pharma's almanac
A NICE INSIGHT MAGAZINE

Q3 2019 VOLUME 5 NUMBER 3

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Balancing Global and Local Concerns in Manufacturing and the Supply Chain

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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

GLOCALIZATION, NETWORKING AND INNOVATION

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

It is my pleasure to introduce the "Networking" issue of *Pharma's Almanac*. It comprises thought leadership and insights by more than 50 contributors from companies spanning the full scope of contract development, research and manufacturing services, specialized technologies, supply chain and third-party logistics providers. These industries provide the foundation for the innovation that drives development and commercialization of pharmaceuticals, biopharmaceuticals and advanced therapies.

I'm also very excited to announce the debut of an initiative appearing in this issue of *Pharma's Almanac*. We are formally expanding our focus to feature a number of younger, exciting biotechnology companies exploring drug development in some very novel categories. The biotechs featured in this issue, which can be found grouped under the "Drug Development" subhead, are exploring areas like microbiome therapies for allergies and neurological conditions, fruit fly tumor avatars for drug screening, the tumor microenvironment and synthetic cannabinoids. Although we have featured biotech companies in past issues, we plan to amp up our coverage going forward and encourage readers in this sector interested in appearing in these pages to reach out.

Of course, the range of topics presented by our more traditional outsourcing contributors are just as exciting. Our thought leaders discuss major concerns that cut across the entire industry, from formulation to technology transfer and scale-up, the logistics underlying international clinical trials, orphan drug manufacturing, semisolid and other alternative dosage forms, issues surrounding containment during highly potent manufacturing, and trends in pharmaceutical and biopharmaceutical facility design and considerations for facility acquisitions.

This issue also features fascinating analysis of next-generation therapies and technologies, including induced pluripotent stem cells, evolving technologies for scaling viral vector manufacturing, the promise of 3D bioprinted organs, and others.

Finally, our Nice Insight team is featured in articles that describe the need to balance local and regional concerns in the context of an increasingly global industry, which is echoed throughout the magazine. We also encourage you to take advantage of highlights from our drug pricing research report, which provides cost insights across the industry. P

"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.

Science of Nature *5-minute short, 1 episode*
In a hidden hollow on the side of a New Hampshire mountain, a scientist built himself a remote respite from the bustle of his professional life — a place where he could clear his mind — absorbed by only the forest landscape that surrounds him. Nothing is taken for granted in the raw solitude of the wilderness.

Everyday Exotic *8-minute film, 1 episode*
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. You can meet the exotic commuter at CPhI Worldwide in Frankfurt, Germany.

Flight of Freedom *5-minute short, 1 episode*
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.

The Road to BIO *51-minute film, 14 episodes*
Nice Passion was launched 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 BIO International 2017 show.

IMPACTS OF GLOCALIZATION ON THE PHARMACEUTICAL INDUSTRY

By **Nigel Walker**, Nice Insight

Globalization in the pharmaceutical industry has occurred simultaneously with glocalization — increasing local drug development and manufacturing in emerging markets. Not only large multinational firms, but regional and domestic drug companies are taking advantage of the opportunities presented by these growing markets.

Glocalization vs. Globalization

Globalization in the pharmaceutical industry has been occurring for many years owing to increasing demand for advanced medicines in emerging economies, a desire for drug manufacturers to reduce costs and the growing challenges with clinical trial recruitment in mature markets. Pharmaceutical companies have established both R&D and production facilities around the world. Similarly, a steady rise in outsourcing of noncore activities has led to the growth of contract research, development and manufacturing organizations with global operations.

At the same time, a movement toward local pharmaceutical development and manufacturing has been occurring. "Glocalization" of the pharmaceutical industry is driven in part by governments, nongovernmental organizations (NGOs) and local entrepreneurs. The overall goal is to develop a reliable supply of low-cost, advanced medicines and increase access in countries/regions that traditionally have lacked the infrastructure, resources and skilled labor to produce and distribute drugs cost-effectively.

Glocalization is also, in part, a response to globalization — and perhaps a more accurate term altogether, according to some.[1] It has occurred as a means for individual countries to reestablish control over their local economies and social, cultural and political norms while continuing to operate in larger regional networks and international industries.[1]

Current State of the Global Pharma Market

Global pharmaceutical industry revenue rose from $390.2 billion in 2001 to $1.2 trillion in 2018, according to trend forecasting by Statista.com.[2] This revenue is predicted (by data science company IQVIA) to expand at a 4–5% CAGR (down from the 6.3% CAGR observed for 2014–2018) to reach $1.5 trillion in 2023.[3] NAVADHI Market Research's estimate is slightly higher, at $1.7 trillion by 2023.[4] The values are based on invoice pricing rather than net revenue, which is the revenue actually received after accounting for rebates and deductions. Net revenue is predicted by IQVIA to grow at a compound annual growth rate (CAGR) of 0–3% through 2023.[3]

Growth in the industry is attributed to the expanding and aging population combined with greater demand in emerging economies, as well as increasing numbers of novel treatments for rare and specialty markets.[4] Trends and issues leading to lower growth in the global pharmaceutical market include a slowing world economy, the growing adoption of biosimilars and downward pricing pressure; this is occurring in combination with changes to reimbursement policies, notably in the United States.[3]

With respect to innovation, IQVIA predicts that next-generation biotherapeutics, prescription digital therapeutics, the application of real-world evidence, artificial intelligence and virtual clinical trials will have a significant impact on the industry over the next five years.[5] Biologics are predicted to account for one-third of new product launches during that time, and spending on new products commercialized from 2019–2023 will average $45.8 billion, up from $43.4 billion for 2014–2018. Key therapeutic areas of focus will include oncology, with 70–90 new medicines introduced in the next five years, along with nonalcoholic steatohepatitis (NASH), migraines, neuromuscular diseases, autism and other developmental disorders and a range of molecular targets for cell and gene therapies.[5]

Increasing Role for Emerging Markets

North America will continue to hold the greatest market share in 2023 (45.33%), followed by Asia-Pacific (24.07%), Europe (20.24%), Latin America (7.53%) and the Middle East and Africa (2.96%).[4] North America is expected to see its market share increase in 2023 compared with that in 2017, while Europe is expected to see a decline in its market share compared with 2017. Emerging markets are anticipated to grow at the fastest rate (4–5%).[5]

The leading emerging economies are the BRICS (Brazil, Russia, India, China and South Africa) countries. Lower-tier economies are grouped in a couple of different ways.[6] One identifies just a few as the MIST (Mexico, Indonesia, South Korea and Turkey). Another interpretation has two groups that include more countries: CIVETS (Colombia, Indonesia, Vietnam, Egypt, Turkey and South Africa) and Bangladesh, Egypt, Indonesia, Iran, Korea, Mexico, Nigeria, Pakistan, the Philippines, Turkey and Vietnam.

Notably, sales of pharmaceuticals in the BRICS and MIST countries doubled over a five-year period to account for approximately 20% of the global market.[6] This growth is due to increasing life expectancies combined with greater prosperity and hence demand for novel medicines. Pharma companies have also targeted emerging markets in recent years due to slower

The overall goal is to develop a reliable supply of low-cost, advanced medicines and increase access in countries/regions that traditionally have lacked the infrastructure, resources and skilled labor to produce and distribute drugs cost-effectively.

growth in mature markets combined with increasing generic competition. Access to generic drugs and biosimilars has also had an impact in emerging markets.

While emerging economies traditionally required access to drugs against infectious and communicable diseases, changing lifestyles accompanying the greater wealth in many emerging markets has resulted in a growing incidence of cardiovascular diseases, diabetes and many forms of cancer. The incidence of diabetes and cancer is expected to increase by 20% or more by 2030.[6]

The value of the Chinese pharmaceutical market, which was the second largest in 2018, is pegged by IQVIA at $137 billion and is expanding at a CAGR of 3–6% through 2023, to reach as much as $170 billion.[5] Other emerging markets of note include Turkey, Egypt and Pakistan, which are predicted to experience the fastest growth through 2023.

It is also worth noting that the cost of performing clinical trials in emerging economies can be lower. Outsourcing of development and manufacturing to companies located in emerging economies has also been a strategy of international biopharmaceutical firms looking to reduce costs and potentially gain access to these growing markets.

One of the key challenges, however, is the prevention of the sale of fraudulent medicines in developing countries. According to the World Health Organization, 25% of marketed drugs in low- and middle-income countries in 2007 were substandard.[7]

What Does Glocalization Mean for the Future Pharma Industry?

The impact of glocalization must be considered within the overall context of the pharmaceutical market as it exists today and expectations for medicine demand going forward. By 2050, over 20% of people globally will be over 60 years of age,[8] and nearly 40% of Americans will be diagnosed with some form of cancer during their lifetimes.[9]

Despite these statistics, the next decade will be challenging for the pharma industry, with a reduced growth rate due largely to difficult conditions in the U.S. market.[10] Although specialty drugs are still growing rapidly, R&D productivity is down at international biopharma companies, and they will face more competition as small and mid-size firms, who, instead of licensing out their new technologies as in the past, are taking them through commercialization.[10]

All companies will be challenged to invest in data management and analysis technologies to fully utilize digital and mobile technologies. As outsourcing of noncore activities has become essential, so has the establishment of global networks for success in everything from R&D to marketing.[8] Large pharma companies are now horizontally, rather than vertically, integrated; rather than relying on a few R&D hubs and controlling all aspects of development and production, pharma companies are outsourcing these activities to develop products for specific markets.[8] Glocalization will also continue to be driven by government policies and the need to meet the requirements of government-sponsored and government-based healthcare providers.

The focus will continue to shift to the patient, driving the development of personalized medicines and creating more opportunities for small firms and startups specializing in targeted disease areas.[8] Pharmaceutical companies that can engage with patients through multiple avenues, including novel digital solutions, will have a competitive advantage. As a consequence, glocalization – and globalization – are only the first steps in a significant transformation of the global pharmaceutical industry.[8] P

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REFERENCES

1. Swyngedouw, Erik. "Globalisation or 'glocalisation'? Networks, territories and rescaling," *Cambridge Review of International Affairs*. 21 Oct. 2010. Web.
2. Mikulic, Matej. "Revenue of the worldwide pharmaceutical market from 2001 to 2018 (in billion U.S. dollars)." Statista.com. 5 Jun. 2019. Web.
3. *Global pharma spending will hit $1.5 trillion in 2023, says IQVIA*. IQVIA. 29 Jan. 2019. Web.
4. *Global Pharmaceuticals Industry Analysis and Trends 2023*. NAVADHI Market Research. 4 Mar. 2019. Web.
5. Miglierini, Giuliana. "Emerging trends for the pharmaceutical market." *Pharma World Magazine*. 20 Feb. 2019. Web.
6. Tannoury, Maya and Zouhair Attieh. "The Influence of Emerging Markets on the Pharmaceutical Industry." *Current Therapeutic Research*. 86: 19–22 (2017).
7. Kohler, Jillian C., Martha G. Martinez, Michael Petkov and James Sale. "Corruption in the Pharmaceutical Sector: Diagnosing the Challenges." World Health Organization. Jun. 2016. Web.
8. "The Globalisation of Pharma." Team Anbrosus. 14 Nov. 2018. Web.
9. Desjardins, Jeff. "Visualizing the Future of the Pharma Market." *Visual Capitalist*. 30 Jan. 2019. Web.
10. Miller, Jim. "Pharma Industry Faces Slower Growth, Changing Business Models." *DCAT Value Chain Insights*. 9 Apr. 2019. Web.

Haig Armaghanian
Founder and CEO
Haig Barrett, Inc.

Is the U.S. Biosimilars Market Poised for Takeoff?

The biosimilars market in the United States continues to lag behind the rest of the world. However, there are promising signs that the market is poised to gain momentum.

Expanding Biosimilars Market

Given biologics' complexity, the global scientific community has rightfully questioned its collective understanding of these therapeutics. Could the industry really develop and manufacture therapeutics that would behave similarly and have the same – or at least similar – clinical outcomes as an innovator biologic? Were biosimilars interchangeable with innovator drugs? These questions were warranted, and the world pushed forward to address them. Most global markets achieved confidence in their biosimilars review and approval processes. Additionally, most nations concluded that their people were better served by having access to lifesaving medications rather than waiting until every question was answered fully.

The United States trailed the EU and other nations in implementing legislative and regulatory constructs to support its biosimilars market. The EU was the first to release biosimilar guidelines, in 2005. The biosimilars market was legislatively created in the United States by the signing of the Biologics Price Competition and Innovation Act (BPCIA), part of the Affordable Care Act, in March 2010. However, the U.S. Food and Drug Administration (FDA) did not release its first biosimilars draft guidance until 2012.

The commercial U.S. biosimilars drug market was effectively established in 2015 with the approval of Sandoz's Zarxio®, which quickly established itself by constituting approximately 45% of the short-acting filgrastim prescribed in the United States. Despite this success, the United States again lagged behind the EU, which had launched its first biosimilar in 2006 – a full nine years earlier.

After the approval of Zarxio in 2015, FDA biosimilar approval rates began to accelerate. As of July 2019, 21 biosimilars have been approved by the FDA, and the approval rate has been rising. However, only six of these approvals have been brought to market – the remaining products have been held up in IP-related litigation. Contrast this with the 40+ biosimilars actively on the market within the EU, not to mention the markets of numerous other nations.

In countries dedicated to providing healthcare services to all citizens, the fiscal relief offered by biosimilars is quite welcome. However, by following the money in the U.S. healthcare market, one is not surprised to learn that the overwhelming energy has been directed toward slowing the development of the market, rather than accelerating it. Slowly but surely, however, the tide is turning, and here are some reasons why.

Biologics Patent Cliff

Similar to the patent cliff small molecule drug manufacturers endured years ago, biopharmaceutical manufacturers are in the midst of their own patent cliff. By 2020, more than $67 billion in biological patents will expire, including patents for blockbuster biologics like Lantus® and Avastin®. Expiring patents, of course, present opportunities for biosimilar development.

Interchangeability

The lack of FDA interchangeability guidance slowed biosimilar adoption, because pharmacists cannot substitute a biosimilar without interchangeability status. However, the FDA released a highly anticipated guidance, "Considerations in Demonstrating Interchangeability with a Reference Product," in May 2019, which offers a path to achieving interchangeability status.

Increasingly Sophisticated Litigation Tactics

In June 2017, the U.S. Supreme Court settled *Amgen v. Sandoz,* determining that biosimilar applicants are not required to participate in the patent dispute resolution procedures (also known as the "Patent Dance") outlined in the BPCIA. Additionally, a biosimilar applicant may provide 180-day notice of commercial marketing before the biosimilar product is licensed, thereby not affecting its commercial launch.

While some legal questions were clarified by *Amgen v. Sandoz,* and numerous other cases are making their way through the courts, biosimilar developers are becoming more comfortable with the rigorous legislative landscape before them.

This said, there is no shortage of opportunity for innovators to continue to slow the pace of biosimilar commercialization.

Legislative Will

While the current legislative environment in the United States is far from predictable, there increasingly appears to be the desire on both sides of the aisle to tackle drug pricing questions.

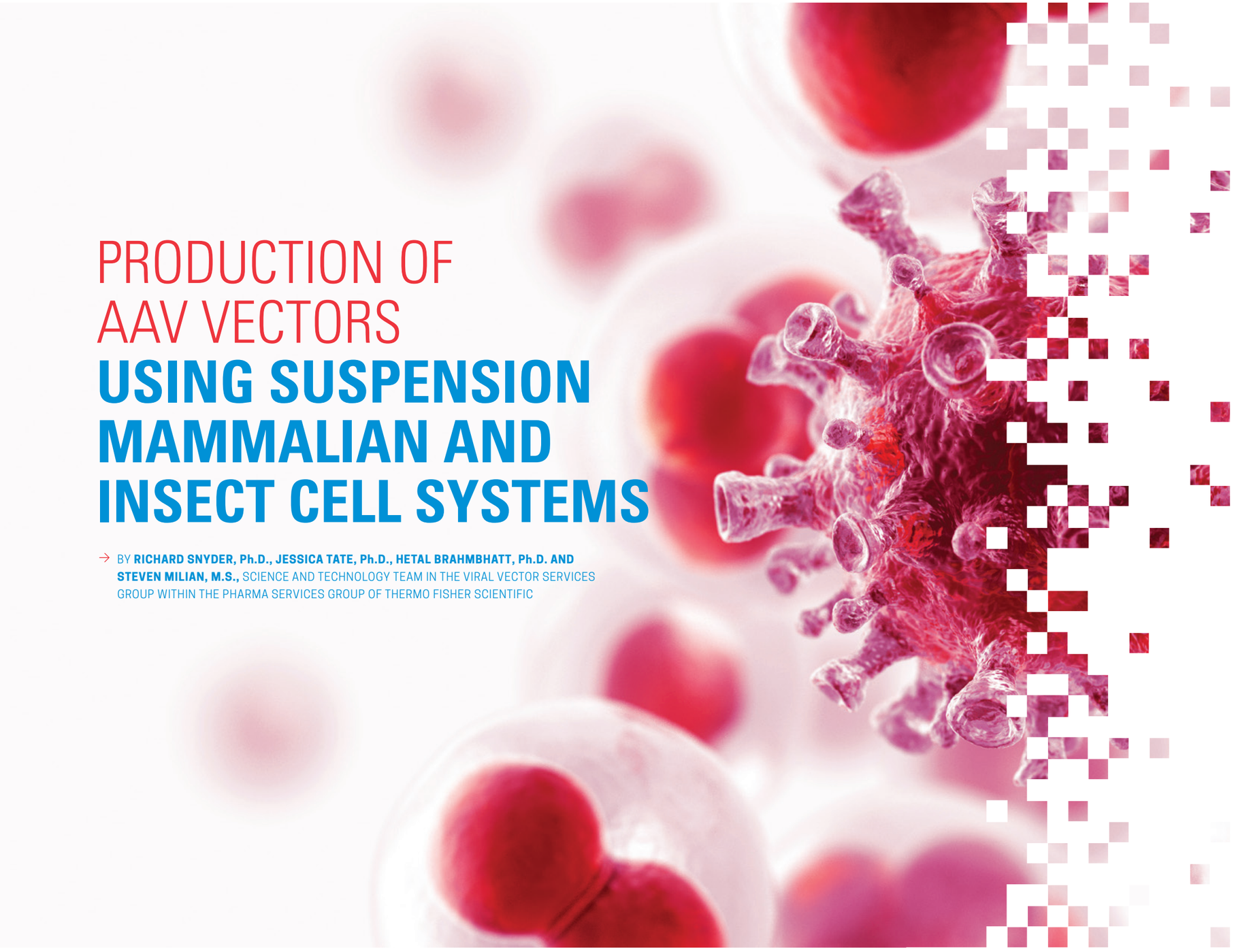
Is the U.S. biosimilars market really poised for takeoff? The signs are positive, but it is truly the legal and legislative arena that will determine the market's fate. P

References

1. Nelson, Kevin and Tara Kurtis. "Three Trends Point to Biosimilars Market Boom Ahead of BPCIA 10th Anniversary." *Pharmaceutical Executive*. 9 Jan. 2019. Web.
2. Kabir, Eva R., Shannon Sherwin and Mohammad K. S. Siam. "The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy." *MDPI*. 24 Aug. 2019. Web.
3. Brennan, Zachary. "Updated: Interchangeable Biosimilars: FDA Finalizes Guidance." *RAPS*. 13 May 2019. Web.
4. Cohen, Joshua. "What's Holding Back Market Uptake Of Biosimilars?" *Forbes.* 20 Jun. 2018. Web.

PRODUCTION OF AAV VECTORS **USING SUSPENSION MAMMALIAN AND INSECT CELL SYSTEMS**

→ BY **RICHARD SNYDER, Ph.D., JESSICA TATE, Ph.D., HETAL BRAHMBHATT, Ph.D. AND STEVEN MILIAN, M.S.,** SCIENCE AND TECHNOLOGY TEAM IN THE VIRAL VECTOR SERVICES GROUP WITHIN THE PHARMA SERVICES GROUP OF THERMO FISHER SCIENTIFIC



Adeno-associated viral (AAV) vectors are currently the most widely used gene transfer vectors in many gene therapies that are in development. Two commercial products, Spark Therapeutics' Luxterna® and Novartis' Zolgensma®, are now approved for sale. In an effort to provide additional gene therapy products for patients, there is a need for manufacturing platforms that can meet the high production demand at both the clinical and commercial stages.

While there are many adherent and suspension AAV production options available, the two leading scalable production platforms are transient transfection of suspension-adapted mammalian HEK293 cells and the infection of Spodoptera frugiperda (Sf9) insect cells using the baculovirus expression vector system (BEVS). With the acquisition of Brammer Bio, Thermo Fisher Scientific now has the capability to offer clinical and commercial AAV vector manufacturing utilizing these suspension processes.

GENE THERAPIES CONTINUE TO ADVANCE TO COMMERCIALIZATION

With the ability to treat and the potential to cure diseases for which no treatments are currently available, cell and gene therapies continue to attract significant attention. According to the Alliance for Regenerative Medicine, there were over 917 regenerative medicines in development worldwide by the end of Q1 2019, including gene, cell and tissue-engineering therapies.[1]

Of the 1,060 clinical trials in regenerative medicine underway worldwide by the end of Q1 2019, 372 involved gene therapies, with 123 in phase I, 217 in phase II and 32 in phase III. In that quarter alone, $2.1 billion was raised to advance gene and gene-modified cell therapies, most of which utilize viral vectors for gene transfer.[1] A few cell and gene therapy products have already been commercialized, with four approved by the U.S. Food and Drug Administration since 2017, including the two AAV products cited above. Regulatory authorities in China, Australia, New Zealand, South Korea, India, Japan, Europe and Canada have also approved gene therapy products.[2] It is predicted that as many as 40 cell and gene therapies will be on the market by 2022.[3]

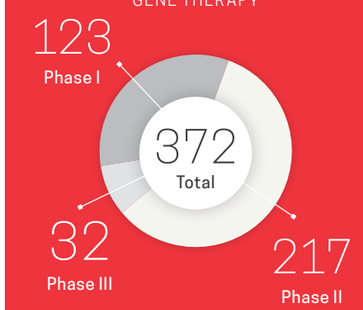
Clinical trials: Q1 2019

1,060

Clinical trials underway worldwide

Number of clinical trials utilizing specific regenerative medicines technology: Q1 2019

GENE THERAPY



Gene & gene-modified cell therapy financing

$2.1 BILLION

Raised in Q1 2019

AAV VECTORS ARE THE PREFERRED CHOICE FOR *IN VIVO* GENE DELIVERY

Viral vectors used in cell and gene therapies include adenovirus (Ad), lentivirus (LV), retrovirus (RV), herpesvirus (HSV) and adeno-associated virus (AAV). Recombinant AAV (rAAV) vectors are attractive for the development of gene therapies due to their efficacy, long-term gene expression and safety.[4] They were first discovered in 1965 as a contaminant of adenovirus stocks and were thus given the name "adeno-associated virus." AAVs are among the smallest viruses and are non-pathogenic members of the *Dependovirus* genus of parvoviruses. More than 12 AAV serotypes have been identified, along with hundreds of naturally occurring capsid variants.[4] The AAV gene therapy products that are in clinical evaluation target a variety of diseases affecting multiple organ types in varying patient populations.

THE AVERAGE PRODUCTION YIELD FROM THE SF9–BACULOVIRUS PLATFORM **IS APPROXIMATELY 10-FOLD HIGHER PER CELL AS COMPARED WITH TRANSIENT TRANSFECTION OF HEK293 CELLS.**

The first approved *in vivo* gene therapy products in Western markets were AAV vectors. These include Glybera (alipogene tiparvovec, (approved by the European Medicines Agency (EMA) in 2012) and the FDA-approved drugs Luxturna® (voretigene neparvovec, 2017) and Zolgensma® (onasemnogene abeparvovec-xioi, 2019). In addition, all viral vector therapeutics that received Priority Medicine status from the EMA in 2017 were rAAV vectors.[4,5]

LEADING SUSPENSION PRODUCTION PLATFORMS

Initial laboratory procedures for the production of AAV viral vectors involved the use of adherent cells in plasticware – an approach with limited scalability. Today, however, the large-scale production of AAV vectors using suspension cell culture in conventional bioreactors has been successfully demonstrated. The two predominant methods include transient transfection of suspension-adapted mammalian HEK293 cells[6-8] and the infection of Spodoptera frugiperda (Sf9) insect cells using the baculovirus expression vector system (BEVS).[4] rAAV vectors produced in both systems have been shown to have comparable biological activity.[4] Production platforms, such as Pall's iCellis large-scale adherent cell culture platform, are also gaining wider use.[9]

Each of these methods have been used to produce rAAVs that are being evaluated in late human clinical trials and are on the precipice of commercialization, with several more products in preclinical and early clinical development. The manufacturing processes are similar in that both start with thawed cells that are expanded through a seed train to a terminal bioreactor. In the differentiating step, HEK293 cells are transiently transfected with plasmid DNA, while Sf9 cells are infected with baculoviruses. After approximately three days, the rAAV virions are harvested, purified, formulated and filled into vials.

There are additional differences between the processes. For transient transfection, a master and working cell bank for HEK293 cells is required. It is also necessary to produce large amounts of plasmid DNA and to use chemical agents that mediate transfection, both of which are raw materials required in sufficient supply for each batch.

In the transfection step, multiple DNA plasmids (helper and transgene-containing) are mixed with the transfection agent to enable delivery of the DNA across the cell membrane and to the nucleus of the producer HEK293 cells. The fluid dynamics of this mixing process must be carefully controlled to prevent the formation of plasmid–reagent complexes that are too large or too small and to ensure an even distribution of the complex into the cell suspension. These requirements can create challenges in obtaining the batch scale at which these processes are required to achieve production demand.

Additionally, it is possible that some transgenes carried by the therapeutic vector may not be compatible with the mammalian manufacturing system. Expression of these genes during production, which is driven by the same promoters that are designed to function in humans during gene therapy, may negatively impact the performance of the culture system. Gene-suppression systems to regulate expression of the therapeutic gene during production are being developed to overcome these challenges.

In contrast to the transfection process, the infection of Sf9 cells does not require carefully controlled mixing times. In addition, any potentially negative impacts to the culture system, due to the expression of the therapeutic transgene, are minimized since the typical mammalian promoters used in vectors have little or no expression in insect cells. During production, a small quantity of the baculoviruses harboring the necessary genes to generate the recombinant AAV vector are infused into the terminal bioreactor to infect the Sf9 cell culture.

For the Sf9–baculovirus production system, the engineering of two recombinant baculoviruses (rBV) must be performed. One rBV contains the AAV helper genes (rep and cap), while the second rBV contains the genome of the AAV therapeutic vector. Master and working banks must be made for these viruses, as well as master and working cell banks for the Sf9 cells. Therefore, this system requires a significant upfront investment in time (several months) and resources needed to clone and bank each of these components.

The average production yield from the Sf9–baculovirus platform is approximately 10-fold higher per cell as compared with transient transfection of HEK293 cells. With the Sf9–baculovirus system, the significant upfront investment in time and resources needed to clone and bank each of the recombinant baculoviruses and Sf9 cells pays off with the ability to rapidly manufacture very large batches of rAAV. In both systems, a significant portion of the capsids do not contain the vectors (i.e., empty capsids), and the full capsids can be enriched in subsequent purification steps.

The final AAV vectors produced using HEK293 and Sf9 cells differ with respect to their impurity profiles. With the HEK293 platform, potential impurities include specific host-cell DNA/proteins and residual plasmid used to generate the vector. For the baculovirus system, the potential impurities include Sf9 host DNA/proteins and baculovirus DNA/proteins. A potential risk associated with the mammalian system is the encapsidation of host-cell genetic material, which may contain oncogenes harbored in the HEK293 cells, but there may be similar risks with packaging Sf9 host-cell DNA. As is typically the case in manufacturing of biologic drug substances well-established downstream purification methods have been shown to remove residual host-cell proteins and DNA that may be present in intermediates produced. Because the HEK293 and Sf9 feed streams are slightly different, the specific purification steps taken for the two platforms may also differ accordingly. To monitor these risks (as with any biologically produced product), tests are utilized to determine whether residual DNA/protein is present in the AAV product.

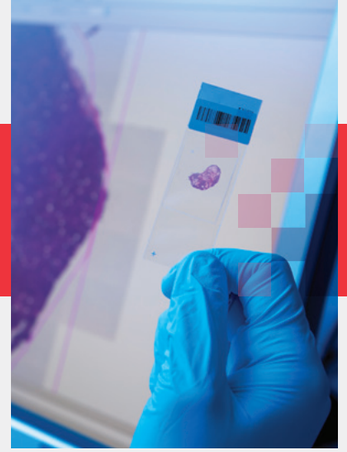
OPTIMIZING DOWNSTREAM PROCESSES

AAV vectors are typically purified using affinity chromatography and end with formulation into a desired buffer, filtration and filling into vials. The specific steps taken to optimize the downstream purification process for any given AAV vector will correlate directly with the specific impurity profile and level of empty capsids in the feed stream. These are addressed with the incorporation of additional chromatography and filtration steps. For each platform, differences in titer will determine scaling parameters and process steps needed during chromatography and filtration. As indicated earlier, common to both platforms is the presence of empty capsids in the feed stream. The degree of optimization taken to limit the quantity of empty particles in the upstream production process will impact the degree of optimization required downstream to remove the empty particles. Purification modalities (chromatography or ultracentrifugation) can be implemented to remove empty capsids irrespective of the production system.

SIMILAR ANALYTICAL TECHNIQUES

Many of the methods used to characterize AAV vectors are utilized independent of the production process and are intended to evaluate both product quality and attributes. They include standard enzyme-linked immunosorbent assay (ELISA) and quantitative polymerase chain reaction (qPCR) techniques that are widely applied in the biopharmaceutical industry. Digital droplet PCR (ddPCR) for

Thermo Fisher Scientific Acquired Brammer Bio, a Leader in Viral Vector Manufacturing



Thermo Fisher Scientific Inc. (NYSE: TMO), the world leader in serving science, acquired Brammer Bio for approximately $1.7 billion in cash in Q2 2019.

Brammer Bio is a leading viral vector contract development and manufacturing organization (CDMO), enabling biopharma customers to deliver breakthrough medicines to patients by unleashing the potential of gene therapies and gene-modified cell therapies. The business has nearly 600 employees at primary locations in Massachusetts and Florida.

Brammer Bio is on track to deliver $250 million of revenue in 2019 and expects to continue to exceed the projected market growth rate of 25 percent over the mid-term. Thermo Fisher expects the business to be accretive to adjusted earnings per share by $0.10 in the first full year of ownership.

Upon completion, Brammer Bio became part of Thermo Fisher's pharma services business within its Laboratory Products and Services Segment.

absolute rather than relative quantification of target DNA molecules is now becoming the industry standard for vector genome and residual DNA titration.[10]

Vector purity is determined by analyzing samples for process-related impurities (e.g., host-cell DNA and proteins) and for product-related impurities (e.g., the ratio of full and empty capsids). Analytical ultracentrifugation (AUC), capillary electrophoresis (CE) and HPLC-based methods are powerful techniques for determining the purity of AAV products. Thermo Fisher's Viral Vector Services business has developed robust analytical technique which was developed in house, for the characterization and composition of empty, partial and full AAV capsids.

