinraza®, developed by Ionis and Biogen for spinal muscular atrophy (SMA). The same oligonucleotide sequence can be used for all patients with SMA. This is a life-changing drug, as infants with the most aggressive form of SMA have a projected life span of less than a year. Instead of being on a respirator, infants are thriving and meeting developmental milestones. The success of nusinersen has opened up opportunities for other diseases of the central nervous system (CNS), especially life-threatening congenital diseases with rare genetic causes. Charles River is working with a number of early stage companies on both cellular and IND-supporting studies to advance this novel drug class.

The second critical technology that is enabling treatment of genetic diseases is the increasing access to whole genome sequencing (WGS), allowing neonatalogists and genetics professionals to learn the exact mutation driving a patient's disease. There are a number of synergies here that can reduce the time between diagnosis and drug treatment. The sequencing data allows a precision diagnosis, but also defines the target sequence for oligo drug development for that patient. Studies on the patient's own cells can be used to screen ASOs *in vitro* for the best cellular genetic and functional readouts. Additionally, the ASO chemistry (the "backbone") can be kept similar to nusinersen, which provided good penetration of CNS tissues and duration of activity. These are key accelerations for treating ultrarare diseases, even when only a single patient with a given mutation has been identified. As we learn more about these rare conditions, the data obtained from a single patient might be cross-applied to multiple patients with related but nonidentical mutations. The cost and time involved in WGS has come down to a few thousand dollars, and less than a month's time — we can only hope that more patients will have access to this key technology soon, so that treatments can start as early as possible and prevent more life-threatening diseases from developing.

David Fischer, Ph.D.,
Executive Director,
Charles River
Laboratories

Amit Raj Dua,
Global Marketing Director,
Cell & Gene Therapy,
GE Healthcare Life Sciences

PURPOSE-BUILT TECHNOLOGIES ARE DEVELOPED TO MEET NEXT-GENERATION THERAPY PROCESS REQUIREMENTS **BOTH TODAY AND IN THE FUTURE.**

Automation is enabling robust, consistent and connected manufacturing, eliminating significant risk from manual and open processes. Complete integrated process workflows, such as the GE FlexFactory for cell therapy, enable therapy innovators to rapidly create the manufacturing capacity needed for both clinical and commercial production.

The cost of manufacturing biologics is among the highest for total investment within the market segment. Drug substance manufacturing, in particular, is labor-intensive and time-consuming due to sensitivity to environmental changes, inconsistent yield and low purity. Because the basis of manufacturing involves living cells, any opportunity to streamline proliferation and purification via continuous processing or real-time monitoring will prove highly impactful for scale-up and commercialization of biotherapeutics.

Jason Spacek,
Vice President of Commercial
Operations, Alcami

NOVEL THERAPIES

What truly novel therapies in the earliest stages of discovery and development do you believe will have a significant impact in the future?

Drug discovery has traditionally been focused on small molecule drugs designed to bind directly to target proteins to decrease their activity. However, around 80% of protein targets are still very hard targets or even undruggable through this approach.

A major and still underexploited area for drug discovery is mRNA. RNAi technologies have been developed to "knock down" mRNAs to prevent protein production. Recently, synthetic mRNA has been suggested as a drug to treat diseases where lack of protein is the problem, but it faces delivery problems and other issues that limit its widespread use.

Small molecules targeting mRNA biology is one of the most promising areas for the discovery and development of new medicines.

In this space, Anima's Translation Control Therapeutics is the first and only platform for the discovery of small molecule drugs that control the translation of mRNA by ribosomes as a novel strategy against a wide range of hard and undruggable targets. Unlike other approaches that target the mRNA itself, we identify small molecules that can bind to the proteins that regulate translation. Through this approach, we can *decrease* or *increase* the production of almost any target protein, leading to drugs for the broadest range of diseases.

Yochi Slonim,
Co-founder and CEO,
Anima Biotech

There are few things as transformative to the pharmaceutical industry as the advent of biologics. Everything from monoclonal antibodies to cell and gene therapy technologies are transforming the way patients are treated and even fully cured. From a pharmaceutical formulator's perspective, we continue to rely on older technology for administering these types of large molecule formulations — namely, as parenterals.

The manufacturing and dosing of these formulations rely on excipients, surfactants and processing aids that are often out-of-date or not designed for large molecule manufacturing or dosing purposes. The cutting edge is where scientists aim to administer biologics using more patient-friendly means; for example, inside of an oral capsule or through the skin as a micro-needle patch. These are revolutionary ideas for administering large molecules, but they rely heavily on having tools, techniques and excipients to bring these ideas into reality. Often, in pharma, we wonder where the new molecules are. Well, the new molecules are here today, but they are fundamentally different and far more sensitive to external forces than their small molecule predecessors. Therefore, the innovation will come not just from the molecule itself, but also how it is formulated and administered to the patient.

Dr. Frank Romanski,
Global Technical Marketing Manager,
Pharma Solutions, BASF Corporation

Q: What truly novel therapies in the earliest stages of discovery and development **do you believe will have a significant impact in the future?**

ROUNDTABLE

Currently, cell and gene therapies, along with advances in gene editing through CRISPR, offer impacts to patients that in many cases have not been effectively treated in the past, including rare disease patients. The broader impact and potential for these therapies is yet unrealized. Additionally, CAR-T therapies and their potential impact to treat cancer patients, as an example, with personalized therapies, has also not yet been fully realized.