Identity testing is conducted on the vector in order to confirm the proper identity of the capsid proteins; this is typically performed using specific antibodies or liquid chromatography – mass spectrometry. Vector genome identity is also performed to confirm the integrity of the therapeutic transgene sequence contained within the vector; this is typically performed using next-generation sequencing (NGS) or Sanger sequencing. The formulated product is also subjected to osmolality, pH and other analytical chemical testing to confirm that the vector was formulated correctly.

Product strength e.g., genome titer (number of vector genome copies per milliliter) is universally used to determine dosing; infectivity and potency (expression of the transgene and therapeutic effect) are also evaluated. Safety tests are performed to confirm that impurities or contaminants like replication-competent AAV (rcAAV), adventitious agents, endotoxin and microbes are below specified levels.

The need to develop more sensitive, accurate, robust assays constantly pushes the industry to search for new technologies, while at the same time adopting proven analytical methods used in the biologics industry.

THE FUNDING PARADIGM FOR THE GENE THERAPY DEVELOPER WILL ALSO HAVE AN IMPACT ON **THE BIOPROCESSING PLATFORM DECISION.**

CHOOSING THE HEK293 OR SF9 PLATFORM

The choice to use the mammalian or insect production platform is contingent on several factors. Overall, the batch size and frequency of AAV production will be dictated by the drug dose, the size of the patient population and the expected market penetration for the product. Some gene therapies are given as ~100 µL doses, such as those administered via subretinal injection. Others are delivered intravenously at doses of ~100 mL. Across the dosing range, the patient population may be very small or very large. Consequently, a commercial process could be viably supported either by a 20- to 200-L bioreactor scale or may require large-scale manufacturing in a 2000-L bioreactor.

The funding paradigm for the gene therapy developer will also have an impact on the bioprocessing platform decision. Many startups supported by venture capital funding receive money from these firms in increments as the project progresses. Milestone payments are typically made when toxicology data is obtained, after phase I trials are completed and safety in humans is confirmed, and as the gene therapy meets efficacy endpoints in later clinical trials. This model encourages minimizing time to the clinic, and the fastest way to achieve proof-of-concept data in humans is typically for companies to employ transient transfection in the adherent mammalian platform. However, the adherent platform has inherent challenges in scale-up, which must be overcome in order to produce consistent, large-scale batches required for commercial production.

On the other hand, there is a new accelerated approval paradigm at the FDA through which consideration for a commercial license can be achieved in an approximate four-year time frame (rather than the typical 10–11 years) if the CMC section is sufficiently robust and a well-designed early clinical study has demonstrated efficacy.[11] For companies that wish to leverage this new paradigm, it is essential to invest in the development of a commercial-ready manufacturing platform and to generate robust data for the CMC package up front and to leverage a process that will enable rapid scale-up to commercial production.

The large-scale production of AAV vectors using both mammalian HEK293 and Sf9–baculovirus suspension cell cultures has been successfully demonstrated and will likely continue to gain in favor owing to their scalability and ability to produce large, commercial batches of drug product.

SUPPORTING AAV PRODUCTION FROM R&D TO COMMERCIALIZATION

Thermo Fisher Scientific offers many of the key reagents needed to support both baculovirus and mammalian suspension processes, as well as adherent mammalian processes for the manufacture of AAV vectors. These reagents are available through the catalog to researchers and in larger quantities for manufacturing.

With the acquisition of Barmmer Bio, Thermo Fisher's Pharma Services business has added a complementary capability servicing the growing demand for viral vector manufacturing. Customers today not only have access to important research reagents for their early work, but the support of a team with decades of experience in GMP viral vector manufacturing that can help them successfully move their projects from development to the clinic and on to commercialization. P

REFERENCES

1. *Quarterly Regenerative Medicine Global Data Report: Q1 2019.* Rep. Alliance for Regenerative Medicine. May 2019. Web.
2. *Global Market for Gene Therapy 2019 - Product Pipeline, Market Size, & Forecasts.* BioInformant. Aug. 2019. Web.
3. "Existing Gene Therapy Pipeline Likely to Yield Dozens of Approved Products Within Five Years." MIT NEWDIGS FoCUS Project. 13 Nov. 2017. Web.
4. Kotin, Robert M. and Richard O. Snyder. "Manufacturing Clinical Grade Recombinant Adeno-Associated Virus Using Invertebrate Cell Lines." *Human Gene Therapy.* 28: 350–360 (2017).
5. "List of products granted eligibility to PRIME—WC500214862." European Medicines Agency. Oct. 2018. Web.
6. Chahal, Parminder S. et al. "Production of adeno-associated virus (AAV) serotypes by transient transfection of HEK293 cell suspension cultures for gene delivery," *Journal of Virological Methods.* 196: 163–173 (2014).
7. Grieger, Joshua C., Stephen M. Soltys and Richard J. Samulski. "Production of recombinant adeno-associated virus vectors using suspension HEK293 cells and continuous harvest of vector from the culture media for GMP FIX and FLT1 clinical vector." *Molecular Therapy.* 24: 287–297 (2016).
8. Blessing, Daniel et al. "Scalable Production of AAV Vectors in Orbitally Shaken HEK293 Cells." *Molecular Therapy Methods & Clinical Development.* 13: 14–26 (2019).
9. Snyder, Richard, Clive Glover, Rajiv Vaidya and Matt Niloff. "Accelerating the Development of Viral Vector Manufacturing Processes." *Pharma's Almanac.* 24 May 2019.
10. Snyder, Richard et al. "Digital Droplet PCR for Viral Vector Analysis." *Pharma's Almanac.* 12 Mar. 2019.
11. Marks, Peter. "FDA's Efforts to Advance the Development of Gene Therapy." U.S. Food and Drug Administration. 1 May 2019. Web.

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MANAGING THE COMPLEXITIES OF INTERNATIONAL CLINICAL TRIALS

→ BY **GULAM JAFFER,** YOURWAY

The number and complexity of clinical trials is increasing dramatically. While trials tend to enroll fewer patients, those patients are often in remote locations and increasingly prefer to be treated in the home rather than at an investigator site. In addition, the drugs being evaluated often have complicated storage, handling and transportation requirements. Sponsor companies can ensure the success of their clinical studies by partnering with a clinical logistics partner that has comprehensive and demonstrated capabilities in customs clearance, transportation and comparator sourcing.

MORE COMPLEX TRIALS IN CHALLENGING LOCATIONS

The World Health Organization (WHO) tracks clinical trials in the WHO International Clinical Trials Registry Platform (ICTRP) and has reported the number of trials by year, country, WHO region and income group for the period 1999–2018.[1] The data includes both interventional and observational trials, with the year corresponding to the date of enrollment of the first trial participant.

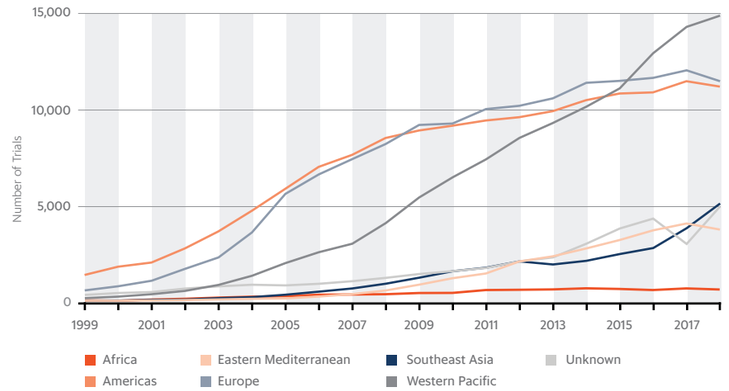
Over this period, there has been a steady increase in the number of newly recruiting trials registered on ICTRP for most WHO regions (Fig. 1). By region in 2018 (counting multicountry trials conducted in the same region as one trial), the most trials in 2018 were initiated in the Western Pacific (14,655), followed closely by Europe (11,291) and the Americas (11,013). The fewest studies were begun in Africa (630), although there is growing interest in conducting trials in this region for drugs and vaccines designed to treat/prevent diseases native to the area, as well as efforts to expand the reach of international trials to include groups that have been historically underrepresented in clinical populations.

Since 2015, the number of trials conducted in the Western Pacific region has increased more rapidly than in other regions, and it is becoming the WHO region with the highest number of trial registrations per year. Most of these trials are taking place in Japan and China. This growth is in part due to the increase in requirements for sponsor companies to register trials in China to be able to gain access to that market. Not only are more clinical drug products being shipped into the country, but the shipment of patient laboratory samples has also increased dramatically.

Furthermore, trials registered in the ICTRP in 2018 originated in over 50 different countries. These trials involve all types of drug substances, from traditional small molecule drugs to highly complex biologics, from engineered proteins and antibodies to gene therapies and personalized medicines such as autologous CAR-T cell therapies.

In 2018 nearly 40% of drugs in the pharmaceutical industry pipeline were biologics,[2] most of which require storage and handling at low temperature. In addition, a growing fraction of drugs submitted for approval are intended for the treatment of rare diseases with small patient populations (orphan drug or equivalent designation), leading to trials with fewer but widely scattered participants.

FIGURE 1: Number of trials by year and WHO region (1999 to 2018)



REACHING DISTANT LOCATIONS

Ensuring delivery of clinical trial materials and shipping biological samples to and from remote locations in a timely manner can pose significant challenges for clinical trial managers. Partnering with a clinical logistics provider that has an established, global network of depots, demonstrated knowledge of the regulations in these regions, centralized management and tracking systems and a highly trained workforce is often the key to success.

Some countries have complex and stringent regulations, the navigation of which requires detailed knowledge. In many developing countries, import and export regulations for drug products and biological samples are evolving rapidly. Having local staff that are in communication with regulators and customs agents is essential under these circumstances.

Through our global GMP-compliant depot network, which includes more than 21 different locations, we provide integrated services, including comprehensive transport of drug products and biologic samples, primary and secondary pharmaceutical packaging, warehousing and distribution support for cold-chain solutions, unused product return services and assistance with logistics project management.

The latter services include sourcing of comparator drugs and other supplies, establishing optimal delivery strategies across global trials and documentation support and the provision of regulatory advice regarding country-specific requirements. We also pay customs fees proactively so that shipments are never held up.

Our team of pharmaceutical transport specialists is highly experienced in supporting customer needs for the shipment of phase I, II, III, IV finished goods and production of raw materials. We guarantee speed of delivery with highly customized transport solutions and work with each client and every shipment on a one-to-one basis to ensure the highest level of service. Our goal is to ensure the fastest, most secure and most reliable delivery possible, anywhere in the world and with no size or weight restrictions.

RAPID GLOBAL RESPONSE

One dramatic example of Yourway's global reach and agility was our involvement in delivering critical experimental drugs to patients during the 2018 Ebola outbreak in the Democratic Republic of the Congo. Ebola is a particularly deadly viral disease, killing about 50% of people who contract the virus.

In response to the growing outbreak, which numbered 58 cases in less than a month, and the limited available treatment options, the WHO and the Congolese government approved five experimental drugs – the monoclonal antibody cocktails ZMapp, REGN-EB3 and mAb114 and the antivirals favipiravir and remdesivir – to quickly address the unmet needs for the infected population.

Yourway was contracted by Regeneron to rapidly deliver REGN-EB3 from the United States to the Congo. We were able to leverage our existing distribution network to get this critical treatment to infected patients within 36 hours of the approval, playing a decisive role in helping contain the outbreak.

PLANNING FOR BREXIT

Challenges with clinical trial logistics are not limited to remote locations. Uncertainties associated with the exit of the United Kingdom from the European Union are creating significant difficulties for sponsor firms with clinical trials taking place in the UK.

Yourway has made preparations for a "hard" Brexit – for the UK to leave the EU with no trade deals in place. In addition to our existing depot in the UK, which offers QP services as required by the Clinical Trial Directive 2001/20/EC and Annex 13 to the European GMP Guide, Yourway has opened a depot in the EU 40 minutes outside of Vienna, Austria.

At Yourway, we are hopeful that, whatever form Brexit ultimately takes, the UK and EU will mutually recognize and accept the processes and procedures implemented in both places. Regardless, we are paying close attention to Brexit negotiations and are prepared to support our customers via the appropriate mechanisms.

MANAGING COMPARATOR SOURCING

To obtain drug approvals today, it is necessary to clearly demonstrate improved performance of a new drug product over existing therapies on the market. The best way to achieve this goal is to perform clinical trials with the candidate drug and a comparator, typically the commercial drug considered to be best-in-class at the time of the study.

Sourcing comparator drugs is rarely simple. In the best-case scenario, the sponsor company will have 12–18 months to organize the supply of comparator products. In practicality, the timeframe is much less, and in the worst-case scenario can be as little as a few weeks.

The complexity of the comparator sourcing problem varies with the drug itself and the countries in which the clinical trials is taking place. Many biologic drug manufacturers look to control the supply of their drug products and require supply agreements, even with sponsor companies looking for comparator material. Special licenses are required to ship comparator materials into some countries, while others require that drugs used in clinical trials be sourced from within the country. If the drug can be obtained at all, it may not be available in sufficient quantity, and multiple suppliers may be needed.

Yourway has developed strong relationships with many drug manufacturers and other key players in the pharmaceutical supply chain. We work diligently to establish supply agreements that will ensure access to sufficient quantities of comparator drugs when they are needed so as to avoid unnecessary delays, under-shipments and oversupply that can lead to the expiry of costly medicines.

PERSONALIZED MEDICINES AND TRIALS

Personalized medicines – and cell and gene therapies in particular – often have very limited shelf lives and require storage and shipment under cryogenic conditions. Material is taken from a patient and shipped to the manufacturing site, where it is processed and formulated into a drug product that is then returned for administration to the patient. Yourway has the capability to ensure chain of identity and effective management of the cold chain combined with rapid shipment to and from locations around the world.

Yourway is also able to provide direct-to-patient shipment of clinical trial materials. Patients can experience the convenience of having their medicines delivered to their homes or workplaces, while clients can be assured that the medicines will be maintained under compliant environmental conditions. We can also develop customized delivery solutions if patients will be traveling or moving to a new location, making it possible to keep all patients enrolled and receiving their medications.

CHANGES ONLY BEGINNING

The pharmaceutical industry is evolving rapidly. As the understanding of disease mechanisms expands, pharmaceutical scientists are developing entirely new ways of curing patients. The types of drugs and formulations being developed today – biologics, patient-specific therapies and other specialized treatments – did not exist just 10–20 years ago.

There are also many more companies – largely small and emerging biotech firms – developing those novel medications. Finding enough patients to fully enroll the rapidly growing number of decentralized, international clinical trials is a challenge.

Innovation in drug discovery and development is driving the need for innovation in logistics technologies. For sponsor companies, efficiently and effectively managing the supply of the specialty clinical materials and patient samples used in and generated by the trials of today – and those in the future – requires partnering with a clinical logistics company committed to continuous improvement and the ongoing development of new packaging, sourcing and other logistics solutions. P

REFERENCES

1. "Monitoring processes to R&D." World Health Organization. Apr. 2019. Web.

2. Lloyd, Ian and Alexandra Shimming. "Pharma R&D Annual Review 2018," Pharma Intelligence presentation. 16 May 2018. Web.

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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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GROWING WITH A FLEXIBLE, COLLABORATIVE CDMO

→ BY **KIM BERGER** AND **PAUL MAGRETA**, GRIFOLS RECOMBINANT PROTEIN CDMO SERVICES

When selecting a contract development and manufacturing organization (CDMO), companies typically place the greatest emphasis on price, quality and capabilities, but do not always appropriately weigh other factors – such as geographic proximity with its benefits to communication and collaboration when close and its challenges when distant – that can have a direct impact on project success. In addition, choosing a CDMO that is agile, innovative, and exhibits a willingness to invest in new equipment, infrastructure and services will allow the innovator company and the CDMO to grow together.

FINDING THE RIGHT STRATEGIC PARTNER

In an increasingly globalized and interconnected industry, pharmaceutical and biotech companies have opportunities to partner with organizations across the world, taking advantage of widely dispersed resources and leveraging opportunities in different global regions at relevant points across the supply chain.

When choosing a strategic partner to guide a project from early development through clinical and, ultimately, commercial manufacturing, there are a range of critical factors to consider and the optimal balance for a given project often depends on the nature of the project itself. When evaluating a prospective CDMO partner, robust quality systems and demonstrated GMP compliance are critical, along with ensuring that the CDMO possesses the spectrum of capabilities needed to support the project, including contingent services and expertise that may be needed if unforeseen complications arise. Of course, cost is always a major determinant when selecting a CDMO, as is the company's legacy of completing project milestones on time. In addition, factors such as technical expertise and collaboration, effective communication, and transparency may be more difficult to quantify but can impact the ultimate success of a program.

CRITICAL FACTORS TO CONSIDER

Grifols is a global healthcare company and has a long history of working with partners across the globe and knows how to overcome the challenges of linguistic and cultural differences – as well as geographic distances – but we also recognize the additional efficiencies that are made possible when communication and collaboration are streamlined.

As a CDMO within a larger healthcare company, Grifols also has experience as a buyer of CDMO services. We understand the importance of transparency and responsiveness and have seen firsthand how long-distance partnerships can create difficulties. Due to time differences, it can take multiple days to coordinate schedules for a call when problems arise. If the process doesn't produce expected results, sending subject matter experts to the CDMO to determine what is happening can be costly. In addition, some raw materials might not be able to be sourced in the country where the CDMO is located, which can extend the timeline to import the reagents.

Efficient communication is important for overall project success and can be particularly critical during tech transfer and troubleshooting, where discussions may be needed in real time to solve problems effectively. This can be mitigated by having client technical experts onsite, but frequent or extended long-distance travel is not always feasible, especially with other projects or activities that require their attention. Cumulative delays can have a significant impact to a project's schedule. We anticipate these kinds of challenges when transferring the technology and planning the project timeline to minimize the impact and keep the project on time.

Although working with CDMOs across oceans is increasingly feasible given current telecommunications and other technologies, there are still distinct advantages to working with a local partner. Clients often want to be heavily involved in the tech transfer, and working with a local CDMO facilitates this ongoing, in-person collaboration. The ability to regularly meet face-to-face with clients can significantly minimize risks of miscommunications, particularly during exchanges of critical technical information or at crucial decision points. For one of our customers, the product produced by a distant CDMO was not active, and the parties were not able to determine the cause. The company decided to transfer the product to Grifols as a local CDMO where we could work closely together. Our collaboration resulted in producing an active product, allowing the company

EFFICIENT COMMUNICATION IS IMPORTANT FOR OVERALL PROJECT SUCCESS AND CAN BE PARTICULARLY CRITICAL DURING TECH TRANSFER AND TROUBLESHOOTING, **WHERE DISCUSSIONS MAY BE NEEDED IN REAL TIME TO SOLVE PROBLEMS EFFECTIVELY.**

OUR STAFF WELCOMES THE OPPORTUNITY TO HAVE FACE-TO-FACE VISITS WITH CLIENTS **WHERE NEW IDEAS CAN BE DISCUSSED.**

to get back on track and move forward with toxicology studies showing the benefits of working locally for complex, difficult projects.

GRIFOLS IS A LOCAL PARTNER IN THE SAN FRANCISCO BAY AREA

Grifols Recombinant Protein CDMO has three decades of experience in recombinant protein technology and partners with companies interested in developing complex proteins into therapeutics, vaccines or diagnostics. Our state-of-the-art GMP biological manufacturing facility located in the San Francisco Bay Area is well positioned to provide long-term, high-quality, commercial manufacturing of recombinant biologic drug substances to our customers, regardless of their global location. This location, in one of the major U.S. biotech hubs – home to many emerging biotechnology companies lacking extensive internal development and manufacturing resources – provides us with an opportunity to effectively serve a host of local customers.

Grifols is staffed by highly experienced and talented people with diverse expertise and educational backgrounds within the field of biotechnology. Our staff welcomes the opportunity to have face-to-face visits with clients where new ideas can be discussed. With their significant tech transfer expertise and access to the state-of-the-art facilities and equipment within the CMF and new pilot plant, including R&D, process development and analytical laboratories, our scientists can rapidly identify solutions for our CDMO clients.

INVESTMENTS TO GROW WITH CLIENT NEEDS

A current challenge in the market is the limited U.S. biopharma CDMO capacity for both drug substances and drug products. We are committed to providing our client partners with the best CDMO services and are investing in new development and manufacturing capacity. We have recently completed an $80-million consolidated manufacturing facility (CMF) at our Emeryville, California campus that received FDA approval in 2018, where we specialize in recombinant *Escherichia coli* and yeast development, and GMP production.

We have initiated a project to build cell culture and purification suites for GMP production of recombinant proteins expressed in mammalian cells. This project is led by our internal Grifols Engineering department in our new facility's expansion space. The suites will use disposable technology, including bioreactors up to 1000 L, and is expected to be completed in late 2020.

To support process development and scale-up, we completed new development laboratories in 2016 and are finalizing the design for a new pilot plant that will be located across the street from CMF, in what was previously a GMP manufacturing space. The pilot plant will have suites for microbial and cell culture processes to support process development and clinical manufacturing and is expected to be operational in 2020.

These investments expand our capabilities and enable Grifols to grow to meet the needs of current and future customers. The expansion space within CMF provides considerable flexibility to our operations and creates an opportunity for strategic growth to support client needs. Grifols is committed to providing opportunities where we align our goals with those of our clients and grow together. P

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CUSTOMER ENGAGEMENT AND INFORMATION SHARING ARE ESSENTIAL FOR SUCCESS IN ORPHAN DRUG OUTSOURCING

→ BY **MARGA VIÑES**, GRIFOLS PARTNERSHIP

Developing cost-effective manufacturing solutions for smaller volumes of highly specialized orphan drugs can be challenging, particularly for small and emerging pharmaceutical companies seeking to bring novel rare disease treatments to market. A contract service provider with experience in specialized technologies and accelerated development programs that is committed to customer engagement, information sharing and the formation of real partnerships can be the key to achieving success.

EXPANDING AN ORPHAN DRUG MARKET

In recent years, drug makers have shifted their focus from the development of blockbuster drugs to the development of therapies to treat rare diseases, also known as "orphan drugs." There have been 7000–8000 rare diseases identified to date; effective medicines have been developed for only a few hundred of these diseases.

A number of unique clinical, regulatory and commercial challenges are associated with the development of therapies for the treatment of rare diseases. In recognition of these challenges, legislation has been implemented in the United States, the European Union and elsewhere to provide regulatory and financial incentives aimed at stimulating investment in orphan drugs.

Since the implementation of the U.S. Food and Drug Administration's (FDA) orphan drug modernization plan in 2017, the approval rate for orphan drugs in the United States has accelerated significantly.[1] Despite the reduction of the Orphan Drug Tax Credit in 2017, the number of new orphan drug approvals continues to hit new records.[2] In Europe, orphan drug approvals by the European Medicine Agency (EMA) more than doubled in 2017 to 17 in 2018.[3] Notably, 40% of the innovative drugs undergoing clinical trials for potentially new targets in mid-2018 were developed to treat rare diseases.[4]

Not surprisingly, the growth rate for the global orphan drug market is quite healthy. Pharmaceutical intelligence firm EvaluatePharma estimates that it is expanding at a compound annual growth rate of 12.3%, which is nearly twice the growth rate for the overall pharmaceutical market.[5] By 2024, the orphan drug market will be valued at $262 billion, and sales of orphan drugs will account for one-fifth of worldwide drug sales and approximately 30% of total R&D pipeline sales through that year.

GROWING USE OF CDMOS

With knowledge of disease mechanisms continuing to expand, novel drug targets are being discovered regularly. Lower development costs for rare disease therapies combined with limited or no generic competition create incentives for drug manufacturers positioned to manage the complexities of the development and commercialization process.

Recent successes in the development of orphan drugs coupled with productivity challenges in the classic pharma R&D model for indications with a higher prevalence have resulted in a number of major pharmaceutical companies establishing business units focused on rare diseases. Investment by venture capital companies in early-stage biotechs with rare disease programs has also increased.

In many cases, the firms developing orphan drugs are small and emerging pharma and biotech companies with missions aimed at developing targeted therapies for specific disorders. The Tufts Center for the Study of Drug Development reported that smaller pharma and biotech firms developing small molecule drugs have higher clinical approval success rates than large companies.[6]

These smaller firms are achieving those successes by leveraging partnerships with effective contract development and manufacturing organizations (CDMOs) that support the unique set of needs that arise during development and commercialization of orphan drugs. These companies rely on CDMOs for expertise in manufacturing, process and formulation development, validation and regulatory compliance.

ORPHAN DRUG DEVELOPMENT CHALLENGES

A fundamental challenge in drug development for the majority of rare diseases is that there is often relatively little known about the pathophysiology or the natural history of these diseases. Typically, there are only a small number of experienced clinical investigators worldwide and in contrast to more prevalent diseases, there is relatively little published scientific literature.

The most obvious challenge in conducting clinical trials in rare diseases is the small numbers of patients available for clinical studies. Enrollment of patients into clinical studies in sufficient numbers to generate meaningful comparative data is difficult and usually requires the participation of many sites across diverse geographies, frequently with only very few patients enrolled at each site. Delays in the recruitment process often occur, adding cost and uncertainty to these programs.

CDMO CONCERNS

It is difficult, in some cases, for CDMOs to commit to projects involving orphan drugs, not only due to the small volumes of product units that are often needed, but also the uncertainty deriving from the lack of deep knowledge about the targeted diseases.

UNDERSTANDING AND ALIGNING COMMERCIAL STRATEGIES

While many CDMOs are disinclined to pursue small-volume projects focused on developing and manufacturing orphan drugs for unmet needs, others, such as Grifols, actively seek out such projects with small and emerging pharma companies. The key to successful project completion is to develop an understanding and alignment of the commercial strategies of both organizations.

CDMOs must understand the commercial strategy of the sponsor to be able to accurately structure the timeline and to guarantee production of the product on time. Many orphan drugs are awarded accelerated approval designations, leading to the need to implement projects in dramatically shortened timelines. In addition, knowledge of the sponsor's commercial strategy allows the CDMO to better support management of its life cycle and prepare for new market demands.

Sponsor companies developing orphan drugs must, in turn, understand the requirements of their CDMO partners. Most importantly, it is essential to agree on a minimum quantity of product for scale-up as the orphan drug advances through each development stage. This type of agreement is particularly crucial when the CDMO must invest in new equipment and technologies specifically for the project, which impacts production costs. The CDMO must also have the capability and flexibility to produce both very small volumes and larger volumes when demand increases.

IN RECENT YEARS, DRUG MAKERS HAVE SHIFTED THEIR FOCUS **FROM THE DEVELOPMENT OF BLOCKBUSTER DRUGS TO THE DEVELOPMENT OF THERAPIES TO TREAT RARE DISEASES, ALSO KNOWN AS "ORPHAN DRUGS."**

OPEN COMMUNICATION IS ESSENTIAL

Guaranteeing that timelines are met also requires honest, two-way communication between the CDMO and the sponsor firm from the beginning of a project. A basis of mutual trust must underlie this communication, resulting in the generation of a true partnership rather than a mere customer-supplier transaction.

Such a partnership can only develop when the individuals that make up the different teams at the CDMO and the sponsor company – including representatives from R&D, Quality, Regulatory Affairs, Manufacturing, Business Development and Business Intelligence – are perfectly aligned and committed to working together. Only under these conditions is it possible to effectively manage the complexities of orphan drug development programs and move them forward meeting all expectations, particularly if unexpected difficulties and complications arise.

Before initiating a project, the CDMO should be provided with information about potential competitors, evolution of the market, regulatory aspects and patient needs to confirm the viability of the program. The sponsor company must also be willing to share all of the relevant

technical process information for each phase of the project, whether the program begins at the development stage or with technology transfer of an established process and product.

During the technical transfer process, the CDMO should welcome the presence of representatives from the sponsor company with expertise in the specific product involved. The efficiency of tech transfer can be greatly increased when technical experts can directly advise CDMO operators and engineers about the details of the process. Grifols welcomes training of plant personnel by sponsor company experts and has found that doing so often leads to reduced project timelines.

Once a project is initiated, regular, frequent communication between multidisciplinary team members from all areas must take place to ensure constant sharing of information and to enable the generation of new ideas and anticipation of possible scenarios that may hinder the progress of the project.

An effective CDMO also recognizes the importance of quickly sharing information with their partners when unexpected difficulties like equipment problems or test lab issues arise. Only with direct and immediate communication can optimal solutions be developed and implemented. Ongoing communication is needed to keep the customer updated on the implementation of the solution and resolution of the issue. Finally, maintaining honest and real communication with the client is crucial for CDMOs in the effort to reduce potential risks in both the development and technology transfer stages.

RISK ASSESSMENTS ARE FOUNDATIONAL

Sponsor firms developing orphan drugs as parenteral products should only work with CDMOs that have the necessary expertise to produce these complex products and those that are committed to conducting extensive risk assessments before beginning any new project.

The performance of a comprehensive risk analysis is crucial to the development of effective processes for sterile injectables. These risk analyses allow for identification of sources of potential problems along with implementation of measures that may prevent those issues from arising. The goal of risk management is not to eliminate downside risks, but to control them within an acceptable range. Once the limits and potential areas of concern have been identified, the next step is to determine the process conditions and controls needed to ensure that the process will be robust and scalable. Orphan drugs are typically very high-value products. Risk assessments can also help identify optimal solutions for minimizing any loss of the expensive API.

COLLABORATING WITH GRIFOLS

Grifols specializes in the terminal sterilization manufacturing of parenteral products. We are also a CDMO business unit positioned within a large, international pharmaceutical company with extensive experience in the development and commercialization of many types of sterile drug products. As such, Grifols has access to financial, technical, regulatory and other resources not readily available to standalone CDMOs, and we remain sufficiently flexible as an ideal partner for small and emerging pharma companies.

While the CDMO business at Grifols is focused on meeting the needs of smaller customers, we maintain access to the resources of our parent company. As a result, we are often able to make investments in equipment and technology for specific projects and are willing to establish a range of commercial arrangements customized for each project and client.

In addition, the equipment used for our CDMO partners is the same equipment used for internal projects, designed specifically for Grifols by Grifols Engineering. This vertical integration fits with Grifols' quality culture and enables us to control the entire process, ensuring achievement of the highest quality.

We are able to leverage the resources and experiences of the larger Grifols organization to provide significant value to our partners, from guiding new drug applications through regulatory approval to determination of patient and caregiver reactions to product delivery systems.

We can also advise our partners on the best container choices based on the intended patient population. We have been working directly with nurses and doctors for decades and understand their preferences regarding parenteral product design. As a result, Grifols can assist clients in selecting the most appropriate containers and delivery systems that will provide the greatest ease of use and ultimately the highest level of patient adherence. P

REFERENCES

1. *Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments. Rep. IQVIA* Institute Report. 17 Oct. 2018. Web.

2. Taylor, Phil. "Orphan drugs dominate FDA's record-breaking year." PMLiVE. 2 Jan. 2019. Web.

3. Schofield, Ian. "EU New Drug Approvals 2018: Anticancers, Orphans, The First CAR-Ts – And More." Pharma Intelligence. 2019. Web.

4. Attwood, Misty M. , Mathias Rask-Andersen, Helgi B. Schiöth. "Orphan Drugs and Their Impact on Pharmaceutical Development." *Trends in Pharmacological Sciences*. 39: 525–535 (2018).

5. *Orphan Drug Report 2018, 5th Edition.* Rep. EvaluatePharma. May 2018. Web.

6. DiMasi, Joseph A. "Pharmaceutical R&D performance by firm size: approval success rates and economic returns." *American Journal of Therapeutics* 21.1: 26–34 (2014).

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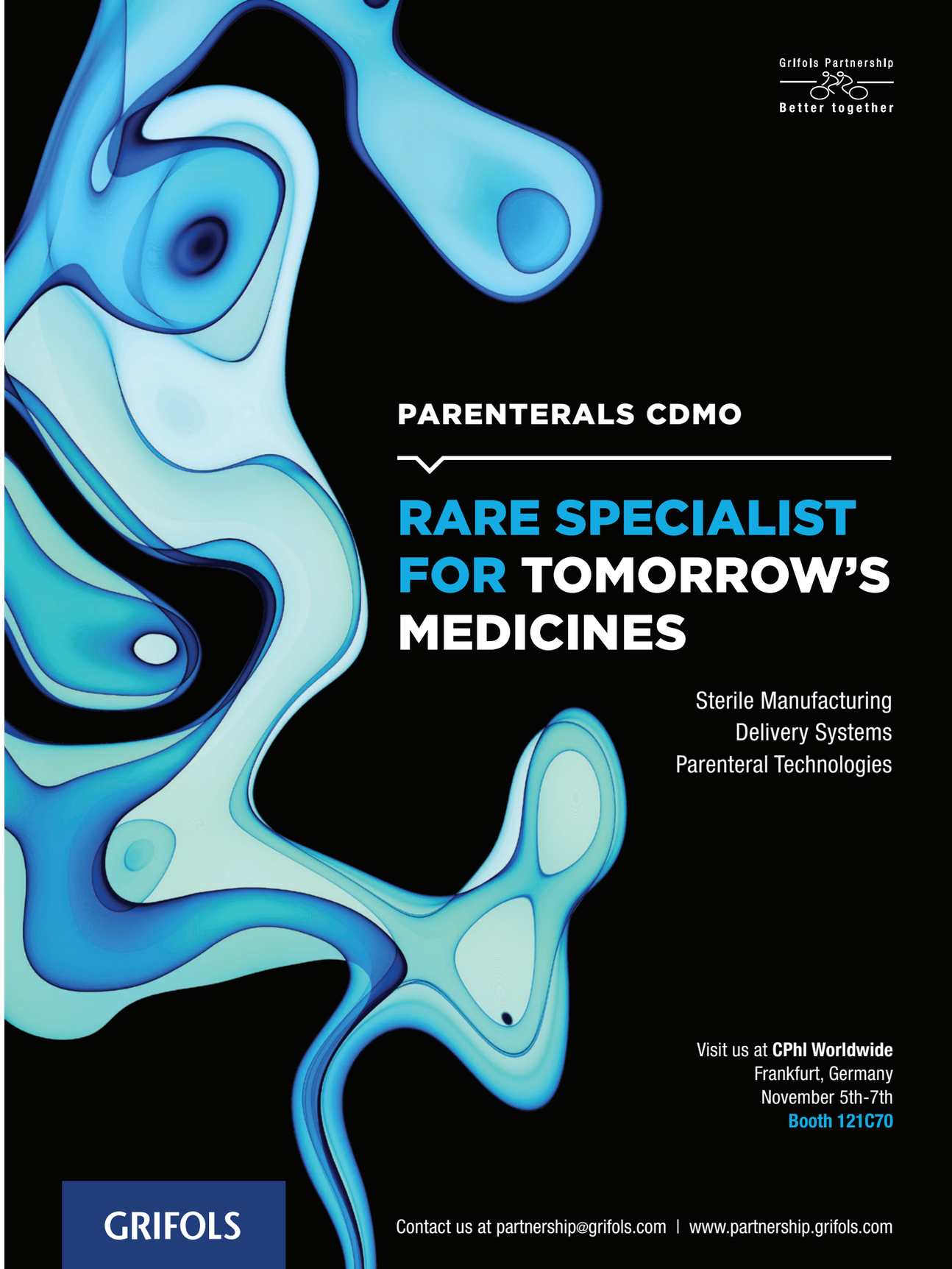

TECH TRANSFER AND SCALE-UP FOR CUSTOM APIS DRIVEN BY A COLLABORATIVE CULTURE

→ BY **JAMES SPRINGER** AND **JAMES RESEK**, ALBEMARLE FINE CHEMISTRY SERVICES

Technical expertise and access to state-of-the-art equipment and facilities are necessary but insufficient for successful completion of small molecule API technology transfer projects. Contract development and manufacturing organizations (CDMOs) must have a collaborative culture that encourages open and transparent communication among internal team members, client representatives and other external partners.

STRONG TECHNICAL FOUNDATION IS A START

The complexity of small molecule APIs is growing rapidly. Many drug substances contain multiple heterocyclic rings and functional groups and are designed with ever-increasing specificity in mind. While these novel compounds targeting cancer and other diseases are enabling increasingly personalized treatments, they pose immense challenges from a manufacturing perspective.

Production of most of these molecules requires multiple process steps involving sophisticated chemistries. A thorough understanding of the pitfalls of these chemistries is needed to enable effective implementation at a large scale. Tight control of process conditions is essential to ensure acceptable yields and to minimize impurities. Often, these large compounds have poor solubility in typical reaction solvents and require unique synthetic strategies. For example, most modern processes employ powerful cross-coupling reactions that are mediated by precious metal catalysts for which the controlling factors are often quite subtle. These reactions frequently require development of unique purification protocols for removal of the catalytic metal, as required by the new ICH Q3D Guidelines on elemental impurities. In another common example, amide coupling reactions often must be performed in the presence of highly sensitive substituents while avoiding unwanted side reactions, which again requires development of a specifically tailored process.

ESTABLISHED SCALE-UP STRATEGY

A strategy for process development and scale-up is essential to the implementation of robust, reliable processes. Albemarle Fine Chemistry Services (FCS) encompasses a GMP manufacturing site in South Haven, Michigan and a non-GMP manufacturing site in Tyrone, Pennsylvania. This allows for domestic production of regulatory starting materials (RSM) and improves our ability to control the supply chain.

In a new project, our process R&D group focuses first on route development, or familiarization, at the 50-mL to 1-L scales. As development continues, high-throughput equipment (<100 mL) is used for design-of-experiment studies to enable multivariate parameter analysis.

In the next phase, we run a lab demonstration batch at the 2-L scale using a jacketed reactor to ensure that we evaluate the reaction under conditions similar to those that will exist in the plant. Throughout this process, we evaluate the technical risks, working closely with process engineers to identify and investigate any necessary safe hold points and to determine process robustness. This work focuses on the reaction and workup steps. At plant scale, these processes generally take much longer than in the lab. It is important to determine the stability of the product under the separation/purification conditions to ensure that it will not degrade.

Frequently, the next phase of tech transfer/scale-up occurs in the kilo lab (25–100 L). Here, a small-scale process demonstration run is performed, allowing identification of any scale-up issues that were not discovered in the lab. In many cases, customers use this material for toxicology testing. We can also produce small GMP batches, which can be used for phase I or smaller phase II trials.

These runs provide significant value to customers, because the R&D chemists involved in the 2-L process demonstration carry their experience directly into the kilo lab and continue to engage with the engineers to evaluate all aspects of the process. In addition, the glass equipment in the kilo lab offers plant operators and engineers the opportunity to view the process and see firsthand how it will behave. This visual experience contributes greatly to successful scale-up.

Throughout the phases of scale-up, our process chemists and engineers apply their experience and knowledge to ensure that the right elements needed for successful validation are built in from the start. They establish process understanding to identify the key points that define the optimal control strategies, including analytical methods, that will be effective as the process scale increases.

At Albemarle FCS, we pursue phase-appropriate application of process understanding, because we recognize that there are always time and cost elements to consider. Once the weak points in a process are identified, we communicate them and our risk-mitigation strategy to our clients.

DEMONSTRATED SUCCESSES

The culture, teamwork and integrated strategy for technology transfer and process scale-up at Albemarle have benefited numerous customers.

In one example, our non-GMP site in Tyrone was supplying an RSM for an API made at South Haven. A new impurity was observed during the development phase of the API, and the structure was rapidly determined using LCMS and NMR analysis techniques. This allowed us to trace its origins to the key raw material for the RSM. Albemarle was able to work with the supplier and set the appropriate specifications on that particular raw material to ensure that the impurity was well controlled.

In another instance, an unstable reaction mixture was discovered while preparing for a kilo lab campaign. A weight percent analysis for this reaction showed product decomposition after reaction completion; this decomposition was not detected in the area percent analysis. Implementing an expedited reaction quench and workup after reaction completion resulted in increased isolated yield from 50–60% to nearly 80%.

Our commitment to teamwork and gaining deep process understanding often leads to improved processes. For example, an existing multistep purification process involving repeated crystallizations and an overall 51% yield was eliminated after the performance of parallel solvent screening studies and LCMS work revealed the identity of the problematic impurities. Minor process changes were implemented to facilitate removal of these impurities, leading to a streamlined process workup and a well-understood crystallization system that resulted in high-purity product and afforded an 87% yield.

Our constant consideration of regulatory agency expectations also enables us to anticipate and manage potential issues before they become real problems. For one customer, analysis of the synthetic route for an intermediate identified the potential for the generation of a genotoxic/mutagenic impurity (GTI). Communication with the analytical group allowed for expedited development of a method to detect the GTI down to its ICH limits. The customer was notified and agreed to a course of action. Screening of the raw material and intermediate revealed that the potential impurity was not present. P

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Reducing Project Timelines with Integrated Cleanroom Solutions

The design of effective cleanroom solutions requires a holistic approach. The demand for cleanrooms continues to evolve, with growing applications for controlled environments in nearly every industry. Whether manufacturing automotive windshields, paints and coatings, optical and electronic devices or pharmaceutical and nutraceuticals, control of the production environment is essential to achieving the highest quality products.

Not Just a White Box Anymore

Just a few years ago, cleanrooms were often seen as "white boxes" installed separately from the air handling and other systems required to ensure effective operation. Today, customers realize that optimum overall performance of cleanrooms, particularly when there are multiple cleanrooms in one facility, requires understanding of the interrelationships among different mechanical systems and between different cleanrooms, as well as the impact of changes in weather and other factors.

Many Factors to Consider

Cleanroom equipment and systems must be designed for the maximum possible temperature and humidity for its geographic location. It is essential to consider the quantity of fresh air needed and potential peak temperatures that can be reached. Future changes in the local climate must also be taken into consideration. The best approach is to envision the worst-case scenario and build in higher potential values so the system can adapt to the changing outside environment.

Achieving maximum energy efficiency is also critical. In addition, cleanroom designs should include redundant air-handling capabilities and be sufficiently flexible to accommodate the introduction of new processes. The best approach is to consider a cleanroom as an integrated ecosystem.

Benefiting from History in Critical Environments

Environmental Systems Corporation was founded in 1983 as a provider of commercial industrial heating, air conditioning and refrigeration solutions, with a strong specialty in electronic control systems and close tolerance temperature/humidity control. For cleanrooms, controlling the temperature and humidity can account for 30–40% of operating costs.

Today, ESC offers tailored humidity and temperature control equipment that ensure optimally efficient cleanroom operation, and we typically build unique and custom systems with our proprietary cleanroom components more quickly than our competitors can using standard production models. In addition, many of our employees have previously worked at pharmaceutical companies and have first-hand experience with the specific design needs for cleanrooms installed in drug manufacturing facilities.

A Collaborative Business Model

ESC customers benefit from our collaborative business model. We rely on our clients' expertise in pharma manufacturing and combine that with our expertise in environmental control. We strive to understand what our clients are trying to achieve in the short term, the critical parameters that must be addressed and potential needs in the future. We then consider our systems and how they can be designed to provide cleanroom solutions with optimal performance, efficiency and flexibility.

Reducing Project Timelines with an Integrated Approach

At ESC, we do not just provide the cleanroom structure alone, but also all of the environmental controls (e.g., temperature, humidity, pressure) and related infrastructure and the integration and validation of the entire solution. This integrated project delivery approach often increases efficiency and reduces the overall timeline.

Our ability to assist at the design stage adds significant value for ESC customers, because it helps our clients select the right design and begin implementation much more quickly. By bringing together mechanical, architectural and electrical expertise with an understanding of the client's unique needs, we help customers not only identify optimized solutions, but get them installed and validated in a minimal amount of time.

Going Digital

Integration today includes aspects of Industry 4.0, with extensive integration of digital information from every possible aspect of the operation. Smart air-handling modules monitor air pressure and activate redundant fan systems before the air in a cleanroom falls out of specification. Cleanrooms offered by ESC also have built-in lighting systems to inform operators of the status of the conditioned air (yellow light indicates that the room is approaching an operating limit, red means the room is outside the operating conditions). More monitoring in real-time is also enabling the reduction of the number of air exchanges, significantly reducing costs, particularly for facilities with multiple cleanrooms.

ESC is excited to work with clients that are looking to adopt new technologies that provide greater energy and cost efficiencies while still guaranteeing high performance. P

Jeffrey Marlough
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Executive Compensation: Essential Factor in Private Equity Transactions

Private equity firms create incentives to retain management teams that create value in their invested companies.

Need to Incentivize

When private equity (PE) firms invest, they want to ensure that the company executives who retain essential knowledge and relationships are fully engaged and sufficiently incentivized to drive performance at the company.

Compensation packages are designed to maintain a strong link between the management team and the company. Plans and compensation structures vary; however, executives should expect to discuss roll-over equity options, a management incentive pool and compensation plans.

When private equity (PE) firms invest, they want to ensure that the company executives who retain essential knowledge and relationships are fully engaged and sufficiently incentivized to drive performance at the company.

Roll-Over Equity

Roll-over equity encompasses two forms of investment. If an executive held equity in the company before the PE firm's acquisition, this equity can be "rolled" into the new transaction. For certain members of management, there may also be an opportunity to invest additional equity in the transaction. These equity contributions are direct investments in the company and, typically, not subject to the PE's carry and management fees.

Management Incentive Pool

The management incentive pool comprises a certain percentage of the equity in the firm set aside for management in the form of options or appreciation rights. It is earned based on company performance metrics determined at the beginning of the transaction – vesting may also be a factor – and is distributed to the management team collectively.

The percentage for a pool will depend on factors including the size of the transaction but typically varies from 5% to 20% for middle-market companies. The portion generally decreases as the size of the deal decreases; management might not be allocated 10% of the equity in a $1 billion deal but could possibly receive that percentage for a deal below $100 million.

Long- and Short-Term Compensation Plans

The third component of the compensation package includes long- and short-term compensation plans, such as those put in place at most companies. Although the plans may have some similarities, each plan may be structured for the individual executive based on his/her position and responsibilities and can include both quantitative and qualitative expectations. Short-term plans are paid out annually, while longer-term plans pay out over a three- to five-year period.

Second Bite of the Apple

When a PE firm sells a company, if the buyer is another PE firm, the management team has an opportunity for the "second bite of the apple." When executives receive their equity stake during a sale transaction, they then have the opportunity to reinvest a portion – or all – of that equity in the new transaction.

By capturing the equity upside through the management incentive pool and rolling its increased equity stake into the new transaction, the executive team can increase their overall stake in the company. The result is that management receives a nice payout and also owns a larger share of the company.

Private equity interest in contract pharma services remains strong, and management teams are compensated to make those investments successful.

CRO/CDMO Considerations

The three components of compensation packages would apply regardless of the type of company being acquired by the PE firm. One area where significant variation occurs is the performance metrics included in long-term compensation plans, which depend on the type of business.

For instance, the profits of many contract service providers are cyclical and fluctuate for a variety of reasons. As such, long-term compensation plans are structured over a number of years to capture those trends.

Private equity interest in contract pharma services remains strong, and management teams are compensated to make those investments successful. P

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Realizing Technology Transfer in a Successful and Sustainable Manner

Successful tech transfer requires recognition of the complexity of the process, effective gap analyses, a focus on product profiles, open and transparent communication, collaboration and strong project management.

The Tech Transfer Challenge

Moving a drug product manufacturing process is a daunting and high-risk task. It is a complicated process in which detailed attention must be paid to all of the necessary elements. If proper planning and management are not executed, the implications of an unsuccessful move can have serious and lasting consequences. For aseptic manufacturing processes, technical transfer is very much like the introduction of a new product and process to a new manufacturing facility.

Importance of Proper Preparation

Due to the complexity of tech transfer projects, success is directly correlated with proper planning and preparation. To enable that any potential issues can be effectively addressed, it is essential to perform a combination of gap and risk analyses between the existing process at the sending site and the envisioned process at the receiving site. The manufacturing and testing steps, organizational issues and logistics should be evaluated to identify the risks posed by differences between the transfer sites.

To be most effective, it is important to follow the requirements of ICH Q8(R2) for Pharmaceutical Development. The results of a thorough evaluation of the quality target product profile (QTPP) of the product and the associated critical quality attributes (CQAs) can be used to define the scope of the transfer.

Trust and Open Communication Are Critical

The complexity of tech transfer projects also creates a significant need for trust and open communication. It is important to involve the individuals that actually make and test the product, since they possess essential personal knowledge and experience.

Successful process transfers are treated as projects with dedicated cross-departmental teams including development, manufacturing operations, quality assurance and quality control, qualification/validation and regulatory affairs, and production planning and logistics. This team is organized and coordinated by a project manager who reports to the project sponsor.

Strong project management is paramount to enable the smooth transfer of a robust process. The roles and responsibilities for all team members must be agreed upon at the start of the project, and a system must be established that enables adequate communication and feedback of information. All functions from both sites should interact with their respective partners in the other organization to enable direct communication between subject experts.

Open communication is also important in dealing with any differences (technical, procedural, regulatory, cultural) between the sending and receiving sites. Transfers between a sponsor company and contract manufacturer may be challenged by all types of differences, while internal transfers may not experience technical differences but may have to manage procedural and/or cultural disparities. Such differences may create underlying resistance to process transfers, particularly from the sending site.

Effective Process Evaluation Is Essential

All manufacturing processes should be evaluated from start to finish. For aseptic fill-finish processes, unit operations include compounding, sterile filtration, filling, visual inspection and secondary packaging. Evaluation of analytical methods that need to be transferred is equally important. In-process testing, release testing, stability testing and other procedures are generally transferred along with the production process, which will require specific analytical capabilities at the receiving site.

The inception of any process transfer is, therefore, the process qualification campaign. This campaign should be based on the FDA's approach, which involves process design followed by process qualification, with continuous process verification pursued once the transfer is complete. The intent is to achieve a robust, reproducible manufacturing process with consistent quality at the receiving site.

It is also important to recognize that transfer presents the opportunity to redesign and modernize elements of the process to achieve improvements in yield, productivity, efficiency and other metrics.

Key Success Factors

One of the most important factors for success in tech transfer is recognizing that it is a complex undertaking, even for the simplest manufacturing processes. It is also essential to expect the unexpected; even with the best preparation, unforeseen challenges can arise. Collaboration and open communication are the keys to solving such problems. P

Stuart Needleman
Chief Commercial Officer
Piramal Pharma Solutions

True Integration Is Integral to Providing One-Stop-Shop CDMO Services

A truly integrated CDMO with the right structural foundation and top-down commitment can provide tremendous benefits to biopharmaceutical customers.

Rising Demand for Contract Services

The value of the global pharmaceutical contract manufacturing market is expected to reach $95.9 billion by 2025, with the API segment accounting for the largest share but the final drug formulation segment growing at the fastest rate.[1] Growth overall is being driven by rising demand for medications around the world, due to the aging population, increases in chronic diseases and growing wealth in emerging economies. Pharmaceutical companies are increasing their dependence on outsourcing partners to achieve increased efficiencies and gain access to advanced technologies.

Renewed Interest in the One-Stop Shop

Over the past decade, innovation in the pharmaceutical industry has shifted to emerging pharma and biotech companies that lack the infrastructure, capabilities and resources necessary to support the entire drug development and commercialization cycle. For these smaller companies that must rely heavily on outsourcing partners, it is much more efficient to develop strategic relationships with integrated CDMOs.

Larger pharmaceutical companies are also realizing that, by working with a company like Piramal Pharma Solutions, it is possible to take a candidate from post-discovery to commercialization with one point of contact and without the need to manage multiple suppliers or the cost and time delays associated with tech transfer between different service providers. Product knowledge and expertise are retained throughout the project life cycle, facilitating collaboration and process scale-up.

Time Is of the Essence

There has never been more pressure for pharmaceutical companies to develop new drugs more quickly and at lower cost. Integrated CDMOs that operate as true one-stop shops help sponsors reduce time to the clinic and the market while also controlling costs and often providing access to unique, advanced capabilities. With one contract, one global master service agreement and one quality agreement, integrated providers help simplify the drug development process.

Integration Is Essential

Integrated offerings are only effective, however, if all of the services are harmonized and presented to the customer as a single system. An integrated offering must not simply be different businesses linked together, but a single business at the operational level. Commitment must come from the top down, with establishment of a company philosophy and systems that create a single customer-facing solution that facilitates easy customer interaction.

Piramal does not consider integrated projects merely as projects, but as programs. We have installed software to manage our integrated programs and hired experts to serve as program managers. All interactions with clients from verbal to written communications follow the same protocols. The technology transfer process is headed by the program manager, who ensures that all necessary documents are exchanged, goals and timelines are agreed upon and met, and routine communications, both internal and external, are managed effectively.

Understand Your Value Proposition

Choosing a service provider ultimately comes down to risk tolerance, which is different for every pharma company. It is therefore essential for integrated CDMOs to have a clear understanding of their value propositions and clearly communicate those benefits to potential clients. Commitment to the company's mission must also be embedded in the hearts and minds of all employees.

Piramal has grown through acquisition, building capabilities in drug substance and drug product development and manufacturing. Our leaders have experience in integrated offerings and leverage our global network to provide maximum efficiency and productivity. We have facilities for the production of drug substances in lower-cost countries and sites in the West with specialized capabilities for drug product manufacturing, including solutions for highly potent products and antibody-drug conjugates. We are one of the few CDMOs able to offer integrated services for oncology candidates, as well as for candidates targeting other indications.

At present, Piramal is evaluating how to further expand upon our existing capabilities, including the addition of oral solid dose development and manufacturing services. We have the necessary organizational structure in place and are excited to build on our early success as a truly integrated CDMO. P

Reference

1. *$95.94 Bn. Pharmaceutical Contract Manufacturing Market, 2025.* Research and Markets. 21 Mar. 2019. Web.

SUPPORTING COMMERCIAL MANUFACTURING OF SEMISOLID DOSAGE FORMS

→ BY **ROBERT N. WHITE III,** UPM PHARMACEUTICALS

Semisolid drugs have advantages over other dosage forms, from limited side effects to ease of use. However, semisolid drugs require special expertise and experience to ensure optimal production of high-quality products at commercial scale. UPM Pharmaceuticals has the experience, knowledge, equipment and tailored customer service approach required to ensure efficient and cost-effective production of even complex cream and ointment formulations.

FUNDAMENTAL ATTRIBUTES OF SEMISOLID DOSAGE FORMS

Semisolid dosage forms are intended for external application, either topically on skin surfaces or mucous membranes (eyes, nasal cavity or inner lining of cheeks) or via suppositories to rectal and vaginal tissues. They include ointments, creams, gels, pastes, rigid foams and emulsions and are designed to enable penetration of the active drug substance through these surfaces via immediate- or extended-release mechanisms.

While oral delivery remains the most common route of administration, topical delivery has some advantages, including the ability to treat local indications, the avoidance of first-pass metabolism – which can be a problem for ingested drugs – reduced side effects due to external application and ease of use for greater patient compliance.[1,2] For manufacturers, semisolids are advantageous because formulation development can generally be completed more rapidly than for other dosage forms.[2]

Most semisolid formulations consist of the API uniformly dispersed along with appropriate excipients, emulsifiers, rheology modifiers (to control viscosity), antimicrobial agents, antioxidants and/or stabilizing agents in a suitable base.

Each type of semisolid has its own structural elements; most have multiple phases (oil, water and the API, if it is not completely soluble) and specific components that often have well-defined physical properties. The choice of ingredients for a given semisolid formulation depends on the type of semisolid, the nature of the API(s) and the desired release profile.[2]

SIZABLE SEMISOLID DOSAGE FORM MARKET

The overall global market for topical drugs, including semisolids, liquids, solids and transdermal products, is estimated by market research firm Markets and Markets to be expanding at a compound annual growth rate of 5.7% from $93.2 billion in 2019 to $123.2 billion by 2024.[3] This modest increase in demand is attributed to a rising incidence of skin and eye diseases and diabetes. This increase is attributed to the aging of the global population and a rise in income levels throughout emerging markets. Semisolid formulations claimed the greatest market share in 2019; by route of administration, dermal delivery is dominant.

MANY QUALITY ASPECTS

Though perhaps easier to formulate than oral and other dosage forms, semisolid drugs require specialized process expertise to ensure the production of high-quality products. These drugs must, in general, be uniform in appearance and physically smooth with minimal grittiness.[4] They should also have a pleasant scent, be easy to apply to the target areas and not cause irritation upon use. Five key properties that must be carefully controlled are homogeneity, particle distribution, spreadability, grittiness and surfactant use.[4]

Homogeneity is important, because semisolids involve more than one phase, and all phases must be properly blended to achieve the desired result. The API as well as all excipients and other ingredients, must be uniformly distributed throughout the mixture. Homogeneity achieved in the production vessel must be maintained in each product unit, whether that is a plastic or metal tube or a plastic or glass jar.[4] The consequences of inadequate homogenization can range from lumpy mixtures to nonuniform API distribution, both of which lead to reduced product efficacy.

Because many semisolid drugs contain particles suspended in solution, uniformity of the particle sizes and their distribution is important.[4] This attribute is particularly important for APIs that have poor water solubility – a rapidly increasing percentage of drug candidates in development today.

Semisolid drugs must also exhibit appropriate spreadability to ensure that the desired therapeutic affect is achieved, because spreadability determines the distribution of the API over the area to which the semisolid is applied.[4] Poor spreadability can also lead to patient dissatisfaction. Spreadability correlates with the viscosity of the drug product and can be impacted by temperature and the particle distribution.

Grittiness is related to particle size and shape, while proper surfactant use enables the formation of emulsions and suspensions of oil and aqueous phases and is crucial to achieving stable formulations.[4]

MANUFACTURING CHALLENGES

Given the complex ingredients and the need to generate specific structural elements, specialized expertise is required to ensure the production of high-quality semisolid drug products on a commercial scale. Careful control of the manufacturing process is essential to providing fully homogenized products containing the appropriate particle sizes and distributions of APIs and excipients in stable emulsions or suspensions.

AS A FULL-SERVICE CDMO, UPM WELCOMES PROJECTS AT ANY POINT IN THE DEVELOPMENT CYCLE.

For instance, adding specific ingredients to the appropriate phase (oil or water) can lead to enhanced product stability.[2] The rate of addition can be important for avoiding undesirable behaviors involving polymers. Addition of antimicrobials at the end of a process helps minimize undesired interactions. Prevention of API degradation under the manufacturing conditions and minimization of process impurities must also be assured. Formulations for controlled- and extended-release semisolid products add a further layer of complexity.

Unlike for oral solid dose drugs, manufacturing processes for semisolid products cannot be halted mid-way through the batch record without risking loss of the entire batch. Process optimization work must be completed in advance, and operators must ensure that everything required for completion of a run is ready before initiation of a process.

An appropriate method for pulling samples must also be established for monitoring the progress of semisolid production runs. While the level of control required is not as strict as that for sterile manufacturing processes, it is essential that the sampling process be designed to minimize the likelihood that contaminants will be introduced into the vessel.

Finally, scale-up to commercial quantities must result in a process that provides a product with the same properties observed in the development laboratory and pilot plant. The equipment, therefore, must be similar (same materials of

GIVEN THE COMPLEX INGREDIENTS AND THE NEED TO GENERATE SPECIFIC STRUCTURAL ELEMENTS, SPECIALIZED EXPERTISE IS REQUIRED TO ENSURE THE PRODUCTION OF HIGH-QUALITY SEMISOLID DRUGS PRODUCTS ON A COMMERCIAL SCALE.

construction with the same mixing systems) at all scales, and its scalability must be clearly demonstrated.[2]

THE IMPORTANCE OF MIXING AND TEMPERATURE

The most important factors when moving to commercial production of semisolid drugs are the mixing/homogenization times/speeds and temperature control. Mixing times become more critical as a process is scaled up, because they depend on the quantity of material that is involved. In most cases, mixing is not achieved in a single pass through a homogenization pump. The material typically needs to circulate through the pump multiple times. Properly calculating the time that is required to complete a sufficient number of passes is, therefore, essential. Minimizing mixing times is important for prevention of ingredient degradation and reducing process run times.

The mixing speed determines the level of shear to which the formulation ingredients are exposed, which influences droplet size and dispersion, particle size and particle size distribution, and other physical characteristics.[2] If sheer levels are too high, mixing can also lead to degradation of some ingredients.

Establishing and maintaining the correct temperature is also necessary when manufacturing high-quality semisolid products. The temperature can impact the homogeneity, particle distribution and spreadability, and heating is often required to achieve appropriate mixing.[4] If the temperature becomes too high, however, some ingredients may degrade or the desired structural elements may collapse. Monitoring and precise control of the temperature are essential for meeting product specifications and avoiding any impacts on the individual ingredients in a semisolid formulation. Control of heating and cooling rates is equally important for avoiding burning and precipitation/crystallization, respectively.[2]

THE UPM DIFFERENCE

UPM's Bristol, Tennessee plant includes a Solids Formulation R&D Facility, modern manufacturing suites and a state-of-the-art, full-service analytical laboratory. We have the capacity to produce up to 750 metric tons of creams and ointments annually.

Our commercial vessels range from 200 to 2000 gallons, with finished products packaged on our automated jar or tube lines. UPM also has the ability to manufacture semisolid products in 200- to 300-gallon pressure vessels. Once filled, weight verified and capped/sealed, jars and tubes are labeled with the lot number and date. Each unit is subjected to inspection, and then the product is placed loose or bundled together into shippers. We currently have an offline serialization solution in place and are preparing to meet aggregation requirements.

Most importantly, we have extensive experience in formulation development and the development and scale-up of production processes for semisolid dosage forms, enabling us to rapidly establish optimal processing conditions for creams and ointments intended for use as over-the-counter or prescription medications.