Tiffani A. Manolis,
Senior Director, Pharma Strategic Program,
Agilent Technologies Inc.

One truly novel technology that could have significant impact on the lives of patients in the future is the use of RNA editing. Targeted RNA editing has the potential to directly correct the causes of genetic conditions. While therapies are still in the early stages of development, RNA editing potentially combines the benefits of both gene therapy and small molecule therapies. Like gene therapy and gene editing, RNA editing can specifically repair a disease-causing gene mutation but can do so without permanently changing a person's genetic code, reducing the chance of permanent off-target effects. Additionally, like small molecule drugs and unlike gene-editing therapies, small molecule RNA-editing therapies can often be administered in simple fashion and delivered without viral vectors. There are thousands of diseases caused by genetic mutations that can be corrected with RNA editing, and we have only just begun to witness the impact these types of therapies can have on the lives of people suffering from devastating genetic conditions.

Daniel A. de Boer,
Chief Executive Officer,
ProQR Therapeutics N.V.

Inhaled biologics have been forecast to grow in importance due to the fact that inhalation presents a highly attractive route for the administration of various classes of large molecules, particularly for the treatment of respiratory diseases. The major driver here is the potential for local, targeted delivery to the lung, opening up new treatment pathways for diseases such as cystic fibrosis, asthma and lung cancer. Delivery directly to the lung is likely not only to be more efficacious, but also to require less of the active ingredient compared with other routes of delivery. Systemic delivery of biologics is also possible via the lungs or the nose. Drug delivery via these routes is more convenient and less painful compared with other routes of administration for biologic drugs, which are generally administered intravenously.

Chris Vernall,
Business Development Director, Intertek Pharmaceutical Services

Of course, pharmaceutical companies would be able to provide further insights on the topic of novel therapies. However, from our perspective as a primary packaging supplier, we see a rise in highly sensitive and complex biologics in the injectable drug pipeline. **These drugs are used for various therapy areas, such as oncology, infectious disease, immunology and cell and gene therapies, to name a few.**

Anil Busimi,
Senior Global Product Manager for
iQ Platform at SCHOTT

It seems not that long ago that monoclonal antibodies were considered novel, and using gene therapies to cure rare diseases was just a dream — however, the mAb process is about 30 years old. In that time, the industry has become smarter and more agile and is keener than ever to make the dreams of the 1990s a reality.

This industry paradigm shift, fueled by forward-looking bioprocessing applications, has reinforced the need for better integration, collaboration and education. High-growth regions like China are moving at the speed of light, and the entire APAC region is poised to train its workforce in biologics GMP best practices to meet the demand for skilled labor. Emerging regions like Africa, the Middle East, Eastern Europe and LATAM are all in the race to get affordable medication to local patients.

MilliporeSigma's deep-rooted industry experience and expertise is relied upon by customers worldwide. Our BioContinuum™ Platform will revolutionize drug manufacturing by setting the standard for improvements in process efficiency, simplified plant operations and consistency in manufacturing. Our Emprove® program helps our customers meet evolving quality and regulatory standards for pharmaceuticals. Our Synthia™ software innovation helps chemists optimize their synthetic pathways for parameters such as yield or raw material cost. These are just a few examples of how MilliporeSigma is defining the future and leading the evolution of drug development and manufacturing of life-enhancing and life-saving drugs, helping to shape the possibilities of tomorrow.

Andrew Bulpin,
Head of Process Solutions at
MilliporeSigma

From an autologous therapy perspective, CAR-T therapies have shown promising clinical outcomes for lymphoma and myeloma, while T cell receptor (TCR) and tumor-infiltrating lymphocytes (TIL) therapies are growing in focus for solid tumors.

From an allogeneic therapy perspective, CAR-T, along with natural killer (NK) cell and induced pluripotent stem cell (iPSC) approaches, are being explored to enable off-the-shelf therapy manufacturing.

Lastly, *in vivo* gene therapies are showing good clinical outcomes for patients with genetic disorders and cardiovascular and ophthalmological diseases. Many of these therapies have curative potential.

Amit Raj Dua,
Global Marketing Director,
Cell & Gene Therapy,
GE Healthcare Life Sciences

Cell and gene therapies represent the leading edge of medicine and have the potential to impact many patients' lives. The advent of CRISPR technology catapulted these emerging therapies into the world, with the first FDA IND approval for clinical trials occurring very recently. This targeted gene-editing technology also enabled the next generation of CAR-T therapy development, which has been shown to drastically improve the quality of life for patients with several different types of lymphoma. By harnessing the potential of genetic engineering, these cutting-edge therapies can be used for tumor-targeting cancer therapies, neurodegenerative disorders, orphan diseases, and so much more.

Jason Spacek,
Vice President of Commercial
Operations, Alcami

▶ Nice Insight and the Pharma's Almanac editorial team would like to thank all the companies participating in this quarter's edition. The following are the profiles of the industry-leading companies that have appeared in this issue.

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Your Passion Is Our Passion

That's Nice is proud to announce the launch of Nice Passion, which is now live at **NicePassion.com.**

Nice Passion is a substantially different offering from all previous That's Nice brand extensions. We are shooting video and short films centered on individuals that work in the Life Sciences community, but the focus of each piece is a passion they pursue with total dedication away from work. Our four films so far have been shot at an airfield in France, on a remote mountain in New Hampshire, in suburban New York and, of course, on our epic cross-country adventure, Road To BIO.

Do you have a passion you pursue outside work that you would like to share? If so, we would like to hear from you!


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