As a full-service CDMO, UPM welcomes projects at any point in the development cycle. With access to reasonable information about the product and existing or potential processes, we can rapidly evaluate a project to determine whether we can implement it with our existing systems or, if not, what additions/modifications would be required.

We are here to help our customers get their products into the hands of the patients that need them. At UPM, we have an open-door policy. Customers are encouraged to seek our assistance and ask the hard questions. We are always available – from the top executives through project managers and project scientists and engineers.

By offering such flexible, affordable and rapid outsourcing services designed to meet our clients' specific development and manufacturing needs, we are able to form truly collaborative relationships and provide highly customized solutions to meet aggressive development and commercialization timelines and project budgets. P

REFERENCES

1. Walker, Nigel. "Semisolid Dosage Forms." *Contract Pharma.* 10 Oct. 2018. Web.

2. Nwoko, Valentine E. "Semi Solid Dosage Forms Manufacturing: Tools, Critical Process Parameters, Strategies, Optimization and Validation." *Scholars Academic Journal of Pharmacy* 3: 153–161 (2014).

3. *Topical Drug Delivery Market, 2024 by Type (Semisolids, Liquids, Solids, Transdermal), Route (Dermal, Ophthalmic, Rectal, Vaginal, Nasal).* Research and Markets. 16 Aug. 2019. Web.

4. Patel, Kalpen and Angela Holley. "Quality Factors Influencing Semi-Solid Manufacturing." *Contract Pharma.* 30 Jan. 2018. Web.

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Robert N. White III serves as the Manager of Manufacturing for UPM Pharmaceuticals. He has an extensive background in technical services, manufacturing and process validation and is professionally certified in tablet compression and fluid bed operations. In his current role Robert leads all the Manufacturing teams involved with the Manufacturing, Packaging of Semi-Solids. Robert graduated with a Bachelor's Degree in Physics from King University.

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MEETING THE NEED FOR HIGHER CONTAINMENT

→ BY **SUZANNE GREENE,** SERVIER

With the addition of OEB level 5 drug product manufacturing capabilities at its Arklow, Ireland site, Servier is positioned to provide high-containment contract services for commercial production.

EXPANDING ONCOLOGY MARKET DRIVING DEMAND FOR HIGH CONTAINMENT SERVICES

Approximately one-third of all drugs in the pharmaceutical pipeline are oncology treatments.[1] Many of those are formulated using highly potent active pharmaceutical ingredients (HPAPIs). As a result, close to one-quarter of newly approved drugs in recent years have been highly potent therapies.[2] That percentage will likely expand, given that the market for HPAPIs is estimated to be growing at a healthy CAGR of 8–10% through 2025.[3-7] While most HPAPIs are found in anticancer drugs, they are also used to formulate drugs for the treatment of cardiovascular, central nervous system, musculoskeletal, hormonal imbalance and eye diseases.[3]

CONTAINMENT LEVELS

Highly potent HPAPIs and drug products cannot be produced under normal manufacturing conditions, as both operators and the environment must be protected from exposure to potent compounds. The level of containment required depends on the potency of the product, and significant expertise is needed to determine the level of containment necessary to adequately prevent exposure. Effective containment is achieved through a combination of appropriate facility and equipment design, including engineering and proper processes, process management systems and training.

Potency is determined by the occupational exposure limit (OEL) and various toxicity properties of the HPAPI or drug product. Typically, the HPAPI or high potency drug product is assigned an occupational exposure band (OEB) or placed into one of the categories established by the International Society for Pharmaceutical Engineering (ISPE).[8] The higher the OEB, the higher the level of containment must be.

STRICTER REGULATIONS LEADING TO NEED FOR HIGHER CONTAINMENT

Potent compounds are considered to have an OEL of 10 µg/m³ of air or lower, as an 8-hour time-weighted average. Ultra-highly potent compounds have OELs of less than 0.1 µg/m³. Unfortunately, there is no single regulatory standard. In addition to the ISPE category approach, guidances have been published by the ACGIH, AIHA, ILO, IOHA, NIOSH, OSHA and the WHO. 21 CFR part 210 (211), 29 CFR 1910, ICH Q7A, OSHA (& NIOSH) and the Controlled Compound Act cover various aspects of potent product manufacturing and handling.

The manufacture of highly potent drug products is becoming more challenging as compounds become more potent and guidelines for the production of potent therapeutics evolve and tighten. The required level of containment has been shifting over time, in some cases resulting in the movement of some products from a lower band to a higher band.

POTENT HISTORY

Servier is a leading European pharmaceutical company that has successfully commercialized 50 products during the last 60 years. We have operated the Arklow, Ireland site, which is currently our second-largest manufacturing facility, for 30 years, for the production of a variety of drug products.

Servier Arklow has been working in the high containment space for 10 years. During that time, Servier has established strong high-containment capabilities and extensive experience handling and managing highly potent drug products. We have established processes and procedures and a highly qualified, dedicated team of operators with years of expertise.

We are committed to the oncology field through the development of our own pipeline candidates, with 50% of our 2018 research spent focused on R&D for anticancer therapies. We have a breadth of diverse potent product manufacturing, packaging and distribution capabilities across our global portfolio. The highly potent drug product manufacturing unit at Arklow are complemented by HPAPI capabilities at our facility in Bolbec, France.

INVESTING IN HIGHER CONTAINMENT

The increasing number of highly potent drug candidates is creating demand for high-containment manufacturing capacity. Many contract development and manufacturing organizations (CDMOs) are expanding capabilities for the production of HPAPIs, and outsourcing by biopharma companies of all sizes is increasing rapidly as they seek to gain access to these specialized capabilities.[9] Less attention has been paid, however, to the expansion of potent drug product manufacturing capacity.

WITH FLEXIBLE BATCH SIZE AND SOLID DOSE FORM PRODUCTION, PACKAGING CAPABILITIES, SERIALIZATION AND AGGREGATION EXPERTISE, **THE NEW DEDICATED HIGH CONTAINMENT UNIT ENABLES SERVIER TO PROVIDE FULLY INTEGRATED SERVICES FOR HIGHLY POTENT DRUGS.**

Recognizing the growing demand for outsourcing services to support development and commercialization of increasingly more potent products, Servier has expanded our high-containment capabilities at the Arklow site to support the production and packaging of OEB-5 (<1 µg/m³) drugs.

Manufacturing services including granulation, tablet compression, tablet coating, packaging and analytical services, have all been incorporated into the dedicated, highly engineered, state-of-the-art high containment unit. At Servier, we are constantly modifying our services based on market demands and responding to customer requirements – in fact, plans for expanding our capabilities are already in progress.

The first batches of an in-house Servier product were produced in September 2019, and qualification for customer products is ongoing.

With flexible batch size and solid dose form production, packaging capabilities, serialization and aggregation expertise, the new dedicated high containment unit enables Servier to provide fully integrated services for highly potent drugs. Our dedicated high-containment team was involved in the design and construction of the new high-containment suite and has the intimate knowledge required to ensure optimal operations. With our location in Arklow, we are ideally positioned to support the rapidly growing pharmaceutical sector

in Ireland and pharma companies worldwide. We export product to over 100 countries worldwide, supported by Servier's extensive global footprint.

ENGINEERED SOLUTIONS

Servier continually invests in strategic growth and is committed to being a strong player with high quality, reliable capabilities in oncology, potent manufacturing and high containment. The new high-containment suite at our Arklow site was designed and engineered to optimize containment within the room structures and equipment trains. We worked closely with suppliers to engineer containment into each piece of equipment, in each room and in the self-contained suite, itself. The approach reduces the need for operators to rely on personal protective equipment (PPE), streamlining processes and shortening timelines while considerably mitigating the risk of operator or environmental exposure. Importantly, the suite is dedicated to a single product at any one time.

INTEGRATED OFFERING

Servier's investment in the new high containment facility enables more flexibility in capacity and batch sizes, alongside higher levels of containment. Our high potent drug product manufacturing capabilities at Arklow integrate well with all other capabilities included in Servier's full-service contract development and manufacturing offering within our global network of 11 sites.

In addition to manufacturing and packaging, we provide all support necessary for commercial launch, including regulatory, analytical, distribution and other services. We can be your unified, long-term, seamless partner. Our customers can therefore fully advance their products within Servier's network.

HPAPIs can be purified down to OEB-5 at our Bolbec, France facility through InnoPrep™, the industrial-scale preparative chromatography service. This is complemented by the latest upgrades at our Arklow site for final drug product manufacturing, which support the rapid advancement of anticancer therapeutics.

As a result, collaborating with Servier over the long term can help minimize risks while ensuring quality, facilitating access to growing markets and reducing time to market.

BENEFITS OF AN EMBEDDED CDMO

Servier's CDMO services are embedded within our long-established, international pharmaceutical operations and thus offer flexibility backed by the resources and operational, technical and regulatory expertise of an internationally recognized pharmaceutical manufacturer.

The same teams that work on the development, analysis, scale-up and commercialization of Servier products are involved in external client projects. As such, they apply their strong industry experience and effective, responsive decision-making to each new project. This embedded expertise is backed by a strong quality culture and project management capabilities.

Furthermore, the longstanding expertise of Servier is complemented by leading-edge technologies proven to accelerate time to market. Our integrated supply chain enables highly efficient workflows, quality assurance and regulatory expertise across global markets.

NEW BRAND LAUNCH COMING

Servier has invested in a brand new, state-of-the-art OEB-5 high-containment facility at our Arklow, Ireland, site, supporting our commitment to oncology therapeutics and our capability to offer the highest levels of containment and flexible manufacturing solutions to third-party customers.

This new workshop builds on a foundation of more than a decade in high containment at Arklow. The new capacity has been designed with containment engineered into the suite itself, optimizing the mitigation of risk and process efficiency in working with potent compounds, enabling projects to progress rapidly without compromising quality and reliability.

This latest investment in Ireland reflects Servier's commitment to high-containment manufacturing of highly potent drug products. We are excited about integrating this capability directly with our CMDO business supporting drug substance and drug product development and production. At CPhI Worldwide in Frankfurt, we look forward to launching a new brand around this capability that will provide our customers with an additional streamlined long-term partnership opportunity. P

REFERENCES

1. "Highly Potent APIs – Markets, Myths and Manufacturing." Cambrex. Nov. 2017. Web.
2. O'Connell, David. "High Potency Drugs – from Molecule to Market." PCI Pharma Services. Aug. 2013. Web.
3. *High Potency API/HPAPI Market Size Worth $34.8 Billion By 2025.* Grand View Research. Jul. 2017. Web.
4. *High Potency APIs /HPAPI Market worth 26.84 Billion USD by 2023.* Markets and Markets. Apr. 2018. Web.
5. *High Potency Active Pharmaceutical Ingredients Market by Type (Innovative HPAPI, Generic HPAPI), Synthesis (Synthetic HPAPI, Biotech HPAPI), Therapeutic Application (Oncology, Hormonal Imbalance, Glaucoma) and Region – Global Analysis and Forecast to 2025.* Converged Markets. 2018. Web.
6. *Global High Potency Active Pharmaceutical Ingredient (HPAPI) Market: Rising Incidence of Cancer to Boost the Market, says TMR.* Transparency Market Research. Aug. 2017. Web.
7. *High Potency Active Pharmaceutical Ingredients (APIs) Market Analysis By Product (Synthetic, Biotech), Manufacturer (In-house, Outsourced), Drug Type, Therapeutic Application (Oncology, Hormonal, Glaucoma, Others), And Segment Forecasts, 2018 – 2025.* Grand View Research. Jul. 2017. Web.
8. Walker, Nigel. "HPAPI Market Trends." *Contract Pharma*. 11 Sep. 2018. Web.
9. Gottlieb, Oliver. "High containment becomes high priority in the pharma industry." *NNE Tech Talk*. 27 Sep. 2018. Web.

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Suzanne is a Business Development Manager for Servier CDMO. With 18 years' experience in the pharmaceutical industry at Servier (Ireland) Industries, Suzanne has extensive knowledge of key areas including quality, GMP and regulatory requirements. In the role of business development manager, Suzanne supports Servier's CDMO business worldwide and CDMO activity at the Arklow site. She identifies new business opportunities and brings them to completion, working diligently with customers and the Servier team to respond to customer needs and deliver their product requirements at the right cost, quality and time.

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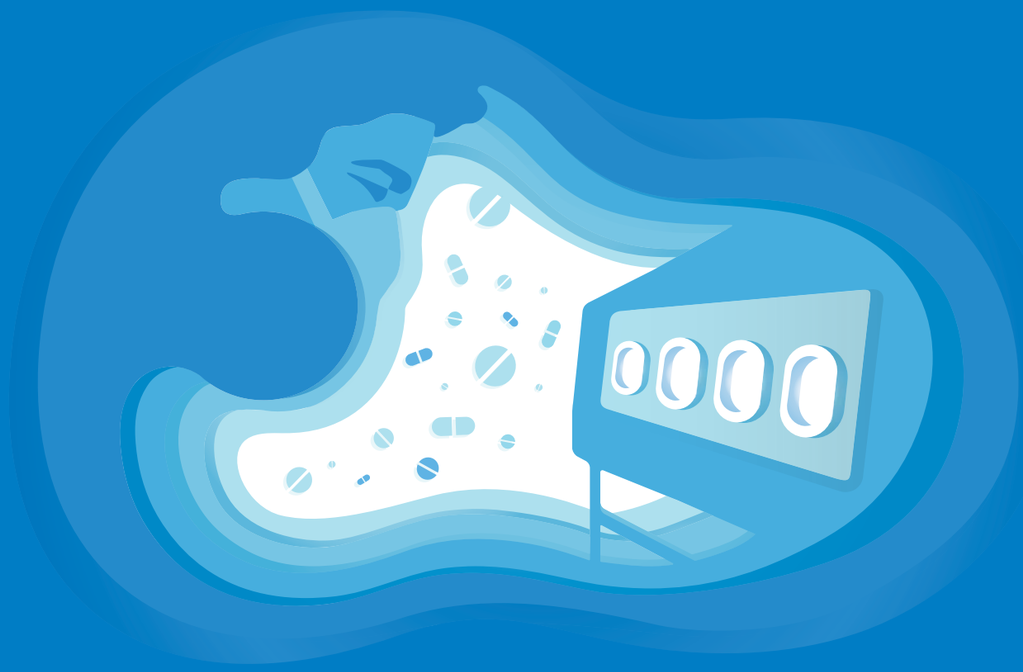

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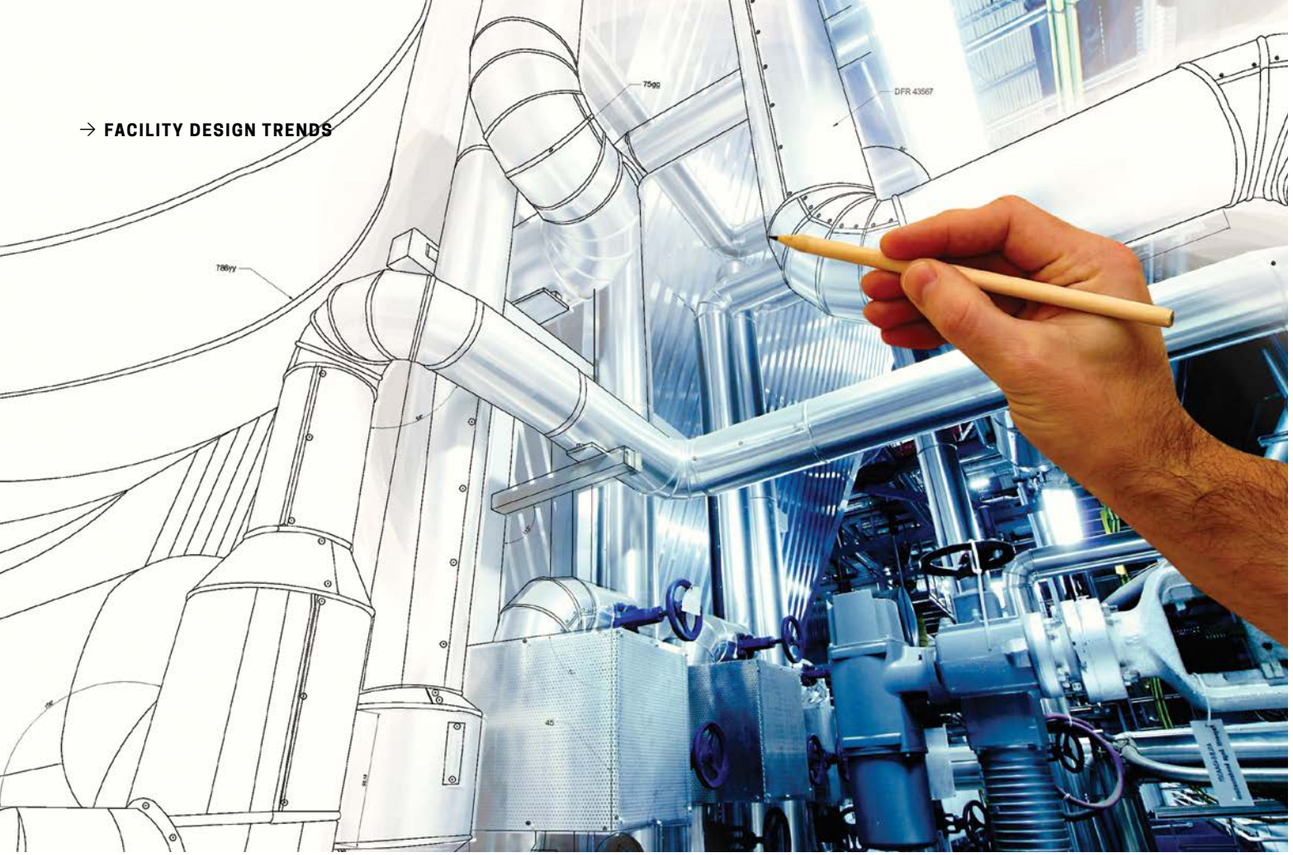

NEW TRENDS IN TECH IMPACTING PHARMA FACILITY DESIGN AND CONSTRUCTION

→ BY **CHRISTA MYERS,** CRB

From personalized therapies to Big Data and digitalization, key trends in technology are driving new strategies for pharmaceutical facility design and construction.

GREATER FOCUS ON PATIENT SAFETY AND SERVICE

In today's healthcare landscape, patient safety is becoming even more important. Finding the best and safest solutions for patients has become a key driver of business within the pharmaceutical industry as a whole. As equipment, component, drug dosage and medical device manufacturers gain a greater understanding of patient needs, they have each begun to offer more patient-centric solutions.

In addition to offering different types of products with novel delivery systems, companies are changing the way they implement manufacturing processes – again, based around patient safety. New digital technologies are being used to help manage manufacturing operations and, perhaps more importantly, track patient behaviors to enable enhanced product development. Many companies are increasingly focusing on how they can help patients through better communication and the offering of comprehensive services rather than just drug compounds.

SHIFT TO PERSONALIZED MEDICINES

One of the biggest changes in the pharmaceutical industry underlying these overall trends is the move away from the development of new medicines that meet the needs of large patient populations and toward the development of personalized medicines. The former typically carry a lower cost per dose, but often do not work optimally on the level of individual patients.

The leading personalized medicines include gene therapies, cellular therapies, oligonucleotide therapies and chimeric antigen receptor (CAR) T cell therapies, but many new immunotherapies also could be classified in this manner. These highly targeted medicines are designed to treat patient populations with specific genetic or other disease characteristics.

From a manufacturing standpoint, this means a batch no longer consists of 70,000 doses, but perhaps eight to ten doses, or even just one. The consequences are enormous; the entire approach to manufacturing, as well as the way patient information is managed, is very different for these therapies.

NOT JUST CHANGES IN HIGH DOLLAR-PER-DOSE BUSINESSES

Significant changes are occurring even in traditional, lower-cost dosage forms. The delivery of many next-generation medicines requires new technology. Conventional biologics are typically administered from an intravenous (IV) bag in the hospital or as an injection from a prefilled syringe or a syringe filled from a vial. Those approaches often are not applicable for cell and gene therapies, for which extensive cryogenic operations may be involved. As a result, dosage forms and processes are changing rapidly, and innovation is being driven into all aspects of the pharmaceutical supply chain.

Facilities for the production of lower-cost drug infusion solutions are changing to enable the production of different types of IV bags and delivery systems designed specifically to meet the needs of cell and gene therapies. This change is new for this market. Unlike the high-cost next-generation drug market, the IV bag market is an extremely low-cost-per-patient market that has focused largely on achieving cost competitiveness.

Today, however, the need to address specific patient needs and patient safety – and operator safety – is impacting even this aspect of the pharmaceutical industry. These facilities are implementing more computerized and mechanized methods of manufacturing with reduced human interactions and potential for operator error to increase quality and patient safety. Platforms based on data acquisition and tracking are also impacting the input methodology associated with manufacturing equipment to enable trending for better decision making and cost control. As a result, low-cost-per-dose configurations that in the past ignored innovation are becoming highly innovative.

ON THE CUSP OF ADOPTING INDUSTRY 4.0

To date, these initial forays into digitalization and the move toward Industry 4.0 have been limited to a few early adopters. In general, equipment manufacturers do not yet fully understand the level of data involved, nor are they positioned to provide equipment that can process and leverage these large quantities of data. It is difficult to drive new standards into pharmaceutical equipment, particularly equipment with communication capabilities, which involves rethinking individual components (e.g., sensors).

In addition, most analysts and scientists do not yet know how to utilize the data that is currently available. The question of whether an issue should be considered a single point problem or a trending problem, which depends on the criticality of the data, has in many cases not been answered.

The use of artificial intelligence (AI) in systems that learn and refine process faces other roadblocks. The principal barrier is the fact that, in the pharmaceutical industry, manufacturing processes are expected to be highly consistent and repeatable to ensure quality and patient safety. Good Manufacturing Practices (GMPs) have been established to ensure that drugs are produced using well-understood and well-defined processes. Change management is a key component – driving AI into equipment so that it can decide to make changes based on trends or function goes against this core principle.

HIRING AND STAFFING ISSUES

When it comes to Big Data and digitalization, it is also uncertain whether management executives understand the impact

ONE OF THE BIGGEST CHANGES IN THE PHARMACEUTICAL INDUSTRY UNDERLYING THESE OVERALL TRENDS IS **THE MOVE AWAY FROM THE DEVELOPMENT OF NEW MEDICINES THAT MEET THE NEEDS OF LARGE PATIENT POPULATIONS AND TOWARD THE DEVELOPMENT OF PERSONALIZED MEDICINES.**

CRB HAS INVESTED IN THE DEVELOPMENT OF A LEAN APPROACH TO PROJECT DELIVERY, **FROM DOCUMENT DEVELOPMENT AND MANAGEMENT TO DESIGN AND CONSTRUCTION EFFORTS.**

that the move to Industry 4.0 is having on hiring and staffing decisions. A recent CRB survey of clients revealed that one of the biggest pain points in the industry today is the inability to find qualified job candidates.

As the pharma industry transitions into the Industry 4.0 paradigm, the skill sets needed for new hires are changing dramatically. Instead of simply recruiting operators with college degrees, it is important to find individuals with computer science degrees that can serve as control or automation engineers. Unfortunately, the college education system is not keeping up with these needs. As a consequence, in some cases, location decisions for new facilities are primarily driven by the ability to access a sufficient base of qualified employees.

FLEXIBILITY IS ESSENTIAL GOING FORWARD

These issues are compounded by the rapid pace of change in the pharmaceutical industry, particularly in the cell and gene therapy space. In five years, the manufacturing technology and supply chain for these next-generation medicines will likely look nothing like it does today.

This rate of change can be exciting for experienced companies like CRB, because with each job, new technologies are available for consideration. It also increases the need to build flexibility into every facility to allow future modifications to be made to accommodate forthcoming innovations – while also ensuring that projects are easier, safer and as cost-effective as possible.

The move to modularity has expanded beyond modular construction approaches and modular facilities (e.g., pods) to include modular equipment (e.g., single-use technologies) and modular production (e.g., bulk manufacturing and packaging at different locations). Modular designs are also often needed. These solutions allow pharma companies to invest in new multi-product facilities where it is required initially, as well as to ensure accommodation of future changes; such designs take significant thoughtfulness.

CRB RESPONDING WITH HOLISTIC APPROACH

At CRB, we recognize that our staff needs to be more informed, more innovative and more thoughtful than ever before. With the increased focus on patient safety, the rapid pace of change in the pharmaceutical industry and ever-shortening project timelines, our clients are looking to CRB for turnkey solutions. In addition to engineering and construction support, they seek assistance with verification, qualification and training. In essence, they want CRB to help them go from the design stage, including the performance of risk assessments, to an operational state.

We have responded to this need and now offer a whole range of services. For each project, we sit down with the client and discuss the right method and approach for achieving that operational state. We work diligently to first observe each project from the client perspective. The goal is to identify what assistance is required from CRB to get the client to where they need to be when they need to be there, and at a reasonable cost.

CRB has invested in the development of a lean approach to project delivery, from document development and management to design and construction efforts. We have investigated the various human behaviors associated with effective teamwork and implemented approaches that enable our teams to work better together and achieve results more quickly. As a result, our clients benefit from shorter times to project completion and better cost control. Improving and saving patient lives is what matters; our lean approach to executing, engineering, construction, verification and all other activities required to achieve a successful startup is designed to increase efficiencies and help get novel drugs to market as rapidly as possible.

At the same time, we are excited that the pharmaceutical industry is just beginning to cross the boundaries into truly novel areas of innovation, including processes, tools and functions that have the potential to dramatically improve drug product manufacturing. P

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Glocalization

Balancing Global and Local Concerns in Manufacturing and the Supply Chain

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

The pharmaceutical industry is increasingly global in nature. Drug companies began outsourcing to contract research and manufacturing organizations to realize cost and efficiency gains. Many APIs found in generic and even branded small molecule drugs are now produced in China, India and other emerging markets, and biosimilars are increasingly produced across the world.

The continued growth of the industry and – particularly the rapid development and commercialization of antibodies and next-generation medicines, such as antibody–drug conjugates and cell and gene therapies – has led to an explosion in the number of clinical trials conducted. Finding patients for all of these trials is not possible in the developed world alone. Trials for orphan drugs – an increasing fraction of the pipeline – present even greater recruitment challenges.

Improved economies and an expanding middle class with greater buying power is driving growth in demand for state-of-the-art medicines in emerging markets, leading governments to require local pharmaceutical production and the inclusion of members of their populations in clinical trials.

The consequences of this globalization are extensive. Drug manufacturers must often conduct multiple clinical studies to satisfy varying requirements of different national regulatory agencies, leading to higher costs and longer approval times. However, many emerging economies lack the requisite infrastructure, skilled labor/expertise and established regulatory frameworks.

Pressure has increased to align pharmaceutical regulations on a global basis. Regulatory harmonization on standards, methods and scientific principles is occurring on a global and regional basis.

The World Health Organization and the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) have been instrumental in establishing standards and guidelines for the global pharmaceutical industry.

Membership in ICH continues to expand, and global regulatory authorities have recently formed organizations to tackle the challenges of harmonization. The United States and the European Union are implementing a formal mutual recognition agreement, while regional efforts have been initiated in Africa, Latin and South America, Asia-Pacific and the Middle East.

Further globalization – and glocalization – of the pharmaceutical industry is expected. All members of the pharmaceutical value chain must be prepared to collaborate and cooperate on true global regulatory harmonization to lower drug costs, reduce time to market, expand access and, most importantly, ensure the development and manufacture of safe and effective medicines.

The Relevance of Global Clinical Trials

Clinical trials have traditionally been limited to North America, Western Europe and Oceania,[1] but factors – including reduced operational costs, speed, logistics, compliance, diversity and regional growth opportunities – have all contributed to the increasing trend of global clinical trials (GCTs), fundamentally shifting the traditional paradigm.

Historical Foundation

The U.S. 1962 Kefauver-Harris Amendments, which overhauled the Federal Food, Drug and Cosmetic Act, aimed to create a framework requiring drug manufacturers to scientifically prove that medication was not only safe for human consumption but also effective.[2] Before this legislation, it was uncommon for a research sponsor to submit foreign clinical trial data to the U.S. Food and Drug Administration (FDA) at all.[2] These amendments were a response to the widespread use of thalidomide, a sedative used to treat morning sickness in pregnant women that caused birth defects in children all over the world.[2] While these regulatory mandates increased the level of scrutiny for which drug manufacturers needed to legally operate domestically, the FDA codified regulations in 1975 that permitted submission of foreign clinical studies not conducted under an investigational new drug application (IND),[3] opening the door for pharmaceutical and medical device companies to conduct global research while still obtaining FDA approval. The trend toward globalization of clinical trials has increased ever since.

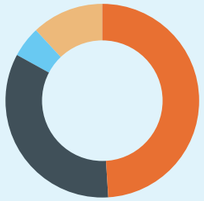
Global Clinical Trial Value Proposition

The overall cost savings of conducting global GCTs is substantial in comparison to holding trials in the United States and Western Europe. The savings can be attributed to a variety of factors, chief among them lower operational costs (salaries, facilities rent, documentation and training).[4] Other benefits include availability of patients (more patients willing and eager to participate), faster recruitment rates/shorter timelines, fewer logistical problems

Figure 1

Percentage of Registered Studies by Location as of Q3 2019

Total of 312,691 Studies



- Non-U.S. only (49%)
- U.S. only (34%)
- Both U.S. and non-U.S.(5%)
- Not provided (12%)

(contract, bureaucratic and regulatory barriers), and the widespread adoption of ICH and Good Clinical Practice (GCP) guidelines.[4] Acceptance and adherence by GCT sponsors to the ICH and GCP guidelines help ease public concerns and instill confidence in patient participants who may otherwise be leery of GCTs based on past failed studies that have hurt subjects or even resulted in death.

Expanded Reach and Access

Over the last decade, many companies have decided to conduct GCTs in new regions across Asia, Latin America, the Middle East and Africa, where the clinical trial environments are not as mature as in North America and Western Europe.[5] Many discovery-based global pharmaceutical companies aim to reduce the time lag of launches in key markets and improve patient access to new and innovative treatments. The drug-lag problem in several countries can be attributed to many causes; among them are underwhelming drug innovation and suboptimal regulatory environments around the clinical trial and drug approval processes.[5] Sponsors from more innovative and technologically advanced regions can increase go-to-market speed and overall quality of new drugs in emerging markets. GCTs provide sponsors with access to untapped pools of patients, as well as early patient access to new medications that otherwise may not be available in emerging markets.[5] GCTs also allow medical professionals in lesser-developed regions to gain access to more advanced technologies leading to an improvement of overall skill sets and increased knowledge.

Inside the Numbers

ClinicalTrials.gov currently lists 312,691 registered studies with locations in all 50 U.S. states and 209 countries, as of Q3 2019.[6] The distribution of locations for all GCT sites favor GCTs occurring in non-U.S. regions, with 49% of study locations outside of the United States, compared with only 34% with U.S.-only locations.

The numbers for locations of recruiting studies are even more favorable for GCTs, with 58% of recruiting studies occurring in non-U.S. locations compared with 37% occurring in U.S.-only locations, out of the 51,510 recruiting studies reported.[6]

Fig. 1 provides a visual representation of the expansive reach of GCTs occurring around the globe, showing the number of studies occurring in each region.[6]

Growth in Africa

Africa may represent the most significant opportunity for growth, as the African pharmaceutical market expanded to $20.8 billion in 2013 from just $4.7 billion a decade earlier.[7] That growth is projected to continue to increase rapidly, with predictions ranging from $40 billion to $65 billion by 2020.[7] Africa embodies many of the attributes that make foreign research so attractive. With urbanization shifting the continent's population to emerging large cities, where GDP is growing and better infrastructure and healthcare capabilities are becoming reality, urban households have more financial resources and are quicker to adopt modern medicines.[7] Between 2005 and 2012, Africa added 70,000 new hospital beds, 16,000 doctors and 60,000 nurses.[7] African governments have introduced price controls, import restrictions, country-specific labeling regulations and limits on retail margins.[7] The implementation of these regulations make it wholly attractive for drug manufacturers to conduct GCT in Africa and produce drugs there as well.

Ethnic and Socioeconomic Diversity

Clinical trial data is often collected from diverse populations to support license applications. Testing in varied geographical trial sites ensures that new drugs are safe and work the same way in varying ethnic groups.[8] Inhabitants of developing countries and regions have traditionally been underrepresented in medical research. As such, there is a reciprocal set of benefits for these populations and the sponsors of GCTs in underdeveloped countries. GCTs are important in efforts to provide effective new therapies and vaccines in areas of the world that typically lack access to quality medicines, helping to reduce or even eradicate diseases in the poorest countries in the world. In parallel, sponsors of GCTs gain access to a robust patient pool of willing participants, increasing development and deployment speeds at reduced operational costs.

Ultimately, there appears to be myriad factors driving the continued growth of GCTs throughout the world. From innovation that leads to increased drug accessibility to underserved populations, to a more streamlined, agile, research and development and approvals process, GCTs are of paramount importance in improving health for the global population. P

References

1. Thiers, Fabio, Anthony Sinskey and Ernst Berndt. "Trends in the Globalization of Clinical Trials." *Nature Publishing Group.* 1 Jan. 2008. Web.

2. *Kefauver-Harris Amendments Revolutionized Drug Development. U.S. Food and Drug Administration.* 10 Sep. 2012. Web.

3. *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions. U.S. Food and Drug Administration.* Mar. 2012. Web.

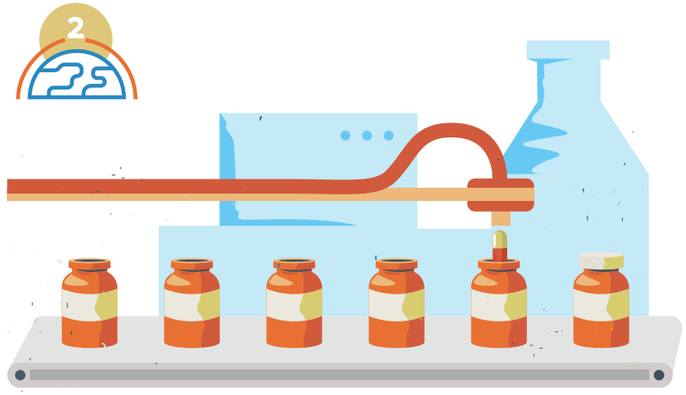
4. Ayalew, Kassa "FDA Perspective on International Clinical Trials." *U.S. Food and Drug Administration.* Web.

5. Shenoy, Premnath. "Multi-regional Clinical Trials and Global Drug Development." *National Center for Biotechnology Information, U.S. National Library of Medicine.* 2016. Web.

6. *Trends, Charts, and Maps. U.S. National Library of Medicine.* Apr. 2019. Web.

7. Holt, Tania, Mehdi Lahrichi and Jorge Santos da Silva. "Africa: A Continent of Opportunity for Pharma and Patients." *McKinsey & Company.* Jun. 2015. Web.

8. Lang, Trudie and Sisira Siribaddana. "Clinical Trials Have Gone Global: Is This a Good Thing?" *U.S. National Library of Medicine.* 12 Jun. 2012. Web.



Glocalization of Drug Manufacturing

Globalization of the pharmaceutical industry has resulted in an increase in local production in many countries. Large, international drug producers have established manufacturing facilities in many different geographic locations, either directly or through partnerships with local companies or contract service providers. Domestic manufacturers, meanwhile, have increased their presence in most emerging markets.

Pharma Industry Growth Driven by Emerging Markets

While the United States remains the world's largest pharmaceutical market, "pharmerging" markets will make up nine of the top 20 markets by 2021,[1] with China already the second-largest pharmaceutical market. Since 2011, the global expansion of the pharma market has largely been driven by pharmerging markets. This is due to increasing global wealth, greater government support, expanding infrastructure and enhanced insurance coverage.[1]

Innovation in pharmerging markets is also increasing dramatically. According to a study conducted by Charles River Associates for the International Federation of Pharmaceutical Manufacturers and Associations, between 2005 and 2010, industry R&D spending increased by 455% in Asia-Pacific (excluding Japan), 112% in Latin America and 303% in India.[2]

Pharmaceutical manufacturing is also increasing in many developing countries, with governments creating pharma production hubs and placing in-country pharma manufacturing as a priority.[3] Examples include Sri Lanka, Kenya, the United Arab Emirates and South Korea. Africa is of particular interest, because it is seen as the last large pharmaceutical market with significant future growth potential.[4]

Many Benefits of Local Pharma Production

Local pharmaceutical production (LPP) has been a focus of the United Nations Industrial Development Organization (UNIDO) for more than a decade. According to UNIDO, LPP can help vulnerable populations – particularly those in rural areas – gain access to quality medicines, reduce dependency on international donations and facilitate control of fraudulent drug products entering emerging markets.[5] In addition, local manufacturers tend to be more responsive to the needs of the local population. Regulators have more access and control of quality at the source, and inventory can be better managed to prevent supply interruptions.[6] Furthermore, local production can contribute to the local economy through job creation and income generation.[7]

Increasing the LPP in Africa is of particular interest.[7] Currently, 95% of the medicines consumed in Africa are imported from countries such as South Africa and Morocco, which produce 70–80% of their medicines locally. As early as 2005, a World Bank Study identified South Africa, Kenya, Nigeria and Zimbabwe as having the industrial capacity needed for successful LPP. In 2012, the African Union Commission's (AUC) Pharmaceutical Manufacturing Plan for Africa (PMPA) was adopted. China and India have, in recent years, shown interest in the development of the pharma sector in the African region.[7]

Challenges to Local Pharma Production

The desire to expand LPP in emerging markets is strong, but it remains unclear whether it is practical in many developing economies. Barriers[7] range from a lack of skilled workers and limited access to key raw materials to inadequate infrastructure. The high capital investment needed to meet GMP requirements and operating costs makes it difficult to offer affordable products.[6] In many cases, a strong regulatory framework is also lacking, and thus ensuring quality can be problematic.[7]

According to the WHO,[8] to be successful, local pharma manufacturers require the existence of a sufficiently large national market, or need to provide medicines that meet specific local demand. However, even highly developed countries do not produce all of their drug substances and drug products locally. In addition, fierce competition and government and payer pressures have driven down the price of many generic medicines, making it difficult for LPPs to compete. In summary, "high-quality, low-cost" medicines are not likely to be produced from the raw materials stage in countries that do not have the required market size and resources, in terms of skilled people, technology and quality control.[8]

Does Government Policy Have a Role?

While production decisions should generally be driven by economic factors and left to private manufacturers, pharmaceuticals directly impact the health of the population. Some government oversight is necessary to ensure that medicines are available, safe and of high quality. There is also an argument that government policies should encourage local drug production.

Brazil is one country that has elected to develop large-scale health-inspired industrial policies. The Brazilian government successfully encourages LPP by providing appropriate incentives for collaboration between competitive pharma companies.[9] Russia introduced its "Pharma 2020" strategy in 2009, which has the goal of raising the market share of drugs produced within the country to 50% by 2020. Its three phases have focused on the construction of new production facilities, domestic production of generics and increasing exports.[10] A 2005 WHO study found that policies were effective only in countries such as China, Brazil, Korea, India, Egypt and Poland with the industrial capacity sufficient to have local production approach or exceed $1 billion (similar to many European countries).[11]

In contrast, a study conducted in 2011 by the United Nations Conference on Trade and Development (UNCTAD), as part of a project funded by the European Union to identify the main challenges and obstacles to local production in developing countries, revealed that, in Argentina, Bangladesh, Indonesia and Jordan, LPP was indeed feasible, with companies in these countries achieving the economies of scale required to produce drugs competitively.[12] However, the researchers found that the most successful companies often started in collaboration with large multinational pharma companies, with technology transfer eventually leading to independent success. Perhaps as importantly, they also determined that LPP may increase access to medicines.

Outsourcing, Modularity and Other Enablers

Increased outsourcing to contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs), the advent of modular manufacturing solutions and the rising adoption of flow chemistry/continuous processing have all facilitated glocalization of pharmaceutical manufacturing.

Outsourcing provides access to specialized technologies and can increase efficiency and productivity while reducing cost. For small/emerging firms that often operate under a virtual manufacturing model, outsourcing is a fundamental business strategy.

Outsourcing to CDMOs in specific geographic locations also provides a foothold into countries that have implemented policies requiring local pharmaceutical production. Furthermore, CDMOs with multiple facilities located around the world can ensure greater security of supply with dual/multiple sourcing solutions. WuXi Biologics with its "Global Dual Sourcing Strategy"[13] and Alcami with its "Protect Your Brand™" offering[14] are just two examples of CDMOs focusing on this issue. CDMOs with the right skill sets can also help pharma manufacturers effectively manage the global sourcing role,[15] which can facilitate the use of in-country manufacturers.

Modular and flexible manufacturing systems are an attractive solution for replicating small production facilities in multiple countries to meet government requirements for LPP.[16] GlaxoSmithKline, Pfizer, GEA and G-CON formed a partnership in 2013 to develop self-contained, POD-based mini-factories for the continuous manufacture of oral solid dosage (OSD) forms. In November 2015, JHL Biotech's prefabricated KUBio plant manufactured by GE Healthcare Life Sciences was assembled from 62 containers in Wuhan, China in 11 days.

Today, Univercells is developing an automated bioproduction system (NevoLine™) that facilitates safer, faster and closed bioprocessing in a much smaller footprint, delivering a low cost of goods and reduced time to market and thus facilitating access to vaccines and biologic drugs.[17] The plant-based expression system offered by iBio is ideally suited for the production of biologics/biosimilars in developing countries that lack the funding and infrastructure to support traditional biologic manufacturing methods.[18]

Many of the key barriers to local pharmaceutical production can be overcome by applying new manufacturing models, most notably flow chemistry and continuous processing. Combined with state-of-the-art cloud computing and automation systems, continuous manufacturing is creating opportunities for cost-competitive in-country drug production using advanced manufacturing technologies.[19] P

References

1. Aitken, Murray, Michael Kleinrock and Deanna Nass. *Outlook for Global Medicines through 2021.* Rep. IQVIA. Dec. 2016. Web.

2. Wilsdon, Tim. "Encouraging pharmaceutical innovation in middle-income countries." *WIPO Magazine.* Apr. 2013. Web.

3. "Where are the pharma manufacturing hotspots?" *Pharmaceutical Technology.* 2 Apr. 2018. Web.

4. Holt, Tania, Mehdi Lahrichi and Jorge Santos da Silva. "Africa: A continent of opportunity for pharma and patients." *McKinsey & Company Insights*. Jun. 2015. Web.

5. "Pharmaceutical production in developing countries." UNIDO. n.d. Web.

6. "Q&A: How local pharmaceutical production can improve access to quality medicines" Devex. 30 Apr. 2019. Web.

7. Kurian, Oommen C. "Expanding pharmaceutical local production in Africa: An idea whose time has come?" Observer Research Foundation. 10 Apr. 2019. Web.

8. "Pharmaceutical Production Policy. (MDS-3: Managing Access to Medicines and Health Technologies, Chapter 7)." WHO Essential Medicines and Health Products Information Portal. 2012. Web

9. de Fonseca, E.M. "How can a policy foster local pharmaceutical production and still protect public health? Lessons from the health-industry complex in Brazil." *Global Public Health*. 13:489-502 (2018).

10. Bessière, Renaud. "Russian Pharma Market Offers Great Potential for Local Manufacturers." *Pharma's Almanac*. 15 Sep. 2017. Web.

11. Kaplan, Warren and Richard Laing. "Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines." WHO Technical Briefing. Jan. 2005. Web.

12. *Local Production of Pharmaceuticals and Related Technology Transfer in Developing Countries: A series of case studies by the UNCTAD Secretariat.* Rep. UNCTAD Secretariat. 2011. Web.

13. Stanton, Dan. "Dual sourcing drives global network as WuXi inks Amicus deal." *Bioprocess International*. 13 Feb. 2019. Web.

14. Hanley, Catherine. "Alcami Announces Innovative Protect Your Brand™ Offering to Secure Your Supply Chain." Alcami. 4 Oct. 2016. Web.

15. "Managing the complexities of global pharmaceutical sourcing." DPT Thought Leadership Issue 10. Mar. 2013. Web.

16. That's Nice. "Flexibility in Manufacturing Is Fundamental to Production Success." *American Pharmaceutical Review.* 29 Sep. 2016. Web.

17. *"Univercells presents NevoLine™ biomanufacturing system.* Univercells. 21 Feb. 2019. Web.

18. Ryan, Terence E. "Plant-based Protein Expression for Rapid, Green Bioprocessing." *Pharma's Almanac*. 24 May 2019. Web.

19. Riley, Darren L., Ian Strydom, Rachel Chikwamba and Jenny-Lee Panayides. "Landscape and opportunities for active pharmaceutical ingredient manufacturing in developing African economies." *Reaction Chemistry & Engineering*. 4: 457–489 (2019).

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From Regulatory Convergence to Global Regulatory Harmonization

Following the globalization of the pharmaceutical supply chain, from clinical trials to drug development and manufacturing, the harmonization of pharmaceutical regulations is essential. Significant progress on regulatory convergence has been achieved to date, but much work is needed before true harmonization can be realized.

Industry Globalization without Regulatory Harmonization Impacts Manufacturers and Patients

There are approximately 300,000 manufacturing facilities located in more than 150 countries supporting the global pharmaceutical industry.[1] In the United States alone, nearly 40% of drug products and 80% of drug substances come from producers located outside of the country.[2] Pharmaceutical R&D is conducted around the world, increasingly in developing markets with little experience in the regulation of clinical trials.[3] Often, different pharmaceutical ingredients, drug substances and final products are manufactured in multiple countries.[4]

Given the extent of globalization of pharmaceutical development and manufacturing activities, it is no longer possible for individual government regulatory agencies to ensure the safety and security of the drug supply in their respective nations on their own.

Unfortunately, the multilateral strategic coordination of regulatory efforts relating to pharmacovigilance, supply-chain integrity and international health crisis management has yet to be established.[1] The patchwork of regulations prevents comprehensive assurance of drug safety and creates barriers to the efficient development of novel treatments.[2]

Many regulatory agencies have limited resources, are lacking sufficiently skilled staff and are challenged to stay abreast of the rapid advances in new treatments and manufacturing technologies.[2] This situation is particularly true for developing nations, but also applies to countries with well-established markets and regulatory infrastructure.

Meanwhile, companies are often required to conduct similar but distinct studies and submit multiple applications for a given product to agencies in different countries, increasing the time and cost it takes to bring new drugs to market.[3] As a result, supply chains are often highly complex, increasing quality risks.[5] Different systems are also generally employed for the monitoring of commercial drugs, driving further inefficiencies and higher costs, while limiting the sharing of vital safety information. Duplication of effort negatively impacts both manufacturers and national medical regulatory agencies (NMRAs).[4]

Regulatory Harmonization Benefits and Challenges

Regulatory harmonization would increase efficiencies and reduce cost by avoiding that duplication of effort.[2] Drug development times and costs could be reduced and funds could be invested in new drug discovery instead of meeting different regulatory requirements.

Acceptance of inspection results and drug approvals across agencies would increase access for patients.[3] It is also possible that regulatory harmonization could increase the likelihood of success for pipeline candidates.

As importantly, collaboration would lead to best practices and standards, which would improve the safety of drug products.[2] Open discussions between NMRAs would also lead to the strengthening of capabilities of agencies with less experience and expertise.[6] More effective pharmacovigilance through international cooperation would lead to greater understanding of the causes of adverse events and allow earlier responses to potential safety issues.[7]

While global harmonization of pharmaceutical regulations would be highly beneficial to regulators, drug makers and patients, there are significant hurdles that inhibit rapid movement toward this goal. Most NMRAs have limited resources to direct toward daily activities, let alone to loftier goals. Unmet medical needs vary widely from one region to another. As importantly, differences in socioeconomic, cultural, political and healthcare systems present key challenges.[6]

The definition of quality is not singular for any given product. Risk tolerance levels, regulatory strategies and decision-making processes (strict, rule-based vs. flexible, principle-based) differ greatly from country to country and can lead to drug approvals in some countries but not others.[3] The need to demonstrate quality for specific local populations can result in regulations that are different from global standards.[5]

Some countries have implemented accelerated approval pathways, while others have not. Further complicating factors relate to the rapid advance of personalized medicines and the increasing use of artificial intelligence and machine learning, all of which require new regulatory approaches that could potentially vary amongst NMRAs.[5]

There is also a general concern that individual countries are leveraging sovereignty to delay harmonization of regulations for drugs and medical devices.[8]

Moving from Convergence to Harmonization

Despite these many challenges, regulatory agencies around the world have been working slowly toward global harmonization, and noteworthy progress has been made in the last decade.

Regulatory harmonization involves the adoption of the same technical requirements, standards and guidelines for quality, safety, and efficacy by all regulatory authorities. While each NMRA has decision-making authority, in general, the same process is followed, with common documentation and alignment of legal frameworks. Collaboration and trust between different agencies are essential to enable recognition of each authority's decisions.[1] However, this goal has yet to be achieved.

Nevertheless, there has been significant regulatory convergence, with the regulatory requirements of different countries and regions becoming increasingly similar over time. This is in respect to scientific principles, practices and procedures, as reflected in the acceptance of internationally recognized technical guidance documents and implementation of regulatory mechanisms that align with them.[9]

One crucial example is the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), which has been in existence for nearly 30 years. This organization develops and implements harmonized guidelines and standards for drug development and registration. It has been instrumental in the harmonization of Good Manufacturing Practice (GMP) and pharmacovigilance activities, the creation of the electronic Common Technical Document (eCTD) and standardization of medical terminology with MedDRA.[6]

Initially, only the European Union, the United States, Switzerland and Japan were participants, but today, China and many other countries are members, making the ICH the leading global operational and standards body.[1] India is the largest nation that produces drugs and medical devices that does not participate in global regulatory harmonization efforts.

The World Health Organization (WHO) has also been involved in regulatory harmonization efforts designed to increase access to medicines in the developing world.[6] Examples include development of the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system for drugs, the International Pharmacopoeia (Ph. Int.) and standards for pharmacovigilance through the WHO Program for International Monitoring; its medicines prequalification program to facilitate distribution of drugs to developing nations; and funding, in conjunction with the World Bank and NGOs, of various harmonization projects.

Other international harmonization efforts include the Pharmaceutical Inspection Convention; the Pharmaceutical Inspection Co-operation Scheme (PIC/S); the Council for International Organization of Medical Sciences (CIOMS), which largely is focused on biomedical products; the Health Level Seven International (HL7), which sets standards for the exchange, integration, sharing and retrieval of electronic health information; and the recently created International Coalition of Medicines Regulatory Authorities (ICMRA), whose members are the top health and drug regulators in 18 of the world's most developed nations and regions. The ICMRA is focused on global strategy and coordination, including the creation of a broad, formal framework with which to enhance communication, collaboration and regulatory alignment.[1,2]

Regulatory convergence takes many forms, from general collaboration to more formal mutual recognition agreements (MRAs), such as the recent agreement between the European Union and the United States, to regional integration, such as within the European Union.[6] Generally, these efforts focus on improving the transparency and alignment of interactions among agencies and between industry and various regulatory authorities; harmonizing inspection criteria, reports and deficiency descriptions; achieving better alignment of pharmacopoeial monographs and procedures; and harmonizing marketing authorization applications and approval timelines.[5]

Regional Harmonization on the Rise

The European Union is no longer the only region focused on harmonization of pharmaceutical regulations. Efforts are progressing in emerging regional markets.[4] The African Medicines Regulatory Harmonization Initiative was launched in 2009. The Zazibona process involves cooperation between NMRAs in Zambia, Zimbabwe, Botswana and Namibia, among others. The Pan American Network for Drug Regulatory Harmonization (PANDRH) focuses on harmonization of regulations for small molecule drugs in the Americas.

Others include Mercosur (South American trade bloc), the Southern African Development Community (SADC), the East African Community (EAC), the Gulf Cooperation Council (GCC), the Association of Southeast Asian Nations (ASEAN), the Asia-Pacific Economic Cooperation (APEC) and the Eurasian Economic Union.[6,7] P

Harmonization Needs for Clinical Trials

With greater numbers of clinical trials performed in developing countries, the harmonization of regulatory guidelines for clinical trials is particularly important for ensuring both the development of safe and efficacious medicines and the rights and safety of trial subjects.[10]

Concerns have included the differences in the definition of legitimate "consent," inadequate supervision of research activities for fraud prevention, potential for conflicts of interest with sponsor firms, obtaining agreement on appropriate endpoints, rules for the handling of trial data and when to disclose them, and challenges in drawing valid scientific conclusions based on data gathered from patients with different ethnic and cultural backgrounds.[3,10] To be accepted in many countries, clinical trials must be conducted with subjects from the specific population, and in some cases, a specific number of national participants is required.[3]

The ICH's Good Clinical Practice (GCP) standard is the internationally accepted ethical and scientific quality standard for designing, conducting, recording and reporting human clinical trials.[11] The U.S. Food and Drug Administration (FDA), for instance, requires that data from foreign clinical trials be obtained by competent clinical investigators that have conducted trials according to GCPs and are overseen by an independent ethics review board.[12]

To overcome many of the challenges with international clinical trials, the FDA is working to harmonize regulatory standards and practices based on aligned science-based goals for product safety, quality and efficacy, as well as conducting joint inspections and sharing inspection reports with other regulatory authorities.[12]

FDA Harmonization Efforts

The FDA currently engages in a number of convergence and harmonization efforts, many of which involve the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Specific organizations include the ICH, the International Pharmaceutical Regulators Forum (IPRF), the International Medical Device Regulators Forum (IMDRF), PANDRH and APEC.[9]

The MRA between the United States and the European Union came into effect in 2017 following three years of FDA and European Medicines Agency (EMA) cooperation as part of the Mutual Reliance Initiative. The MRA allows the United States and the European Union to use each other's GMP inspections of pharmaceutical manufacturing facilities once the capability of the various regulatory authorities has been assessed. As of July 7, 2019, the FDA had recognized 28 countries and expected to complete all of its assessments by the end of the month.[13]

The United States also established the Canada–United States Regulatory Cooperation Council (RCC) in 2011. The RCC was formed to better align the two countries' regulatory approaches, where possible, for pharmaceutical and biological drugs, over-the-counter medicines, medical devices and veterinary drugs.[14]

References

1. *Current Challenges (and Solutions) in Global Regulatory Harmonization*. Premier Research. 7 Aug. 2018. Web.
2. Zerhouni, Elias and Margaret Hamburg. "The need for global regulatory harmonization: A public health imperative," *Science Translational Medicine.* 8:338 (2016).
3. "International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary." Forum on Drug Discovery, Development, and Translation. V. Weisfeld and T.A. Lustig, Eds. National Academies Press (US), Washington (DC). 24 Oct. 2013. Web.
4. Ball, Douglas, Jane Parry and Susann Roth. "Better regulation of medicines means stronger regional health security: Strengthening and convergence of national regulatory agencies has benefits beyond country borders." *ADB Briefs.* Apr. 2016. Web.
5. Sandler, Susan. "Patient-Focused Harmonization Efforts in the Spotlight." *ISPE InTouch.* Sep./Oct. 2018. Web.
6. Strachan, James. "Harmonization: Regulation Goes Global." *The Medicine Maker.* 13 Oct. 2017. Web.
7. Reggi, Valerio. "Medicines Regulatory Harmonization: International Collaboration as a Key to Improve Public Health." *Medicine Access @ Point of Care.* 1 Jan. 2017. Web.
8. International Alliance of Patients' Organizations. "Sovereignty preventing global drug regulation harmonization-International Conference of Drug Regulatory Authorities." Conference Summary. 1 Dec. 2016. Web.
9. "Regulatory Harmonization and Convergence." U.S. Food and Drug Administration. n.d. Web.
10. Eccard da Silva, Ricardo, Angélica Amorim Amato, Dirce Bellezi Guilhem and Maria Rita Carvalho Garbi Novaes. "Globalization of clinical trials: ethical and regulatory implications." *International Journal of Clinical Trials.* 3: 1–8 (2016).
11. "Regulatory Harmonization." PhRMA. n.d. Web.
12. Ayalew, Kassa. "FDA Perspective on International Clinical Trials." 12 Dec. 2013. Web.
13. "Mutual Recognition Agreement (MRA)." U.S. Food and Drug Administration. 9 Jul. 2019. Web.
14. "Canada-United States Regulatory Cooperation Council (RCC)." Canada.ca. 6 Oct. 2017. Web.

APPLYING AN ESTABLISHED AND CONTINUOUSLY UPGRADED GLOBAL NETWORK FOR CDMO SERVICES

→ BY **LORRAINE HILL,** ASPEN PHARMACARE

From pre-filled syringes to oral contraceptives to eyedrops, Aspen Pharmacare has a global network of highly integrated and advanced centers of manufacturing excellence. With a commitment to quality, expertise in manufacturing – including a range of high-demand niche capabilities – Aspen Pharmacare is an ideal outsourcing partner for pharma companies with complex manufacturing needs.

THE STRATEGIC APPROACH TO MANUFACTURING AT ASPEN PHARMACARE CENTERS AROUND FIVE PRIMARY MANUFACTURING SITES **THAT SERVE AS SPECIFIC CENTERS OF PRODUCTION EXCELLENCE.**

GLOBALLY INTEGRATED VALUE CHAIN

Aspen Pharmacare offers an extensive portfolio of cost-effective, high-quality, niche manufacturing capabilities across a global network. We have a range of scalable production capabilities and capacities aligned with our current and future commercial objectives, including injectables, oral solid and semisolid, liquids and active pharmaceutical ingredients (APIs).

We operate 23 manufacturing facilities across 15 sites, and we hold international manufacturing approvals from some of the most stringent global regulatory agencies, including the United States Food and Drug Administration, the Australian Therapeutic Goods Administration and the European Directorate for the Quality of Medicines. We operate with an established business presence in approximately 56 countries/regions and supply products to more than 150 countries.

We focus on achieving efficiencies across our global manufacturing network through vertical integration of many aspects of our supply chain, combined with end-to-end global supply chain management overseen by a highly experienced team.

MANUFACTURING CENTERS OF EXCELLENCE

The strategic approach to manufacturing at Aspen Pharmacare centers around five primary manufacturing sites that serve as specific centers of production excellence. These five locations – Notre Dame de Bondeville in France, Oss in The Netherlands, Bad Oldesloe in Germany, and FCC Cape Town and Port Elizabeth in South Africa – each offers specialist capabilities and expertise.

Several additional regional facilities supply local/regional needs across diverse territories, including Brazil, Australia and multiple African countries. We also have a product development site in Hyderabad, India that supports commercial manufacturing programs.

All of the manufacturing centers are closely integrated. Manufacturing and leadership councils comprising the various business heads are in constant communication, sharing challenges and best practices and looking for common solutions. They all share a commitment to quality and customer service and a desire to optimize operating efficiency and productivity to ensure the manufacture of high-quality products.

ASPEN NOTRE DAME DE BONDEVILLE (NDB)

Aspen Notre Dame de Bondeville, located in France, offers brand-new high-quality, automated, prefilled syringe (PFS) filling under isolator with E-beam and automatic inspection. NDB's manufacturing capability for PFS is as automated as any CDMO in the industry. Today, 90% of products manufactured at Aspen NDB are exported to regulated markets around the world, including North America and Japan.

In addition to thrombosis products (e.g., heparin, synthetic factor Xa inhibitor), NDB produces diluents for vaccine reconstitution. The NDB site has been audited by many regulatory authorities, including ANVISA (Brazil), ANSM (France), EMA (Europe), FDA (USA), HPB (Canada) and JMHRA (Japan).

Over the past five years, Aspen Pharmacare has invested more than €70 million in the NDB site and has committed an additional €100 million over the next five years. In response to growing demand for both heparin products and sterile products in PFS (which are considered a safer and more reliable delivery option) NDB is currently constructing a new state-of-the-art facility for anesthetics, including additional capacity for blow–fill–seal (BFS). The latest PFS line to be installed (Groninger) will be dedicated to contract manufacturing projects and will be operational in Q1 2020.

"We welcome all potential customers who are looking for a high-quality solution for their prefilled syringe projects. The new, state-of-the-art automated and contained filling line is backed by a track record of excellent customer service,

which is reflected in our 95+% on-time, in-full delivery rate," remarks Jean-Charles Rousset, site director of the NDB facility. The high level of automation ensures a low level of quality deviations that could delay product supply. Dedicating our third PFS line to our CDMO business means that potential customers will benefit from accessing the flexibility and dedication of a pure CDMO offering while still leveraging the expertise and quality commitment of an embedded CDMO.

We have also developed intellectual property around a PFS device technology for enhanced safety, and are open to discussion with future clients about providing this technology for their products.

OSS, THE NETHERLANDS

Aspen Pharmacare's Oss business in the Netherlands is a manufacturing center of excellence for biochemical and chemical APIs, including cytotoxics and hormone products. Founded in 1923, it has a long history of developing biochemical APIs from waste material taken from slaughterhouses, including insulin and heparin. Aspen Pharmacare acquired the Oss facilities from Merck in 2013.

The business comprises facilities located at De Geer, Moleneind and Boxtel. The Moleneind site focuses on biochemical (heparin) and chemical (peptides, steroids, etc.) API production and is where all of the main support functions are located. The De Geer facility has wet chemical API capabilities, as well as powder handling technology to mill, micronize and sieve the final APIs. Boxtel is a state-of-the-art biochemical manufacturing site, including virus filtration capabilities.

Oss is highly integrated with the entire Aspen Pharmacare manufacturing network, providing heparin API to NDB and utilizing raw materials produced at the regional facility in India and advanced intermediates from the FCC Cape Town facility. It also has a worldwide customer base and has been audited and certified by all of the major health authorities.

On average, Aspen Pharmacare has invested approximately €20 million per year to maintain and upgrade the broad portfolio of capabilities at the three Oss sites. Dirk van Leemput, Oss site director, states "We are also working intensively to increase our efficiency and productivity, achieving optimization of individual processes by as much as 30% in some cases. These ongoing efforts continue to reduce our operating costs and free up additional capacity for external customer projects."

ASPEN BAD OLDESLOE, GERMANY

The Bad Oldesloe, Germany facility is a center of excellence for finished dose manufacturing of solids, semisolids and topical liquids, as well as BFS processing and full-service packaging, including secondary packaging and serialization. The site was established in 1973 and acquired from GlaxoSmithKline in 2009. We currently supply Europe, Japan and other international locations; in all, we supply 170 customers in 130 countries.

Our unique capabilities include low-dose (microgram) solid drug manufacturing, segregated, highly contained processing of highly potent APIs down to occupational exposure band 5 (OEB-5), solid and semisolid hormone and the production of controlled substances. In addition, we offer testing and release services and hub services for APIs and finished packs.

At Bad Oldesloe, we have been providing contract development and manufacturing services for very small– to large-volume products for many years. Our capabilities and technical expertise for product transfers reflect a high number of successful transfers over the last 20 years.

"Our CDMO customers benefit from the long-standing and stable employee base at the site. More than a quarter of the staff have worked at the facility for more than 20 years and have extensive experience in the tech transfer process," says Andrea Bretschneider, site director at Bad Oldesloe.

WE CAN SUPPORT YOUR NEEDS FOR API AND DRUG SUBSTANCE MANUFACTURE **FROM GRAMS TO TONNES FOR SOLID, SEMISOLID AND LIQUID PRODUCTS. WITH OUR HIGH QUALITY AND AUTOMATED SYSTEMS, WE CAN BE VERY COMPETITIVE.**

Over the last ten years, Aspen Pharmacare has invested approximately €55 million has been invested to upgrade our facilities and add new equipment to ensure we maintain state-of-the-art operations.

FCC CAPE TOWN, SOUTH AFRICA

Aspen Pharmacare's FCC Cape Town site is also a center of excellence for API manufacturing and has been providing contract development and manufacturing services for over 54 years. Established in 1965, the high-containment multipurpose site focuses on classical chemical synthesis and the extraction of natural APIs from plants. Overall, the facility has 38 active products in manufacture and supply supported by 212 regulatory filings in 41 countries, with the United States being its primary market. It has been audited by all leading regulatory authorities and has never received any critical findings, reflecting the fact that quality is the cornerstone of its culture.

"We have invested heavily in highly efficient, and versatile state-of-the-art containment facilities, engineering protection into our systems rather than relying on personal protective equipment, as is the case with all Aspen sites. With our high quality and automated systems, we can be very competitive," states Andre van der Walt, the site director at Aspen's API facility in Cape Town.

Products are manufactured in 10 segregated production buildings comprising 24 process centers, using equipment constructed with a diverse array of materials and protected by a wide range of containment technologies. Capacity is product specific and currently ranges from 1–3 kg pa output for highly specialized ONCO products, to 20 tonnes pa for HPAPI products. All process and analytical method development and scale-up activities are performed in house, allowing us to provide support on lab scale (gram quantities), pilot plant scale (1–10 kg) and commercial scale (up to 500 kg batch size).

Over the past five years, Aspen has invested close to $105 million in the FCC Cape Town site, building three new facilities, including a process center for hormones and cytotoxics with the highest levels of containment. Today, we can offer containment at the 1 ng/m^3 down to the 10 ng/m^3 level.

The FCC Cape Town site also benefits from its location in South Africa and its place within the Aspen network, with the Port Elizabeth finished dosage manufacturing plant located just up the coast.

WE HAVE INVESTED HEAVILY IN HIGHLY EFFICIENT, STATE-OF-THE-ART CONTAINMENT FACILITIES, ENGINEERING PROTECTION INTO OUR SYSTEMS **RATHER THAN RELYING ON PERSONAL PROTECTIVE EQUIPMENT.**

PORT ELIZABETH, SOUTH AFRICA

The Aspen Pharmacare site at Port Elizabeth, South Africa is a center of excellence for sterile and solid finished dosage manufacturing and packaging, including high-containment OSD, hormone OSD, oral contraceptive OSD, and ophthalmics. The site has received accreditation from regulatory authorities in North and South America, Europe, Australia and Africa and serves both the domestic and international markets.

Port Elizabeth specializes in sterile drug products packaged into vials and ampoules, as well as eyedrops using a three-piece dropper technology and various OSD forms.

Over the past five years, Aspen has invested ~€300 million in the Port Elizabeth site to increase efficiency and productivity and to construct a new sterile fill-finish facility for the production of vials, ampoules and PFS. This facility is due to start commercial operations in Q4 2019.

"Customers benefit from not only these advanced technologies, but the packaging and technology transfer expertise of our employees, many of whom helped transfer in the initial products when the facility, which previously resembled an R&D center, opened 20 years ago," says Grant Swart, site director for Port Elizabeth.

AN IDEAL CDMO PARTNER

Our global network of highly integrated and advanced centers of manufacturing excellence, and our commitment to ongoing investment in complex, state-of-the-art manufacturing capabilities, make Aspen Pharmacare the ideal choice as a contract development and manufacturing partner. We can support your needs for API and drug substance manufacture from grams to tonnes for solid, semisolid and liquid products.

Let us leverage our geographic footprint, valuable infrastructure and extensive portfolio of manufacturing capabilities to meet your challenging pharmaceutical production needs. We are enthusiastic about providing the benefits of our extensive manufacturing experience – including niche, in-demand capabilities – to other innovator pharmaceutical companies and ultimately to the final and most important customer, the patient. P

ABOUT THE AUTHOR

Lorraine Hill
Aspen Group Operating Officer and Responsible Pharmacist, Aspen Pharmacare

Lorraine Hill graduated from Rhodes University with a B. Pharm degree and formally entered the pharmaceutical industry in 1987. In 1994, she joined Garec Pharmaceuticals to head up the Regulatory Affairs department and later took up the pharmaceutical responsibility of Managing Director. Garec was integrated into Aspen in 1998, and as such she has worked for the Aspen Group, through this combined tenure, for more than 21 years. Over the past 9 years, responsibilities have grown from managing the Regulatory Affairs department at Aspen to being appointed the Group Operating Officer, reporting directly to the Group Chief Executive.

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RIGOROUS QUALITY CONTROLS FOR COLD-CHAIN DRUG SHIPMENTS

→ BY **ANDREW BOYLE,** BOYLE TRANSPORTATION

Life science organizations invest heavily in quality and product integrity within the confines of their own facilities and the facilities of their contract manufacturing organizations (CMOs) and contract packaging organizations (CPOs). However, those investments are for naught if drug makers fail to apply similar standards to the soft underbelly of their supply chain — transportation and logistics.

NEED FOR RIGOROUS QUALITY CONTROLS

It has been estimated that 20% of drug products and more than 33% of vaccines experience temperature excursions en route to their final destinations,[1] at enormous monetary cost and – more importantly – at the risk of patient adverse reaction or reduced efficacy. This issue is particularly stark for vaccines, as patients who believe that they have been vaccinated with a compromised vaccine may be at greater risk of contracting the relevant disease than patients who know that they have not been immunized.

Whereas the European Union promulgates regulations for transportation quality in the form of "Good Distribution Practices," no such prescriptive regulation exists in North America. Rather, a combination of government and industry groups establishes and disseminates recommended standards and best practices, such as USP <1079>.[2] Therefore, it is incumbent upon life science organizations to ensure that service providers apply rigorous quality controls when transporting their products. The layperson is often shocked when he or she peels back the onion of logistics. Many North American providers use business models with labels like "non-asset/asset light/intermediary/3PL/4PL." There has been an explosion of entities that happily insert themselves between you and the actual transporter of your product. The intermediary provider brokers the shipment to a carrier, who, in turn, may subcontract to an independent truck owner, who may then hire drivers to accomplish the delivery. This model works well for e-commerce and lower-value commodities that do not require much in the way of quality, safety or security. However, this multi-tiered "game of telephone" is typically not a good fit for pharmaceutical and biologic shipping, where accountability and execution of protocols are paramount.

Given the value of pharmaceutical and biologic shipments, it is imperative that life science organizations have representation from their quality, security and logistics groups when engaging a transportation provider. Shipping can either pose a huge risk or it can serve as an extension of the quality management practices found within the shipper's walls. Pharmaceutical logisticians charged only with cost control often bemoan this dynamic. A common complaint goes something like this: "We spend billions making this drug, and now we're supposed to hand it over to the cheapest carrier?" The risk of forfeiting control over a drug is an obvious concern.

In contrast to the multi-tiered subcontracting model described above, our company operates a closed-loop system – our fleet of vehicles is company-owned, and our professional drivers are highly qualified, vetted, trained and uniformed employees (not independent subcontractors). There are no handoffs to a third party. As a result, we are able to apply rigorous quality, safety and security protocols. Our history is rooted in the transportation of sensitive cargo for the U.S. military, so we have applied that disciplined expertise to life science commodities for the past 12 years.

GIVEN THE VALUE OF PHARMACEUTICAL AND BIOLOGIC SHIPMENTS, IT IS IMPERATIVE THAT LIFE SCIENCE ORGANIZATIONS **HAVE REPRESENTATION FROM THEIR QUALITY, SECURITY AND LOGISTICS GROUPS WHEN ENGAGING A TRANSPORTATION PROVIDER.**

THINK INSIDE THE BOX

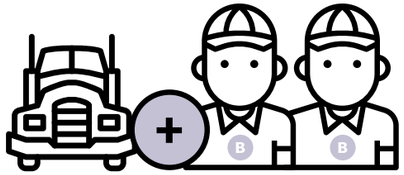
We use tractor-trailers to transport pharmaceuticals and biologics within the United States and into/out of Canada. One might think that, after buying a $95,000 temperature-controlled trailer outfitted with premium specifications and technologies, we'd be able to start transporting such products, right? Though this would seem reasonable, several steps are still required. Before ever putting such equipment into service at Boyle Transportation, we perform both validation and calibration, all in accordance with USP <1079>.

The thermal mapping/validation study follows a comprehensive protocol established in cooperation with our partners at Sensitech. Thirty data loggers are placed throughout the trailer to record temperature performance for more than 24 hours at the prescribed set point. An exhaustive analysis (and a 30-page report) reveals whether all cargo spaces in the trailer are conditioned within the established tolerance. When we began this process more than 10 years ago, one study resulted in a failure. Embracing the credo that "failure is an opportunity to improve," we adjusted the specification of our trailers to increase thermal performance. In essence, the validation process proves the efficacy of the trailer's temperature control.

OUR COMPANY CHOOSES TO PERFORM BOTH THERMAL MAPPING/ VALIDATION AND CALIBRATION BEFORE EVEN PUTTING A TRAILER INTO SERVICE, **AND WE REVALIDATE AND RECALIBRATE AT REGULARLY SCHEDULED INTERVALS THEREAFTER, FOR 100% OF OUR FLEET.**

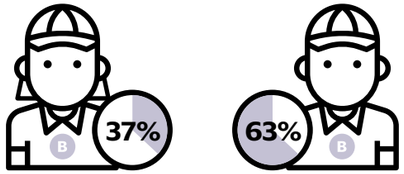
Elite Professional Driver Teams

Each truck is staffed by a team of two professional drivers, which ensures continuous movement and attendance to the loaded vehicle.



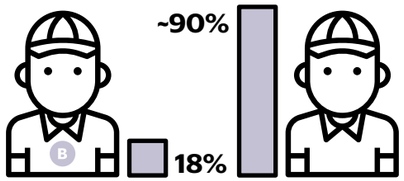
Employee Demographics

Thirty-seven percent of our professional drivers are women. The majority of our professional drivers are military veterans, and all drivers must have clean motor vehicle records and qualify for U.S. government clearance.



Employee Retention

We achieve significant retention of the drivers in our fleet, with a turnover rate of 18%, while the industry averages ~90% turnover. Our professional drivers average seven years of tenure with the company.



The calibration process involves proving that the temperature sensors within a trailer are accurate. Our protocol mandates that we use a reference thermometer that itself must be calibrated to National Institute of Standards and Technology (NIST) standards annually. By comparing the reference thermometer to the trailer's sensors, we can document that the temperature we report to shippers is accurate.

Some transportation service providers perform mapping and calibration on only a portion or "representative sample" of their fleet. As someone who has witnessed the extremely manual job shop of a trailer manufacturing process, I would not be comfortable representing to a pharmaceutical shipper that 10% of a batch of trailers accurately depicts the temperature performance of an entire lot. As one of our valued customers experienced during a recall, the U.S. Food and Drug Administration (FDA) does not want to hear that "the particular trailer that's bringing the product back for analysis has not been validated, but there's a similar one that has."

Our company chooses to perform both thermal mapping/validation and calibration before even putting a trailer into service, and we revalidate and recalibrate at regularly scheduled intervals thereafter, for 100% of our fleet. By proving the temperature efficacy of all of our containers, to use a football analogy we can say, "they are who we thought they were."

IN-TRANSIT VISIBILITY

Some transporters may furnish a printed temperature history receipt at the end of a trip, or the receiver may download a temperature data logger that had accompanied the product on its voyage. While such methods are nice to have, they serve as an *ex post facto* record. If a temperature malfunction had occurred in transit, it is now too late to do anything about it. You won't ever hear: "Your product suffered an excursion. Here's your receipt. Have a nice day."

Instead, we apply real-time communication technology to view a vehicle's location, route and estimated time of arrival (ETA), as well as its temperature throughout transportation. If we incur a mechanical issue, or if the temperature veers outside the predetermined tolerance, an alert is communicated both to the professional drivers and our 24/7 operations center. That way, we can take action immediately and mitigate the risk of any effect on the product.

We also provide complete visibility to customers, via a web or email interface that allows them to see their shipment moving across a map, along with the temperature and ETA to destination. The temperature and location history is downloadable as a PDF in case the customer needs to retain it for quality or security purposes. It also remains accessible at any later date from our system.

ADVANCED SAFETY AND RISK MANAGEMENT

Your product is subject to substantial risk once it leaves your facility – in the form of temperature, product integrity or motor vehicle accidents. While that will never get to zero, it is crucially important to have a partner that manages that risk as close to zero as possible.

We have always been an early adopter of onboard safety technologies. All of the trucks in the Boyle Transportation fleet are equipped with radar-based automatic emergency braking and adaptive cruise control, speed limiters, roll-stability control, and lane-departure warning. These systems were designed and implemented to arm our people with the tools necessary to do their job as safely as possible.

Furthermore, our fleet is outfitted with video cameras. The purpose of the camera system is twofold: to exonerate us from false claims and to continuously improve driving habits. The system generates weekly safety scores for each professional driver and helps to determine whether anyone is exhibiting unsafe or suboptimal habits. If so, we can proactively train the drivers. A significant portion of their incentive compensation is linked to this score, and we have achieved substantial improvement. Through such advanced management, we reduce risk for customers. This commitment to managing and reducing risk was validated as evidenced by our being awarded the Grand Prize in the National Fleet Safety Awards.

PEOPLE — OUR MOST IMPORTANT ASSETS

We invest heavily in our most important assets – our people. Most North American carriers compensate drivers on a "per mile" basis, which incentivizes people to go over on their allowable hours or drive fast and erratically in order to make a decent paycheck. Our clients entrust us with precious cargo, so our salary-based package is predicated on drivers executing quality, safety, and security protocols – thereby aligning the incentives of our professional drivers with the goals of our customers. By ensuring predictable earnings and predictable schedules, we achieve significant retention of the drivers in our fleet, with a turnover rate of 18%, while the industry averages ~90% turnover. Furthermore, 37% of our professional drivers are women. Each truck is staffed by a team of two professional drivers, which ensures continuous movement and attendance to the loaded vehicle.

Our drivers undergo a robust training and credentialing process, including an extensive background check, a hazardous materials handling course and certification, Transportation Worker Identification Credential (TWIC), Smith System defensive driving course, pharmaceutical protocol training, security awareness training, quarterly safety training and Truckers Against Trafficking instruction. At Boyle Transportation, we view our operation as a "virtuous circle" – the company invests in its people, the people, in turn, take care of the customer, and, therefore, the customer wants to continue doing business with the company. By focusing on a high touch customer experience, Boyle Transportation has achieved a Net Promoter Score of 85.7 for 1H2019 (i.e. 92% of customers rated us either 9 or 10 out of 10). We're delighted to say that we've been named one of the "20 Best Fleets to Drive For" in North America for 5 years running!

If a product's quality and temperature has been controlled throughout the entire supply, manufacturing, and distribution chain, it can almost be considered to be a small miracle. But given the amount of risk that exists in the transportation and logistics component of that chain, life science organizations are wise to engage service providers as strategic partners rather than counting on divine intervention. Mitigating those risks requires a comprehensive approach that includes processes, technology, and most importantly – people.

ABOUT BOYLE TRANSPORTATION

Boyle Transportation is a specialized trucking firm providing exceptional quality, safety, and security to select clients in life sciences and defense. By combining expertise in highly regulated and valuable military cargo with rigorous quality and temperature protocols, Boyle Transportation is now widely regarded as the premier provider of end-to-end, secure cool and cold chain truckload services for pharmaceutical shippers in the U.S. and into/out of Canada. P

REFERENCES

1. Hanson, Celina M. et al. "Is Freezing in the vaccine cold chain an ongoing issue? A literature review." *Vaccine.* 17: 2127–2133 (2017).

2. *<1079> Good Storage and Distribution Practices for Drug Products.* U.S. Pharmacopeia. 2019. Web.

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Andrew T. Boyle was an investment banker with J.P. Morgan, before returning to the company in 2003. He earned an MBA from Northwestern University's Kellogg School of Management and an AB from Bowdoin College. Andrew is vice chairman of the American Trucking Associations, and a director of the American Transportation Research Institute (ATRI). He is a member of the Business Advisory Committee of the Northwestern University Transportation Center, a director of the (Lowell, MA) House of Hope, and a trustee of Eastern Bank.

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INTERNATIONALIZATION OF A EUROPEAN CDMO

→ BY **CLAUDIO RONDENA, GIANPIERO POLLASTRO** AND **SALVATORE AGOSTINO,**
DOPPEL PHARMA CDMO

Doppel is a leading Italian, finished dose contract development and manufacturing organization (CDMO) with aggressive plans for expanding its presence in international markets. Backed by a private equity firm with a strategic outlook, the company has been investing in new capabilities and capacities designed to meet the evolving needs of its customers. Recent U.S. Food and Drug Administration (FDA) approval of solid oral dose manufacturing at our Rozzano facility in Milan, Italy is just one of many steps the firm is taking to internationalize its business.

25 YEARS OF EXPERIENCE IN FINISHED DOSAGE FORM DEVELOPMENT AND MANUFACTURING

Doppel was established in Italy in 1994 and over the last 25 years has become a leading European CDMO offering a range of clinical and commercial finished dosage form manufacturing and packaging services for our worldwide clients.

With highly advanced research and development labs and pilot-scale facilities, Doppel provides customized product and formulation development services for over-the-counter (OTC), generic and branded drug products ranging from pre-formulation to industrial-scale production, including manufacturing of investigational new drug/investigational medicinal product (IND/IMP batches), clinical labeling, regulatory support and common technical document/drug master file (CTD/DMF) drafting services. We currently manufacture more than 1000 SKUs, including non-sterile and sterile (injectable) liquid, semisolid, capsule, tablet and other oral solid dosage forms, and have supported the registration of more than 50 pharmaceutical products. **We** also possess the facilities and capabilities to work with highly potent actives and formulations.

Excluding multinational firms, Doppel is one of the largest CDMOs in Italy. Even so, we pride ourselves on the agility and responsiveness we offer and the close relationships that we develop with our clients. We have a strong track record in building and forging close partnerships and providing high-quality services tailored to the specific needs of each individual customer at all stages, from formulation, development and manufacturing all the way to marketing and post-marketing controls. All of these attributes have earned us the business of more than 100 clients, including leading multinational branded and generic pharmaceutical companies.

Doppel is a CDMO that emphasizes development. We strive to deliver the best service possible and support our clients with the extensive expertise we have gained in new product and formulation development. We are focused on developing novel and optimized solutions for our customers and doing so in the shortest time possible and at a fair price. Those products can then be produced at commercial scale with the highest degree of reliability.

Our development and manufacturing activities take place at two state-of-the-art facilities located in Italy. The Rozzano plant in Milan was acquired in 2001 from Pfizer, while the Cortemaggiore facility in Piacenza was constructed by Doppel in 2004. The closely integrated and synergistic capabilities and capacities at both sites guarantee business continuity and on-time-in-full (OTIF) service delivery.

SEMISOLIDS, LIQUIDS, SOFT-GEL CAPSULES AND HIGHLY POTENT TABLETS

Doppel's Cortemaggiore plant covers an area of approximately 44,000 m^2 and employs more than 260 people with extensive experience in the development, manufacture and packaging of semisolid and liquid finished pharmaceutical products and medical devices.

Small-volume (drinkable liquids, drops, topical sprays, nail lacquers and throat sprays) and large-volume (syrups, mouthwashes, vaginal solutions, oral suspensions and topical solutions) liquids are produced in glass and plastic vials and bottles. Semisolids include creams, ointments, gels and steriles (terminal sterilization). Suppositories, ovules and soft gelatin capsules are also produced at the plant. Highly potent drugs in tablet form are manufactured in a separate, independent building designed with the facility controls and equipment necessary to effectively achieve high containment.

Doppel Cortemaggiore has been inspected and approved by AIFA, Korea KFDA, ANVISA and the Ministry of Health of Kenya Republic and is certified to manufacture both investigational and commercial medicinal products.

The site is also certified according to the environmental and safety management systems ISO 14001 and OHSAS 18001 and according to ISO 13485 for the manufacture of medical devices.

OVER THE LAST FOUR YEARS, NEARLY $45 MILLION HAS BEEN INVESTED IN FACILITIES, EQUIPMENT **AND CAPABILITIES AT DOPPEL'S TWO MANUFACTURING SITES.**

OUR R&D DIVISION IS CURRENTLY DEVELOPING AN INTERNAL PIPELINE OF INNOVATIVE PRODUCTS **BASED ON OUR PATENTED TECHNOLOGY PLATFORM FOR CHRONOTHERAPEUTIC TARGET DELIVERY.**

NON-STERILE LIQUIDS, SOLID DOSAGE FORMS AND INJECTABLE PRODUCTS

The Rozzano plant covers an area of approximately 25,000 m² and employs more than 260 staff with expertise in the development, manufacture and packaging of non-sterile liquids, solid dosage forms and injectable products.

Solid dosage forms include tablets, mini- and micro-tablets and granules. In addition to uncoated tablets, we manufacture film-coated single and multilayer tablets that can be formulated as immediate- or sustained-release dosage forms. Uncoated and coated mini- and micro-tablets can be filled into hard gelatin capsules. Granules are produced using conventional technologies and can be filled into sachets, hard gelatin capsules and tank caps or be compressed into tablets.

Sterile ampoules are manufactured using either aseptic processing systems or via terminal sterilization.

Doppel Rozzano has been inspected and approved by AIFA, China FDA and Ministry of Health of Kenya Republic; and is certified to manufacture both investigational and commercial medicinal products. The site is also certified according to the environmental and safety management systems ISO 14001 and OHSAS 18001.

FOCUSED ON TARGETED DELIVERY FOR ORAL SOLID DOSAGE FORMS

Within Doppel, our applied research services include analytical development studies, formulation development, stability studies (ICH), process development, scale-up, process validation, regulatory affairs, technology transfer, life cycle management support, CTD documentation and product manufacturing and labeling for clinical trials.

The R&D Division, which is hosted at the Rozzano site and include pilot facilities approved by AIFA, also develops a range of highly innovative formulation technologies, including sustained- and controlled-release oral solid dosage forms with various release profiles, including site-specific delayed-release delivery; multi-layered tablets possessing combinations of release profiles of the same or different drugs in a single tablet; multi-particulate systems, such as granules or micro-tablets containing different dosages and release profiles, filled in a single capsule; bioavailability enhancement drug delivery systems for increasing permeability or solubility of active drugs; and innovative delivery systems containing solids and liquids in one dosage form.

These capabilities provide added value for our customers by offering novel approaches for the targeted delivery of active pharmaceutical ingredients (APIs) and can be applied to both new chemical entities and generic products. Targeted delivery ensures the release of the right quantity of API at the correct site of action. The end result is safer and more effective drugs and the potential for lower-dose formulations.

Our R&D division is currently developing an internal pipeline of innovative products based on our patented technology platform for chronotherapeutic target delivery. This technological platform is a modified controlled-release pharmaceutical composition that has been developed with the aim of the delivering drug substances into the gastrointestinal tract by combining both pH-dependent and pH-independent polymers applied on multi-particulate and/or multilayer solid dosage forms. We are proud to note that the first drug candidate has been successfully submitted to a phase I clinical trial, and we expect to conduct more phase I/II clinical trials in 2020 with other molecules from this pipeline.

For our customers, using our established formulation platforms reduces the effort and time required to develop novel formulations, saving them money and accelerating their development programs. They also enable customers to meet increasing expectations from regulatory authorities for patient-centric formulations, achieve product differentiation and establish a competitive advantage. For existing drugs, they also provide a means to extend patent life and create opportunities to address new indications and new patient populations. Patients benefit from greater convenience and ease of use, which often leads to increased medication compliance and better outcomes.

BACKED BY PRIVATE EQUITY WITH A CLEAR VISION FOR GROWTH

Since 2015, Doppel has been part of the private equity firm Trilantic Europe, which holds 100% of the shares. Trilantic Europe is focused on control and co-control investments in Western Europe, using flexible transaction structures, partnering with family-owned businesses and providing growth capital to outstanding management teams.

We are grateful that Trilantic Europe has more than just financial objectives for their investment in Doppel and has established a clear vision for our growth. Indeed, Doppel is viewed as a strong base in the CDMO industry that can be built upon through organic growth, investment in greenfield facilities and the acquisition of other CDMO businesses.

Most importantly, Trilantic Europe has been willing to invest significantly in Doppel to enhance and expand our capabilities. In fact, we have substantial investment plans and strategies for growth in terms of size and presence across diverse geographic regions. In particular, we intend to strengthen our research and development, achieve strategic growth through the acquisition of niche capabilities and increase Doppel's presence in international markets, such as the United States and the Far East.

INVESTING FOR THE FUTURE

Over the last four years, nearly $45 million has been invested in facilities, equipment and capabilities at Doppel's two manufacturing sites. Major investments have included the installation of an innovative sterile gel production plant, increasing our capacity to produce hormonal and other highly potent drugs and expansion of our soft-gel capsule manufacturing capacity.

Investments have also been directed at upgrading or replacing older equipment to increase efficiency and productivity.

Doppel has also adopted an aggressive plan to improve the sustainability of our manufacturing operations. We are currently in the midst of an ongoing process to harmonize both production sites and put into place various systems designed to decrease our energy consumption and reduce the CO_2 emissions from our facilities. We intend to educate the company in this way in order to attain a high greenfield facility level, with state-of-the-art equipment and technologies.

Going forward, Doppel is focused on expanding our capability for the production of sterile injectables, including vial fill. The percentage of biologic drugs in the pharmaceutical pipeline continues to increase, and we feel Doppel cannot exclude establishing a foothold in this technology to stay current and relevant in the future.

With respect to external investments, Doppel is evaluating potential acquisition targets that will fit with our existing business and vision for growth. Appropriate targets are being considered in all locations with well-developed and capable manufacturing industries, including but not limited to other European countries, the United Kingdom, the United States and Canada.

INCREASING INTERNATIONAL PRESENCE

When Doppel was founded in the early 1990s, our focus was on serving smaller generic producers within the domestic Italian pharmaceutical industry. Over the last five to six years, we have focused on expanding our customer base to include small and large OTC, generic and branded pharmaceutical manufacturers with operations around the globe. Today we supply more than 100 customers all over the world, including many international big pharma companies.

DOPPEL IS A CDMO THAT **EMPHASIZES DEVELOPMENT.**

Our international reach is now expanding to the United States as well. In April 2019, the Doppel Rozzano Plant was inspected by the U.S. FDA, with a 0 (zero) 483 form being issued for dispensing, bulk preparation (mixing), bulk finishing (encapsulation), primary packaging (bottles) and secondary packaging in cardboard boxes for oral solid dosage forms (capsules), including serialization capabilities. We plan to follow up on the approval for this area with expansion to the remaining areas of the Rozzano Plant and Doppel Cortemaggiore.

At the same time, Doppel has an initiative in place to reduce internal complexity and improve the efficiency of our manufacturing lines by significantly selecting the critical mass of customers. By the first quarter of 2020, we will have created a proactive loop targeted at reducing our internal costs. The gains we achieve will be shared with our partners, thereby enabling us to be more competitive. P

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Gianpiero is Commercial Director at Doppel Pharma CDMO at the Rozzano plant in Milan, Italy. He joined the company in 2007 from UCB, where he was Director of the Supply Chain, dealing with purchasing activities, CMO management and quality assurance. Previously, he worked at Takeda Italia Farmaceutici as Logistic Manager and SPA (Società Prodotti Antibiotici) responsible for production and later for logistic activities. He was also responsible for quality assurance and production at Rhône-Poulenc Pharma.

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DRUG DEVELOPMENT

NEUROLOGY

Harnessing the Gut–Brain Axis to Treat Neurological Disorders

Neurological diseases have traditionally been treated with limited success using large and small molecule drugs that must penetrate the blood–brain barrier (BBB). Axial Biotherapeutics is taking a radically different approach to treatment with candidate drugs designed to influence the gut microbiome.

Two-Way Communication

The gut–brain axis (GBA) involves the central and enteric nervous systems, linking the emotional and cognitive areas of the brain with peripheral intestinal functions influenced by the gut microbiome. The communication occurs in both directions through neural, endocrine, and immune links.

GI Manifestations in CNS Diseases

Disturbances in the commensal bacteria in the gastrointestinal (GI) tract have been associated with a number of different diseases, including neurodegenerative diseases and neurodevelopmental and psychiatric disorders of the central nervous system (CNS). The gut microbiomes of patients with Parkinson's disease (PD) and autism spectrum disorder (ASD) are clearly different from those of typically healthy people.

Many academic researchers and startup biotech companies are exploring the possibility of treating PD, ASD, multiple sclerosis, Alzheimer's disease, major depressive disorder, anxiety and other debilitating conditions via the gut microbiome.

Gut-Retentive Approach

Axial Biotherapeutics is taking a revolutionary approach to treating CNS diseases. It has traditionally been assumed that any drug developed for these types of disorders must reach the brain via passage through the BBB – a frequently challenging goal to achieve. With our novel drugs that provide localized, gut-retentive treatment, there is no need for systemic delivery of high doses to reach the brain, potentially leading to both greater efficacy and improved safety profiles.

Mechanistically Driven

The development of these new treatments at Axial focuses on exploring the mechanisms by which the gut microbiome is driving or contributing to disease. Transplants of human microbiota into germ-free mouse models (humanized models) allows the interrogation of microbe function, genetic dysregulation and metabolite production that can be linked to disease symptoms.

We then consider oral small molecule drugs or possibly live commensal bacteria that will interact with the gut microbiome and effect positive changes in the brain. For our oral small molecule drug candidates, Axial has developed proprietary delivery systems that enable delivery to the lower part of the GI tract, where the microorganisms reside.

Novel Therapy for Parkinson's Disease

GI problems often occur in people with PD years before the onset of motor problems, suggesting that the gut microbiome may be a driver of the disease. Our co-founder, Caltech Professor Dr. Sarkis K. Mazmanian, has demonstrated that gut bacteria potentiate numerous PD-like features in a validated mouse model of disease, suggesting that alterations in the human microbiome may be a novel and causal risk factor for PD.[1] In mice overexpressing human *α*-Synuclein (*α*-Syn), intestinal microbiota are required to induce GI and motor deficits and *α*-Syn pathology in the brain. Antibiotic treatment ameliorates pathophysiology in adult animals, while microbial colonization promotes this pathophysiology, suggesting that disease arises from postnatal signaling between the gut and the brain. Colonization of *α*-Syn–overexpressing mice with microbiota from PD patients enhances motor and GI impairments compared with microbiota transplants from healthy human donors.

Evaluation of the organisms and genes overrepresented in the PD microbiome has enabled identification of a druggable pathway sufficient to induce motor and GI symptoms and brain pathology in a validated disease model of PD. Axial's PD program includes the AB-4166 and the AB-4000 series. AB-4166 is a first-in-class intervention that is currently being evaluated for safety and tolerability in a subpopulation of PD subjects. Axial has also identified multiple novel chemical entities in the AB-4000 series, which are being developed for improved selectivity as potential next-generation drug candidates for PD and other neurodegenerative diseases.

Axial is collaborating with the Parkinson's Institute and Clinical Center (PICC) on preclinical research using our candidates and the PICC's unique cellular and animal models for PD.

Paradigm Shift in Treatment of Autism

Similar studies in ASD mouse models have enabled Axial to characterize metabolites produced in high concentrations that appear to drive autistic behaviors. Axial has developed an oral, gut-retentive small molecule therapy (AB-2004) shown to remove key metabolites in ASD animal models, resulting in the reduction of leaky gut symptoms and improvement in repetitive behavior, communication, anxiety and ASD-related sensorimotor gating deficits. P

Reference

1. Sampson, Timothy et al. "Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease." *Cell*. 167: 1469–1480 (2016).

Yuan Zhang, Ph.D., MS
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Seurat Therapeutics

DRUG DEVELOPMENT

MIGRAINE

Mimicking Environmental Enrichment for Migraine Therapy

Although migraines affect a significant portion of the population and can be debilitating, treatment options remain limited. Seurat Therapeutics is developing a patient-centric treatment that could be life changing for migraine suffers.

Prevalent and Debilitating Disease

Migraine attacks affect approximately 1 billion people worldwide, including adults and children – almost 12% of the global population,[1] and migraine is considered the 6th most disabling illness in the world. Most migraine sufferers experience attacks once or twice per month, but as many as 4 million people worldwide deal with chronic, daily migraine and have at least 15 migraines per month. Healthcare and lost productivity costs associated with the condition are estimated to be as high as $36 billion annually in the United States alone.

The current standard of care for acute treatment is one of four different triptan drugs, which are serotonin receptor agonists. However, patients must limit their usage of triptan treatments in order to avoid undesirable cardiovascular side effects. Dosing can also be difficult for patients that suffer from nausea and emesis as part of the prodrome of the migraine.

Antiseizure drugs and other medications have also been prescribed to migraine patients, but they too can have significant side effects. These drugs are also known to create a lethargic and "fuzzy" sensation after the migraine has passed. Botox (onabotulinumtoxinA) injections were approved by the U.S. Food and Drug Administration (FDA) in 2010 for the treatment of patients with 15 or more migraines per month. In 2018, the FDA approved three new monoclonal antibody drugs for migraine treatment. These drugs inhibit calcitonin gene-related peptide (CGRP) binding and have been shown to reduce the number of monthly migraine days, but must be administered via subcutaneous injection.

Early studies demonstrate that our nasal delivery formulation halts the underlying cause of migraines in animal models.

Learning from Environmental Enrichment

Seurat Therapeutics is currently developing new treatments for migraines based on research performed at the University of Chicago Medical Center. This work, led by neurologist Dr. Richard Kraig, who is also Seurat's co-founder and Chief Scientific Officer, demonstrated that environmental enrichment (EE), a naturally induced biological phenomenon associated with rich, stimulating environments, can reduce brain diseases by half, suggesting that therapeutics based on EE can improve brain health.

It is believed that people who suffer from migraines exhibit neural hyperexcitability, which can lead to neuroinflammation and oxidative stress. EE results in the overexpression and greater transport of insulin-like growth factor-1 (IGF-1), a protein produced by the liver, across the blood–brain barrier. In the brain, IGF-1 alters the action potential threshold of neurons, thereby reducing neural hypersensitivity. It also leads to decreased expression of CGRP. Replicating EE through a therapeutic approach has potential as both an acute treatment and prophylaxis for migraines.

Upstream Targeting

During a migraine attack, abnormal electrophysiological signals lead to downstream effects, including neuroinflammation and blood vessel dilation, which then cause the sensation of pain. Current medications target these downstream effects. At Seurat, we are taking a more direct approach to treatment by developing a drug that interferes with the upstream production of abnormal neural activity. We believe this solution will be the first treatment to address the underlying cause of migraine headaches, rather than just the symptoms.

A Simple Solution

The drug in development is repurposing IGF-1. IGF-1 has been on the market and safely used to treat patients for decades; preclinical animal studies demonstrate that our nasal delivery formulation halts the underlying cause of migraines.[2]

Delivering our new medication in a nasal spray will make it easy for patients to self-administer anywhere. This delivery system could also allow for lower doses and avoidance of undesirable side effects.

To date, Seurat has raised over $1.4 million to support initial evaluation of our migraine candidate and is based out of the Polsky Exchange in Chicago, IL. We are currently at the preclinical stage and are performing dose ranging and toxicity studies. We hope to initiate clinical trials in approximately two years. P

References

1. "About Migraine." Migraine Research Foundation. n.d. Web.
2. Yelena Y. Grinberg, Lois A. Zitzow and Richard P. Kraig. "Intranasally administered IGF-1 inhibits spreading depression *in vivo*." *Brain Res.* 1677: 47–57 (2017).

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DRUG DEVELOPMENT

FOOD ALLERGIES

Developing a Microbiome-Based Treatment for Food Allergies

The incidence of food allergies has increased dramatically in both children and adults over the last few decades. This increase has been linked to changes to lifestyle and in the environment that have impacted the gut microbiome. To address this, ClostraBio is developing treatments inspired by the microbiome designed to reestablish tolerance to food allergens.

A Growing Allergy Problem

Eight foods, including milk, egg, peanut, tree nuts, wheat, soy, fish and crustacean shellfish are responsible for most of the serious food allergies in the United States, but more than 170 foods have been reported to cause allergic reactions.[1] According to the Centers for Disease Control & Prevention, the prevalence of food allergy in children increased by 50% between 1997 and 2011.[2] Childhood hospitalizations for food allergy tripled between the late 1990s and the mid-2000s, and medical procedures to treat anaphylaxis resulting from food allergy increased by 380% between 2007 and 2016.[1] A recent population-based survey of 40,443 U.S. adults revealed that an estimated 10.8% were food allergic, and nearly 19% believed they were food allergic.[3] Food allergies are also closely linked to other diseases, such as eczema, asthma and allergic rhinitis.[4] There is a monetary cost as well – caring for children with food allergies costs U.S. families nearly $25 billion annually.[1]

Driven by Environmental Factors

The rapid increase in food sensitization cannot be explained by genetics. Evidence suggests that numerous environmental factors have had an impact, including the widespread use of antibiotics, consumption of processed foods, greatly improved sanitation and the increased reliance on formula feeding. All of these are changes that can impact the composition of the microbiome – the organisms that live in and on human bodies.

No Preventive Treatments

Avoidance of food allergens is the only approach available to allergy sufferers, and, in the event of exposure, administration of epinephrine is the sole acute treatment option. Consuming increasing amounts of a food allergen under monitoring can lead to desensitization in some cases, but this approach carries significant risk and must be continued lifelong, or a patient risks losing desensitization.

The Role of the Microbiome

It has been theorized that allergic hypersensitivity to certain foods is the result of overactivation of the immune system in response to the presence of potentially harmful substances.[5] Mouse models of food allergy have shown that gut microbes from the group *Clostridia* play a role in the regulation of immune responses.[6] ClostraBio's co-founder and President Cathryn Nagler, who is also the Bunning Food Allergy Professor and Professor of Pathology, Medicine, and Pediatrics and the College Biological Sciences Division at the University of Chicago, recently showed that germ-free mice that received a transplant of microbiota from human infants with an allergy to cow's milk developed the allergy.[7] In contrast, germ-free mice inoculated with microbiota from human infants that were not allergic were protected against the allergy, demonstrating that transfer of the microbes could confer allergy protection.[7]

Microbiome-Based Therapy Development

ClostraBio is developing both biological and synthetic modalities as novel treatments for food allergy. The former utilizes a formulation of bacteria shown to be protective, along with their dietary fiber fuel sources, into an oral drug. The other involves identifying metabolites produced by protective bacteria that signal appropriate responses to allergens, and then modifiying them using a proprietary polymer for oral delivery. A combination of these two approaches may be optimal. The hope is that such a treatment will be antigen agnostic and protect against all potential food allergens.

Moving Towards the Clinic

ClostraBio has raised $4.6 million to fund preclinical development, including proof of concept work regarding efficacy; mechanism of action, pharmacokinetic and pharmacodynamic studies; and scale-up and optimization of the manufacturing process. We are currently pursuing Series A financing to support the initiation of a clinical program in humans, which we hope to begin by late 2020 or early 2021. P

References

1. "Facts and Statistics." Food Allergy Research & Education. n.d. Web.

2. Jackson, Kristen D., LeJeana D. Howie and Lara J. Akinbami. "Trends in Allergic Conditions Among Children: United States, 1997–2011." NCHS Data Brief No. 121. May 2013. Web.

3. Ruchi S. Gupta et al. "Prevalence and Severity of Food Allergies Among US Adults," *JAMA Netw. Open*. 2:e185630 (2019).

4. Alduraywish, S.A., C.J. Lodge, B. Campbell et al. "The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies." *Allergy*. 71: 77–89 (2016).

5. Wesemann, Duane R. and Cathryn R. Nagler. "The Microbiome, Timing, and Barrier Function in the Context of Allergic Disease." *Immunity Review*. 44: 728–738 (2016).

6. Stefka, Andrew T. Taylor Feehley, Prabhanshu Tripathi et al. "Commensal bacteria protect against food allergen sensitization." *PNAS*. 36:13145–13150 (2014).

7. Nagler, Cathryn R. et al. "Healthy infants harbor intestinal bacteria that protect against food allergy" Nature Medicine (2019).

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Founder and CEO
My Personal Therapeutics

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DRUG DEVELOPMENT

TUMOR GENOMICS

Personalizing Cancer Treatment with Genomics Technology

Tumor adaptability is determined by unique genetic mutations. Identifying the optimum combination of chemotherapies and non-cancer drugs for each patient requires modeling the tumor profile in a whole animal model. My Personal Therapeutics (MPT) is using proprietary fruit fly avatars in combination with artificial intelligence and high-throughput screening to provide personalized treatment recommendations.

Leveraging Genetic Drivers

Tumors can rapidly adapt to chemotherapies, leading to low response rates and relapse. As a consequence, the best cancer treatments comprise drugs, either single agents or more often combinations of substances, that target multiple specific nodes of the tumor network – an approach referred to as polypharmacology.

Recapitulation of the tumor with maximum fidelity in a whole-animal model is needed to enable unbiased testing of potential drug treatments. Genetic information from a patient's tumor is used to identify specific drivers for tumor growth in that patient, which can link patients to specific clinical trials or possible targeted treatments.

Introducing My Personal Therapeutics

MPT was founded in August 2019 to leverage fruit fly avatar technology developed by Ross Cagan and colleagues at the Icahn School of Medicine at Mount Sinai Center for Personalized Cancer Therapeutics (CPCT) and offer personalized, genomics-based cancer treatment recommendations.

MPT exclusively licensed the Personal Discovery Process (PDP) technology from Mount Sinai for global commercialization. PDP leverages Big Data to build personalized fruit fly avatars that model individual patients at an unprecedented level of complexity. Using robotics, thousands of drugs are screened in combinations to identify drug cocktails able to target the tumor while preserving the patient's quality of life.

This approach enables us to account for each tumor's genetic complexity at a level never before achieved in a clinical setting. All recommended treatment combinations include a cancer drug and one or more non-cancer drugs, making treatments less toxic and more affordable.

The genomic information and drug treatment data collected are being used to develop TuMatch, an AI-powered service that enables rapid and affordable personalized treatment recommendations. We hope to have TuMatch available by early 2020 for colorectal cancer, followed by other cancers.

Advantages of Fruit Fly Avatars

Drosophila melanogaster fruit flies are small, genetically tractable and live for a very short time, allowing the rapid screening of hundreds of drug combinations. The PDP serves as a massive clinical trial for each individual patient. We can generate fruit fly avatars incorporating multiple tumor mutations, effectively modeling the complexity of those tumors. For each patient, 400,000 avatars are screened against up to 1,200 FDA-approved drugs to identify optimal combinations.

The technology was demonstrated in a U.S. patient with advanced chemotherapy-resistant colon cancer.[1] The tumor was found to contain at least nine cancerous mutations. Over 300,000 flies engineered with these mutations were screened against 121 existing drugs both singly and in combinations of up to three. The optimum combination consisted of the cancer drug trametinib and the osteoporosis treatment zoledronate – the patient was able to survive for an additional two years because of this combination therapy.

Choosing the Right Patients

A patient or oncologist only needs to provide My Personal Therapeutics with sequencing results from a tumor biopsy and a blood sample, which we use to determine the mutations that act as drivers for tumor mutation and growth. We are currently focused on colorectal and related cancers, lung cancer and rare cancers.

Following screening, the identified drug cocktails are discussed with the patient's oncologist, and the optimal drug combination is selected based on the patient's overall medical condition.

Just the Beginning

For colorectal cancer, we have established a database of drugs based on previous results that, using AI, enables us to eliminate non-relevant drugs from the screening process, reducing the time and cost of the service. Currently, we know that five specific drug cocktails work for approximately 75% of colorectal cancer patients.

We envision developing TuMatch solutions for all types of tumors and ultimately other genetic diseases. We are also interested in exploring the impact of comorbidities on cancer treatment and are modeling diabetic fruit flies with cancer to determine how diabetes might affect drug recommendations. Finally, we are investigating the mechanisms of action behind the effective drug combinations we have identified to apply this knowledge to new drug design and development. P

Reference

1. Bangi, Erdem et al. "A personalized platform identifies trametinib plus zoledronate for a patient with KRAS-mutant metastatic colorectal cancer." *Science Advances*. 22 May 2019. Web.

Michael Luther
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Leveraging Biosynthetic Expertise to Access a Wide Portfolio of Cannabinoids

Deployment of new biosynthetic methods are enabling robust, reliable and economical cannabinoid production at scale, for applications ranging from consumer to pharmaceutical markets.

Established Potential

The human endocannabinoid system (ECS) comprises endogenous receptors and enzymes that are involved in the regulation of numerous physiological processes.[1] Cannabinoids act as exogenous ligands that interact with the ECS via these same receptors and enzymes, leading to a number of different physiological effects. The modulation of the ECS provides an opportunity to develop cannabinoid and cannabinoid analog products that have the potential to treat various disease conditions, including but not limited to CNS disorders (e.g., epilepsy, anxiety and depression), as well as nausea, appetite control, diabetes and inflammation.

Benefits of Biosynthetic Cannabinoids

Producing highly pure minor cannabinoids in large quantities via extraction from plants is not economically efficient. There are over 100 known different minor cannabinoids produced in the plant and most are expressed at very low and varying levels. The use of biocatalytic methods for the synthesis of cannabinoids provides a cost-efficient and reproducible means to produce these minor cannabinoids.

With cannabinoid biosynthesis, the controlled, selective production of highly pure, specific cannabinoid and cannabinoid-like compounds is possible. This enables the production of large-scale amounts of cannabinoids under cGMP for various applications, including pharmaceuticals.

The production of cannabinoids using biosynthetic and biocatalytic processes – including the minor cannabinoids and analogs – provides a set of tools to better understand how the ECS is involved in the regulation of a number of biological functions, including disease processes. This knowledge base, along with the platform to produce cannabinoid analogs and libraries, will accelerate the development of new therapeutics to address unmet medical needs.

The Teewinot Process

Teewinot's proprietary CannSynthesis™ biocatalytic platform enables the production of natural and non-natural cannabinoids in commercially scalable quantities today. Teewinot has engineered various *Cannabis* enzymes for overexpression and improved enzymatic properties, which can be combined with a variety of substrates and conditions to produce a wide variety of cannabinoids, including proprietary cannabinoid analogs.

Using this CannSynthesis™ approach, Teewinot has achieved >150 grams per liter scale production at 10–15 grams per liter per hour, yielding cannabinoids that are >99% pure. The reaction conditions are such that, in a single 10,000-liter reactor, this process can produce more than a metric ton per day of certain cannabinoids.

Growing Portfolio

Today, Teewinot produces over 25 different minor cannabinoids. In addition to biocatalytic production of these minor cannabinoids, Teewinot has also produced a large and proprietary set of cannabinoid analogs, ranging from prodrugs to cannabinoid libraries, as new chemical entities for pharmaceutical development.

Pharmaceutical Pipeline

Regarding drug development, Teewinot is leveraging its platform in combination with internal expertise and partners to develop a proprietary pharmaceutical pipeline. Currently, Teewinot has two programs that are actively moving through IND-enabling studies. These include improved formulation and delivery systems, as cannabinoids are known to be highly hydrophobic and have issues with metabolism, duration and drug-drug interactions. As part of its drug development programs, Teewinot is working with external companies to develop new formulations and delivery approaches, including novel device combination applications.

Partnering for Commercialization

Teewinot is taking advantage of its early mover advantage in the production of minor cannabinoids and is working with partners and looking to establish new partnerships from bench to manufacturing, given the robust and scalable capabilities of its CannSynthesis™ platform today.

Teewinot currently has 18 issued or allowed patents and more than 40 provisional patents. The company's patent strategy is focused on three major areas: (1) composition of matter, (2) manufacturing methods and processes and (3) methods of use.

With a new management team in place to accelerate the platform and market opportunities, Teewinot is initiating a $50 million Series C funding round with the intent to conduct an initial public offering in 2020. P

Reference

1. Challener, Cynthia. "Accessing Cannabinoids Using Biocatalysis." *Pharmaceutical Technology.* 41: 20–22 (2017).

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Looking Beyond Current Treatments for CNS Diseases and Disorders

Major depressive disorder (MDD) and social anxiety disorder (SAD) are two common mental health conditions for which current treatments fall short of patient needs.

Challenges with Current CNS Medications

MDD in the United States is treated with a limited variety of FDA-approved antidepressants. Approximately two-thirds of patients with MDD do not respond to initial treatment with current antidepressants, and positive responses can take months to achieve. The drugs often carry side effects that can also lead patients to halt treatment. Even the new ketamine-based therapies have limiting side effects and safety issues, including hallucinations. They may also be unsuitable for patients suffering from cardiac conditions, diabetes or obesity.

New Treatments for Major Depressive Disorder

MDD affects nearly 300 million people and is the leading cause of disability worldwide, according to the World Health Organization.[1] VistaGen has two drug candidates in phase II development for MDD: AV-101 and PH10.

AV-101 is a novel, oral NMDAR GlyB antagonist that inhibits NMDA receptor function rather than blocking it altogether (such as ketamine). AV-101 is intended for use at home (rather than in a clinical setting like ketamine) and has potential for fast-acting benefits without troubling side effects.

In preclinical studies, AV-101 demonstrated rapid, dose-dependent and persistent antidepressant-like effects following a single treatment, without the psychological side effects of ketamine.[2] In two randomized, double-blind, placebo-controlled phase I safety studies in healthy individuals, AV-101 was safe, well-tolerated and not associated with any severe adverse events.[3]

VistaGen's phase II clinical trial of AV-101 for MDD is underway to evaluate the efficacy and safety of AV-101 as an add-on treatment (with an oral antidepressant) for patients with inadequate response to their current antidepressant. VistaGen's initial objective for AV-101 in MDD is to reduce or replace the current widespread use of oral atypical antipsychotics, which have limited efficacy and a separate set of side effects, as add-on treatments for MDD.

The FDA has granted Fast Track designation for the development of AV-101 as an add-on treatment for MDD. Next, we hope to expand AV-101's use to maintain the benefits of successful ketamine therapy on a at-home basis. AV-101 also has potential as a novel treatment for neuropathic pain, for which the FDA has granted Fast Track designation, levodopa-induced dyskinesia (LID) affecting patients with Parkinson's disease, suicidal ideation and epilepsy.

VistaGen's second late-stage drug candidate for MDD – PH10 neuroactive nasal spray – is a novel, odorless neurosteroid designed to rapidly activate nasal chemosensory receptors that trigger neural responses in parts of the brain believed to be related to depression. In an exploratory phase IIa clinical study, PH10, at microgram doses and without systemic exposure, demonstrated rapid antidepressant effects with exceptional safety and tolerability.

With its unique mechanism of action and excellent safety profile, PH10 has potential to provide ketamine- and esketamine-like antidepressant effects without their psychological side effects or safety concerns. PH10 is being developed as a stand-alone, at-home treatment for MDD, and VistaGen is currently preparing to advance phase IIb clinical development in late 2020.

PH94B for Social Anxiety Disorder

SAD is characterized by excessive fear, anxiety and avoidance of everyday situations. VistaGen's PH94B neuroactive nasal spray is another synthetic investigational neurosteroid. PH94B activates nasal chemosensory receptors that trigger a subset of neurons in the limbic amygdala, which processes fear and anxiety. Activated neurons in the limbic amygdala release GABA, which then broadcasts calming impulses to other parts of the brain associated with fear and anxiety. In a 91-patient phase II clinical study in patients with SAD, at microgram doses and without systemic exposure, PH94B significantly reduced anxiety within 10–15 minutes of self-administration.[4] The drug has also been successfully evaluated in a pilot phase III crossover study.[5] In all clinical studies to date, PH94B's safety and tolerability were exceptional, with no serious adverse events. VistaGen is currently preparing for pivotal phase III development of PH94B as a treatment for SAD, expecting to launch in mid-2020. P

References

1. "Preventing suicide: a global imperative." World Health Organization. 2014. Web.

2. Zanos, Panos et al. "The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition." *J. Pharmacol. Exp. Ther.* 355: 76-85 (2015).

3. Wallace, Mark et al. "Randomized, double-blind, placebo-controlled, dose-escalation study: Investigation of the safety, pharmacokinetics, and antihyperalgesic activity of L-4-chlorokynurenine in healthy volunteers." *Scandinavian Journal of Pain* 17: 243-251 (2017).

4. Liebowitz, Michael R. et al. "Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder." *Am. J. Psychiatry.* 171: 675-682 (2014).

5. *VistaGen presents new data from Phase study of PH94B nasal spray for social anxiety disorder.* VistaGen. 1 Apr. 2019. Web.

Shaan Gandhi
Co-Founder and President
Pyxis Oncology

Focusing on the Tumor Microenvironment Leads to Novel Drug Targets

Pyxis Oncology is using new insights about the genetics of immune cells in the tumor microenvironment to develop a pipeline of new antibodies that enhance the immune response, even in tumor types historically unresponsive to cancer immunotherapies.

Why the Tumor Microenvironment Is Important

While many patients with cancer exhibit immune responses to tumors, the T cells involved in that response often do not function properly in the tumor microenvironment. Most patients do not have these "hot" tumors; they have what are known as "cold" tumors, or non-T cell–inflamed tumors with hostile microenvironments that prevent immune cells from entering their cores and eliminating the tumor. These "cold" tumors require novel therapeutic approaches to interrupt the negative regulation driven by tumor cells and to promote increased immune cell infiltration and motility.

Current medicines, including leading immunotherapies such as PD-1 and PD-L1 inhibitors, target T cells located within the tumor microenvironment. However, despite success to date, many patients still do not respond clinically. By focusing more deeply on the properties of immune cells within the tumor microenvironment, a better understanding of the mechanisms involved in their deactivation/inactivation is being achieved, and additional novel therapeutic targets are being identified for restoring or initiating endogenous immune cell function. As several of these targets appear only to be expressed by T cells within tumors, it is possible that drugs specifically targeting these molecules will have fewer off-target effects.

Transitioning from the University Lab

The initial research exploring the tumor environment was conducted in Dr. Thomas Gajewski's laboratory at the University of Chicago. By focusing on the unique biology of T cells within tumors, the team discovered immunoregulatory targets tied directly to the biology of the tumor microenvironment. Analysis of tumor antigen–specific tumor-infiltrating lymphocytes (TILs) within hot tumors, and of tumor cell signaling pathways within cold tumors, led to the identification of new genes representing hundreds of molecules not previously identified in the literature as having importance in T cell function or anti-tumor immunity.

Molecules studied to date can act as positive or negative regulators of T cell infiltration and function. These molecules were only observed on dysfunctional T cells in the tumor microenvironment but were not detected when properly functioning T cells led to tumor shrinkage. These are being pursued by Pyxis as targets for novel antibody-based immunotherapies.

Genetic mouse models have already been developed for the top candidates. When tumors were implanted in these models, strong changes in tumor growth were observed, indicating that these are mission-critical molecules for regulating cancer growth. These genetic and interventional preclinical proof-of-concept studies suggest the potential for new effective foundational monotherapies or drugs that can be used in combination with other cancer therapies.

The Longwood Fund, a Boston-based life sciences venture capital firm that focuses on founding, managing and building healthcare companies, drove the launch of Pyxis Oncology with the assistance of the University of Chicago's Polsky Center for Entrepreneurship and Innovation. In July 2019, Pyxis Oncology announced its $22 million Series A financing with the support of Leaps by Bayer, Longwood, Agent Capital and Ipsen.

Forming Pyxis Oncology enables the evaluation of multiple candidates simultaneously with the goal of speeding up their translation from the lab to first-in-human studies. Initially focusing on antibodies and fusion proteins allows for the use of a well-established path to development and commercialization.

Head Start

With access to the research already underway, Pyxis is hitting the ground running and is well-positioned to ramp up the scale of production of antibodies for its priority candidates based on the work already completed. Pyxis is also developing the next tier of targets for additional candidates.

Maintaining Close Relationship

Pyxis will continue to maintain a close relationship with Gajewski's laboratory through a Sponsored Research Agreement (SRA). The company will focus on development and commercialization of new therapies, while the academic laboratory will continue to explore in greater detail the deeper biology and mechanisms underlying the control of immune cells in the tumor microenvironment. As additional insights are gained, they will benefit Pyxis in terms of improving how new drugs are developed and what biomarkers will be used for patient selection. In essence, the relationship will serve as a catalyst for accelerating and derisking the entire development and commercialization process. P

Kurt Pickle
Business Line Leader
IDEX Health & Science

Facilitating Modern Bioprocessing with Real-Time Protein Titer Monitoring

An automated analytical technique that provides real-time protein titer data is designed to boost efficiency and productivity in bioprocessing.

Impact of Real-Time Protein Monitoring

The accurate and reliable measurement of protein titer is essential for ensuring optimal cell culture performance for the production of many biologics. The ability to reliably monitor protein titer in real time throughout a bioprocess allows operators to rapidly adjust the process conditions for maximum protein output while minimizing the process time. Quick access to titer data also enables earlier decisions regarding preparation of downstream purification systems (e.g., protein A), further reducing the production timeline.

Real-time monitoring of protein titer facilitates the adoption of continuous bioprocessing.

New Purpose-Built Solution

IDEX Health & Science has developed the first fit-for-purpose chromatographic device for rapid, automated at-line measurement of antibody titers from stirred bioreactors using an aseptic sampling device. The Tridex™ Protein Analyzer is compact and easy to use. The unique trap-and-elute technique, which quantifies the amount of IgG in a cell-free sample, delivers accurate titer measurements over a dynamic range of 0.1–10 g/L with minimal sample manipulation. The sample flowpath is completely enclosed, lending itself to the requirements of single use.

As a result, the Tridex Analyzer is a complete solution for at-line titer monitoring in a bioprocess environment that provides actionable data quickly, enabling critical decisions to be made in real time.

Performance Comparable to HPLC

High-performance liquid chromatography (HPLC) is the current standard technique for determining protein titer. Performance of the Tridex Protein Analyzer has been shown to provide at-line results that directly correlate to offline HPLC methodology. In-house[1] and field testing[2–4] have shown that the system provides results within +10% of those obtained using offline HPLC over the full titer range. In one example, excellent intra-assay precision (CV <3%) was demonstrated for both off-line and at-line measurements obtained with the Tridex Analyzer and a commercial protein A HPLC system.[1] Measurement data were also shown to be unaffected by changing BSA levels up to 2.5% (v/v).

Many Advantages

Unlike HPLC, for which specialized chromatographic expertise and experience are necessary, no scientific background is required to operate the Tridex Protein Analyzer. No method development is required, nor are sample dilutions or other sample manipulation steps, such as centrifugation. Results are provided within five minutes of sample injection, and the system is immediately ready for the next sample following completion of an analysis.

User Friendly

The Tridex Protein Analyzer is designed for simple operation and maintenance. Protein titer is determined in four easy steps: selection of a calibration curve and entry of sample information, sample loading, running the sample (push-button start) and review of the results. The software is easy to navigate and consists of four user-friendly screens.

The overall footprint is quite small – just slightly larger than a legal-sized piece of paper – and the system weighs only about 20 pounds, so it is quite portable and easy to maneuver. The Tridex Analyzer is also easy to install and typically can be up and running within one afternoon.

Designed with IIoT in Mind

IDEX Health & Science, with extensive experience in the development of advanced optofluidic technologies for the life sciences, recognizes the increasing pressure that biopharma companies are facing to reduce cost and increase biomanufacturing productivity and the role that automation and process analytical technologies will play going forward.

We have applied our engineering expertise to the design of a real-time protein titer determination with the Industrial Internet of Things (IIoT) and Industry 4.0 in mind. The Tridex Analyzer incorporates key capabilities for interconnectivity with internal networks comprising commonly used software systems.

Commercial automated sampling systems that pull samples aseptically from bioreactors can also be connected to the Tridex Analyzer via a "trigger" that tells the system to initiate an analysis. While manual operation is available if required, this solution allows for real-time monitoring of protein titer without the need for any human intervention. P

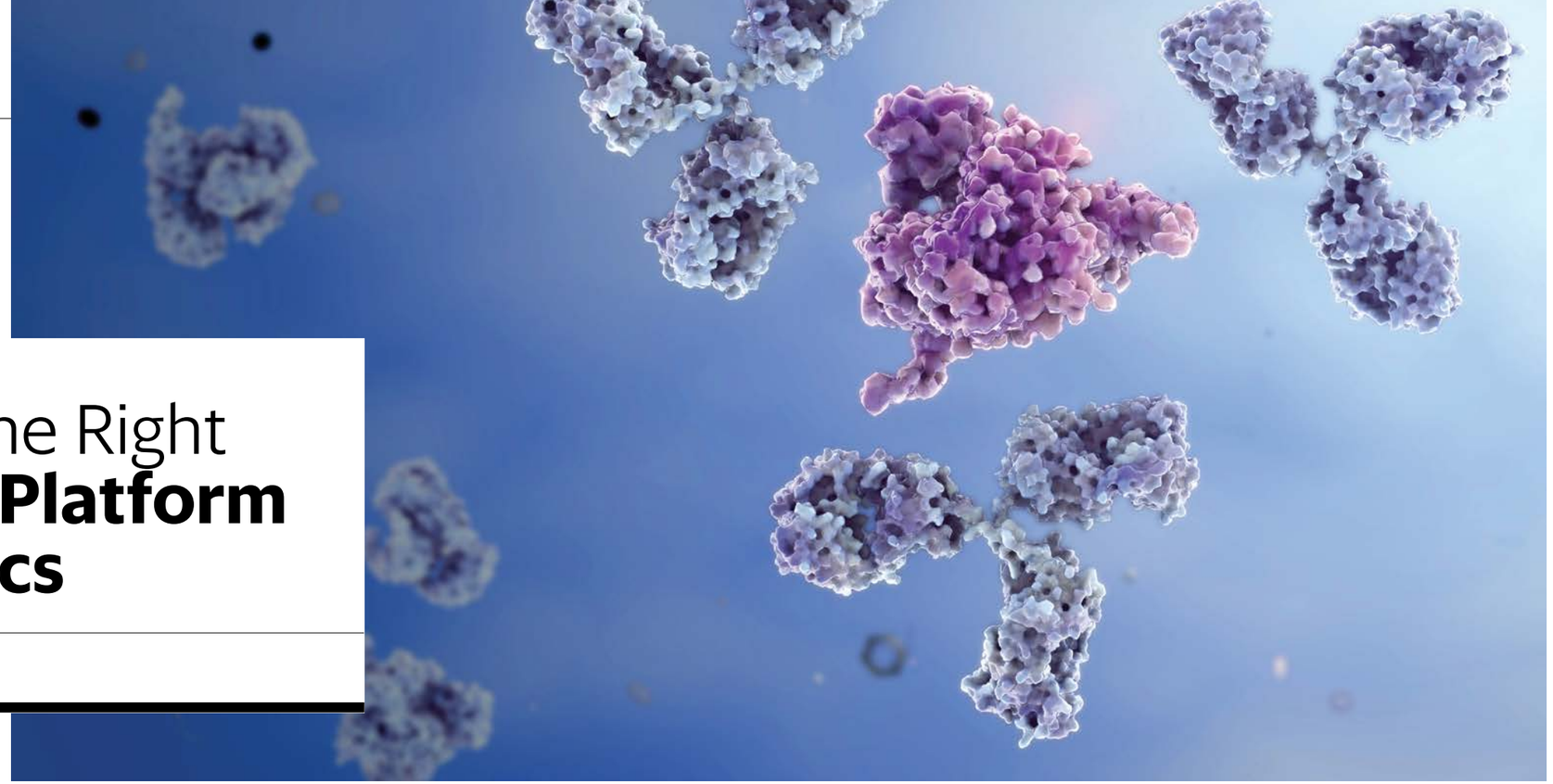
References

1. Bravo, Jaime, Connie Yuan and Craig Love. "Automating At-Line Titer Measurement with a Novel Fit-For-Purpose Chromatographic Device." *Appl. Microbiol. Biotechnol.* 99: 4645–4657 (2015).

2. Karim, S. et al. "Comparing Bioreactor Antibody Titer Measurements Obtained in Real Time to Other Antibody Measuring Techniques." Aragen. n.d. Web.

3. Kottayil, I. et al. "Novel Device Enables Direct Measurement of Antibody Titers Up to 10 g/L in Real Time Without Sample Manipulations." Aragen. n.d. Web.

4. Pagila, R. et al. "A Novel Approach to Real-Time Monitoring of Antibody Titer in a Fed-Batch Bioreactor Run." Aragen. n.d. Web.



Choosing the Right Expression **Platform for Biologics**

BY **KSHITIJ (TJ) LADAGE,** NICE INSIGHT

Biologic drugs are formulated with a range of biologic drug substances. Established active biomolecules include engineered proteins and antibodies, hormones and growth factors, peptides and enzymes. Next-generation biologic drug substances include cell and gene therapies, antibody–drug conjugates (ADCs) and bi- and multi-specific antibodies. **While these biomolecules can vary significantly in terms of their structures and properties, they are generally produced using a limited number of production methods.**

Some biologic drug substances are extracted from plasma or other biological materials. Most, however, are produced using mammalian cell culture or microbial fermentation. There is also growing interest in alternatives to mammalian cell culture, including bioprocessing using plants and insect cells.

In all of these cases, the cells are engineered to produce the desired biologic drug substance in the highest yield and purity possible. Access to CRISPR/Cas9-based genome editing technologies is enabling the engineering of all types of expression platforms with enhanced properties and performance and new functionalities.[1]

Mammalian Expression Systems

Just a decade ago, microbial fermentation was relied upon heavily for the production of recombinant proteins.[2] Since that time, there have been tremendous gains in the efficiency of cell culture. As a result, by 2018 nearly 70% of biologic production capacity in terms of volume (excluding blood/plasma products) was based on mammalian cell culture, primarily in Chinese hamster ovary (CHO) cells.[3]

Cell culture remains the fastest growing segment of the biologics market, mainly due to ongoing advances in cell-line development.[1,4] In addition, mammalian-expressed biologics account for the greatest percentage of candidates in the biopharma pipeline. As a consequence, both pharmaceutical companies and contract service providers continue to invest in additional cell culture manufacturing capabilities, particularly in single-use systems with smaller footprints and solutions that enable process intensification for greater efficiency and productivity.

Microbial Expression Systems – Growth Drivers, New Technologies

Microbial fermentation is most commonly performed in *Escherichia coli* bacteria, but is also achieved using other bacteria, yeast and fungi. It is typically preferred for smaller biologics (e.g., peptides, proteins, cytokines, growth factors, plasmid DNA, nucleic acids, single-domain antibodies, peptibodies and non-glycosylated antibody fragments).[5]

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. *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.

According to BCC Research, in 2017, the market for microbial-produced biopharmaceuticals was valued at approximately U.S. $100 billion and was expanding at a modest 6% CAGR.[6] The markets for microbially produced protein drugs, peptide hormones and vaccines are expected to reach U.S. $60 billion, $28 billion and $19 billion, respectively, in 2020.[6]

One of the key drivers of growth in the microbial fermentation segment is the development of next-generation biologics, many of which are smaller biomolecules, such as antibody fragments, peptibodies, ADC payloads and small peptide fragments.[7] In many cases, CHO cells are not suited for the production these complex substances.

As with cell-line development, advances are also being made in the genetic engineering of higher-performance microbial strains. Typically, engineered microbes are capable of producing large quantities of drug substances at concentrations higher than what can be achieved via cell culture. In addition, the development timelines and costs for microbial fermentation processes can be much shorter than those for mammalian cell culture.[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

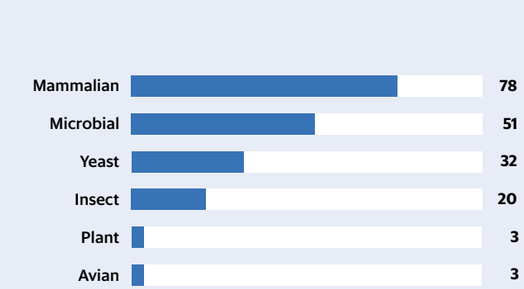


Figure 1
Breakdown of the protein expression platforms offered by a selection of the top 100 biologics CDMOs. The total shown here exceeds 100, as many of these providers offer multiple expression systems.

Nice Insight's 2019 Biologics Market Report and CDMO Pricing Study

This article was adapted from a chapter in Nice Insight's 2019 Biologics Market Report and CDMO Pricing Study, which is currently available for purchase at **PharmasAlmanac.com/bio-report**

This report was developed to be an invaluable source of due diligence and pricing for innovator companies looking to outsource their biologics development and manufacturing, as well as a peer comparison resource for CDMOs serving the biologics outsourcing market or private equity companies/investors looking to define their investment strategy.

The report provides a segmented breakdown of the biologics development market by expression platform, therapeutic area, region, and clinical and commercial production and a comprehensive survey of the competitive landscape, including a directory of the Top 100 Biopharmaceutical CDMOs across major regions, including capabilities, capacities, proprietary technologies and locations.

Significantly, the report contains Nice Insight's proprietary Pricing Study, which includes current 2019 pricing benchmarks for over 60 typical service line items within biologic development projects, obtained through comprehensive surveys conducted with a range of CDMOs in North America, Europe, and Asia.

The Pricing Study allows outsourced service providers the ability to measure whether their pricing levels are appropriate against high, low and median pricing in the marketplace and grants innovator companies a resource to gauge appropriate pricing and connect with the most suitable CDMO for their needs.

Seven tiers of buying options:

- Full Report
- Market Report + Executive Pricing Summary
- Executive Summary Only
- Pricing Summary Only
- Company Profiles Only
- Company Profiles + Key Contacts
- Company Profiles + Raw Data

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.

Examples of two new microbial expression technologies include Dyadic's C1 Gene Expression Platform based on technology originally developed for industrial biotech applications and Lonza's XS Pichia 2.0 Expression and Manufacturing Platform based on *Pichia pastoris* for the production of next-generation biologics.

Plant- and Insect-Based Expression Systems

The same limitations of mammalian cell culture driving interest in microbial fermentation – long development timelines, high cost and inability to produce newer, complex non-natural protein formats – are also driving interest in the development of alternative expression platforms for both existing and next-generation biologics.[9] Indeed, nearly half of respondents to a *BioPharma Reporter* survey conducted in late 2017 indicated that the biopharma industry relies too heavily on CHO cell culture for antibody production.[1]

Expression systems based on plant and insect (Baculovirus) cells have already been proven to yield biologic drug substances that have been formulated into therapeutics that perform in the clinic and meet regulatory approval requirements.[9]

Plant-Based Expression

According to Coherent Market Research, the global cell-free protein expression market, which includes plant-based protein expression, was valued at U.S. $ 177.1 million in 2017 and is expected to witness a CAGR of 6.2% through 2026.[10]

Therapeutic proteins have been produced in plant-based expression systems for more than 20 years.[11] Human trials were first conducted in the late 1990s, and since then, antibodies, vaccines, enzymes and other therapeutic proteins have been developed by several companies, including iBio Inc., Protalix BioTherapeutics, Medicago, Icon Genetics and Kentucky Bioprocessing; many have reached clinical trials and some achieved regulatory approval.

The markets for **microbially produced protein drugs, peptide hormones and vaccines** are expected to reach U.S. $60 billion, $28 billion and $19 billion, respectively, in 2020.[6]

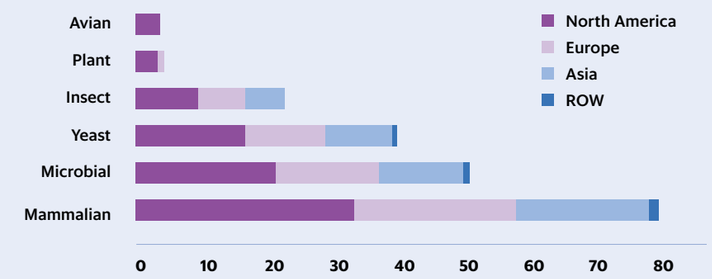


Figure 2
Distribution of expression platforms across global regions among the profiled CDMOs.

Plant-based expression systems generally do not require the development and optimization of cell lines for successful large-scale manufacturing.[11] Scale-up issues are also non-existent, as producing larger quantities simply requires growing more plants. Concerns over contamination by adventitious agents are dramatically reduced, because no animal-derived materials are used in the process, and plants cannot be contaminated by human pathogens.

iBio Inc. reports that with its technology, the cost of goods for mAb production can potentially be reduced by 50% compared with that for a mAb produced in a CHO system.[11] In addition, the company says construction of its facility costs <10% of what it costs to build a typical CHO facility.

Insect Cell-Based Expression

Insect-baculovirus systems offer high expression levels similar to those of bacterial fermentation systems yet afford proteins with posttranslational modifications, as well as protein folding, similar to those obtained from mammalian cell expression.[12] Like plants, they are also non-pathogenic to mammals. In addition, the cells can accommodate large or multiple genes, and the cells are well suited to growth under suspension cell culture conditions. The proteins are readily isolated from the insect cells via chromatography.

Furthermore, insect cells are suitable for the production of viruses and viral vectors used in the production of viral vaccines and gene therapies.[13] P

REFERENCES

1. Challener, Cynthia. "Platform Technologies Improve Protein Expression." *BioPharm International.* 30(11): 20–22 (2017).
2. Rios, Maribel. "A Decade of Microbial Fermentation." *Bioprocess International.* 1 Jun. 2012. Web.
3. Rader, Ronald A. and Eric S. Langer. "Biopharma Manufacturing Markets." *Contract Pharma*. 8 May 2018. Web.
4. *Large & Small-Scale Bioprocessing (Biopharmaceutical Manufacturing) Market Analysis By Workflow (Downstream, Upstream, Fermentation), By Product, By Use-type (Multi-use, Single-use), By Mode (In-house, Outsourced), And Segment Forecasts, 2018 – 2025.* Rep. Grand View Research. Dec. 2017. Web.
5. Bumelis, Vladas A. "The Renaissance of Microbial Fermentation." *Pharma's Almanac*. 24 May 2019.
6. Dewan, Shalini Shahani. "Global Markets and Manufacturing Technologies for Protein Drugs." *BCC Research*. 2016. Web.
7. *Biopharmaceutical Fermentation Systems Market to be Worth US$ 17.8 Billion by 2026, Says TMR.* Transparency Market Research. 19 Jul. 2018. Web.
8. Challener, Cynthia. "The Search for Next-Gen Expression Systems." *Pharmaceutical Technology.* 42:29–31 (2018).
9. Stanton, Dan. "Bioprocessing survey report: Is the CHO CHO train slowing down?" *BioPharma Reporter* . 3 Nov. 2017. Web.
10. Ranjane, Abhijit. "Cell Free Protein Expression Market Leading Players Analysis and Forecast Up To 2025." *Business Herald*. 5 Apr. 2019. Web.
11. Ryan, Terence E. "Plant-based Protein Expression for Rapid, Green Bioprocessing." *Pharma's Almanac.* 24 May 2019.
12. "Baculovirus with Benefits: Expression System Advantages." Oxford Expression Technologies, 14 Aug. 2014. Web.
13. Lubelski, Jacek, Wim Hermens, and Harald Petry. "Insect Cell-Based Recombinant Adeno-Associated Virus Production: Molecular Process Optimization." *BioProcess Journal*. Fall 2014. Web.

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Kshitij (TJ) has been a part of Nice Insight since 2014. TJ's role involves research design and operations, developing and maintaining syndicated studies, business intelligence data analysis, content development and article writing on the latest developments in the biopharmaceutical industry. Prior to market research, TJ spent time in academia research working on a broad range of subject matter, including pharmacoeconomics, drug delivery and genetics. TJ holds a masters of biotechnology degree from the University of Pennsylvania.

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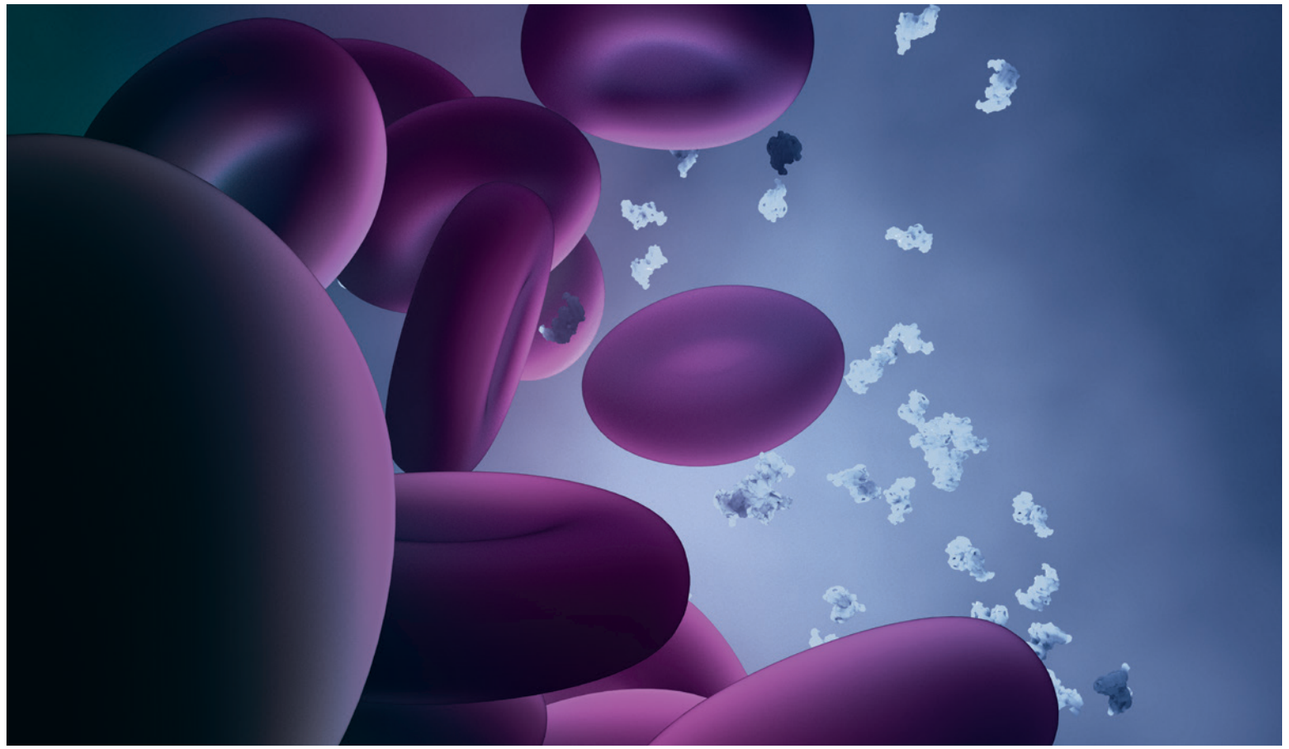
SUSTAINABLE PRODUCTION OF PLASMA PROTEINS

BY **NICK GREEN,** EVOLVE BIOLOGICS



Current methods for the extraction of plasma proteins have several limitations. Evolve Biologics is advancing a proprietary expanded bed chromatography solution that provides higher yields of high-quality proteins in a simpler, safer and more sustainable process that can be cost-effective at multiple scales.

IMPORTANCE OF PLASMA PROTEINS

Many of the thousands of proteins found within human blood plasma have therapeutic value in treating a range of diseases, including immune deficiencies, autoimmune and neurological disorders and hemophilia, many of which are considered rare diseases.

The three most important plasma proteins from a market perspective include albumin, immunoglobulins (IgGs) and plasma-derived factor VIII. In 2017, immunoglobulin captured the leading position with more than 45% market share.[1] Other plasma proteins of note include α_1-antitrypsin (AAT), hyperimmune immunoglobulins, coagulation factors, fibrogammin and c1 esterase inhibitors (C1 INH).

The global market for therapeutic plasma proteins has grown significantly, increasing from approximately $5.8 billion in 2003 to over $21 billion in 2016 (excluding recombinant products).[2] This strong growth has been driven in particular by greater diagnosis and expanded use in patients requiring treatments such as IgG, which includes the more recent introduction of subcutaneous IgG (SCIG), in addition to C1 INH and AAT.[3] The global plasma market is expected to continue to grow in value terms to more than $31 billion at a CAGR of more than 7.5% through 2024,[4]

This future growth will be driven largely by the increasing demand for IgG for the treatment of patients for both new and existing indications, including primary immunodeficiency disorders (PIDs), in addition to continued geographic expansion.[3] The global immunoglobulins market in 2016 was valued at over $10 billion for 2016, making up almost 50% of the global plasma market. The U.S. IgG market alone which accounts for over 40% of the global market in volume terms, is predicted to expand rapidly, growing at approximately 8% over the next five years.[5]

Demand for albumin is also expected to rise, owing to improved diagnosis of hypoalbuminemia caused by liver cirrhosis and hepatitis B, potential new indications and growing use in China,[1] as well increasing use as a drug formulation agent, sealant in surgeries, vaccine ingredient and coating for medical devices.

HISTORY OF PLASMA PROTEIN PRODUCTION

Plasma proteins have traditionally been isolated from plasma using cold ethanol fractionation. Acid, alcohol and salts are employed at cold temperatures to precipitate proteins into fractions containing many proteins in their non-native forms. Specific proteins are purified by resolubilizing the precipitated fractions. The method was initially developed in the 1940s by Harvard University professor Edwin Cohn to provide albumin for treatment of soldiers injured during World War II.

LIMITATIONS OF COLD FRACTIONATION

Cold ethanol fractionation was developed to extract albumin, not the 15–20 other proteins that have since been approved as therapeutics. Many of these other proteins are not stable in ethanol. In addition, ethanol is flammable and its storage, handling and use require extensive protective measures. Because the process is run at low temperature, it consumes significant energy and produces greenhouse gas emissions. As a result, cold fractionation presents significant safety and environmental issues.

DEVELOPING MORE SUSTAINABLE TECHNOLOGY

As Therapure Biopharma's plasma products and technology division, Evolve Biologics is developing an alternative plasma protein production technique that eliminates the need for cold ethanol fractionation.

The company has been developing its proprietary PlasmaCap EBA® technology since 2012. PlasmaCap EBA uses proprietary affinity adsorbents in expanded bed adsorption (EBA) chromatography to capture plasma proteins directly from plasma without the use of precipitating solvents. The plasma is passed through a series of chromatography columns arranged in a particular sequence and designed to capture the proteins in their native form with a higher degree of efficiency and selectivity.

Each column contains dense, adsorbent, tungsten carbide beads coated with agarose modified with ligands designed to bind to a specific protein. The expanded bed columns provide more space between the beads than in traditional packed-bed chromatography, allowing the viscous plasma to flow through more quickly and without clogging.

A fluidizer rotates gently as the plasma passes through the column, generating optimal conditions for binding of the target protein and allowing the remaining proteins to flow through without any structural alterations. This design enables the extraction of more valuable proteins from each liter of donor plasma compared with legacy techniques.

SCALABILITY FOR MODULAR MANUFACTURING

The expanded bed chromatography approach to plasma protein purification is also readily scalable. Due to its simplicity, it can be easily scaled up – and down. As a result, the technology enables economic operation at scales not typically employed by today's cold ethanol fractionators.

With our PlasmaCap EBA technology, it is possible to construct small, modular facilities in countries and regions that collect smaller quantities of plasma (150,000–200,000 L annually). It is thought that dosing populations with indigenous proteins may lead to improved therapies, particularly for plasma proteins intended to treat immune diseases. The composition and quantity of IgG in plasma has been shown to vary greatly with the local environment and exposure to different infective agents. Domestic production of plasma proteins would also reduce the dependence of many countries on U.S.-derived plasma products.

POTENTIAL FOR MANY NEW PLASMA PROTEIN PRODUCTS

Although no new plasma proteins have been introduced in the major markets in last decade[3], there are a number of products in clinical development, including plasminogen and reconstituted HDL.[2] Several companies are also at the early stages of investigating the potential therapeutic effects of novel proteins not yet isolated from plasma. In addition, existing plasma proteins are under investigation for the treatment of expanded indications, such as IVIG for neurological diseases, AAT for type 1 diabetes, fibrinogen for aortic aneurysm surgery and C1 INH for antibody-mediated rejection in organ transplantation.[3]

AMBITIOUS GOALS FOR EVOLVE BIOLOGICS

Evolve has a three-pronged approach to the development and commercialization of human plasma proteins using our PlasmaCap EBA technology. Our first priority is commercialization of IVIG and albumin. IVIG is in the advanced stages of regulatory approval in Canada and the United States, having completed its phase III trial for PID in adults and with an ongoing phase III trial in pediatrics with regulatory submission expected in 2021. Regulatory submission is also expected for albumin in 2021. AAT is at the early development stage.

Once we have established a commercial facility for the manufacture of IVIG and albumin, growth will be driven by volume expansion, adding additional capacity to process larger volumes of plasma, complimented by geographic expansion utilizing a modular approach for countries that collect plasma domestically at volumes not generally addressed by those employing cold ethanol fractionation.

We also believe that, having already innovated on the process for capturing plasma proteins, we now have the opportunity and the benefit of many years of hindsight to work with healthcare providers, patients and other market partners to innovate further to improve the way that these valuable plasma products are delivered and ultimately administered to the patient.

Finally, we plan on utilizing PlasmaCap EBA to mine the human proteome contained in our plasma for other proteins and build a robust pipeline. Evolve believes that our PlasmaCap EBA technology will provide enormous benefit to the industry and patients alike, not only by advancing the quality and reliable supply of plasma proteins, but also by enabling the cost-effective production of novel proteins present in small concentrations in human plasma.

Plasma is a scarce and valuable resource, one that in many countries is donated altruistically by their citizens. For me, this means that we have a moral obligation to provide the maximum therapeutic benefit we can from such a gift. In my opinion, a major obstacle to innovation is a focus on the solution as opposed to the problem. I have a great deal of admiration for professor Cohn and the process he developed –- without a doubt, this was an outstanding solution for the problem at hand. However, I find it difficult to believe that anyone would argue that the challenge we face to today is the same one faced by professor Cohn more than 70 years ago. It is clear to most people I meet that the challenge facing the industry is no longer one focused on how to extract and purify a single protein (Albumin) but how to extract, purify and maintain the integrity of multiple proteins from a single liter of plasma. If we are to truly innovate, one must avoid becoming wedded to the solution and instead fall in love with the problem. At Evolve, we are seeking the best solution to a new problem, starting from a position with nothing invested and no allegiance to any approach (or solution). Today, we believe that our approach using the PlasmaCap technology is the best solution to this new problem, but as we invest and become committed to the solution we have developed, we must and do ensure that our scientists continue to challenge their own solution on daily basis in search of improvements, lest we too fall in love with the solution and not the problem. P

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Evolve Biologics Inc./Therapure Biopharma Inc.

Nick currently serves as President & CEO of both Therapure Biopharma Inc. and its wholly owned subsidiary Evolve Biologics Inc. Nick previously served in senior executive roles for several contract manufacturing organizations and life sciences companies, including Managing Director of Nipa Laboratories Ltd, Head of the Life Sciences Division in the U.S.A, President and CEO of Rhodia Pharma Solutions and President of Codexis Pharma Division. Nick is also a current Board Member at Induce Biologics Inc. and Red Rock Regeneration. Nick holds a BSc (Hons) in chemistry from Queen Mary University of London and an MBA from the University of Huddersfield in the UK.

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REFERENCES

1. *Plasma Protein Therapeutic Market Size, Share & Trends Analysis Report By Product (Albumin, Immunoglobulin, Factor VIII), By Application (Hemophilia, PID, ITP), By Region, And Segment Forecasts, 2018 – 2025*. Rep. Grand View Research. Dec. 2018. Web.
2. *MRB: The Worldwide Plasma Proteins Market 2016* (Published Dec 2017).
3. MRB Data: Worldwide Report 2017 "The Plasma Industry: A Look to the Future." *Marketing Research Bureau*. n.d. Web.
4. "Plasma Protein Therapeutics Market to Rise US$31 Billion By 2024." *Market Watch*. 30 Jan. 2019. Web.
5. *MRB: IgG 2018-2025 US Forecast Data Report* (Published 2019).

Michael Scholl
Chief Executive Officer
Leukocare AG

Stabilizing and Protecting Biologic Formulations

Stabilization and protection of biomolecules enables development of formulations that exhibit optimal product characteristics, increasing shelf life, reducing the cold-chain burden, enabling patient-centric routes of administration and reducing manufacturing bottlenecks.

Growing Need for Stabilization and Protection

All drug products and medical devices containing biologic drug substances – from traditional proteins and antibodies to advanced therapies – benefit when the stability of the biomolecule is enhanced.

Increasing the stability of the API enables product optimization with respect to storage and ease of use. Biopharmaceuticals that can be stored at room temperature do not require cold-chain management. Formulations that do not require lyophilization are easier to administer. Higher-concentration parenteral drugs are often viscous, making them difficult to deliver subcutaneously and subject to API aggregation. Avoiding these issues facilitates, alternatives to IV administration and extension of product shelf life.

LEUKOCARE's SPS® Technologies

Our proprietary Stabilizing and Protecting Solutions (SPS®) formulation technology platform provides next-generation formulation technologies to increase the stability and protection of therapeutic proteins in dry and liquid formulations. The platform comprises two elements: a database of ~100 excipients approved for use in pharmaceutical formulations and a rational software- and algorithm-based approach to excipient selection.

The SPS® technologies allow consideration of the specific characteristics of the biologic and the target product profile. Unlike standard formulations that rely on 3–4 excipients, our algorithms allow us to evaluate the full design space with a far higher number of potentially applicable excipients for a given biomolecule type, resulting in a higher probability of success.

The optimum combination (generally in the range of 5–8 excipients) is determined after considering factors such as whether the product should be liquid or dry, the relevant physical and chemical stresses and the major degradation pathways. The performance of proposed stabilizing formulations is then evaluated using appropriate analytical methods specifically developed for their characterization.

Many Stability Issues Addressed

Increased stability of the biologic drug substance leads to preservation of functionality and extended shelf life. The entire formula is also better protected during processing and/or terminal sterilization with β- or γ-irradiation or EtO if required. This is particularly relevant in the case of medical devices functionalized with biological compounds. In addition to increased drug product quality, SPS® technologies typically afford cost savings and enable reduced development times. They also allow the development of new, highly differentiated products that can extend the product life cycle and enable entry into new market segments.

Clients benefit from our standardized technology platform, which is readily adaptable for a range of products and formulations. Using this standardized platform allows a faster and more reliable approach, leading to shorter development times and a higher probability of success.

The SPS® platform has been applied to traditional and fusion proteins; antibodies and bispecifics; biosimilars; non-enveloped and enveloped RNA and DNA viruses of many kinds, including live viral vectors; and biofunctionalized medical devices.

Bringing SPS® Benefits through Strategic Alliances

Through a strategic alliance with Rentschler Biopharma, LEUKOCARE serves as the dedicated formulation development partner for Rentschler's clients. Advanced formulation development activities are integrated into process development efforts from the start, so LEUKOCARE has access to information regarding the biologic of interest in possible target product profiles.

LEUKOCARE provides the downstream processing group at Rentschler with recommendations regarding buffer development and other aspects that might impact the purification process. Rentschler's clients thus benefit from formulations with higher stability in less time.

While LEUKOCARE is a pure formulation developer with a strong background in protein and virus analytics, we recognize the positive impact that our formulation knowledge and expertise have and are working to identify opportunities to leverage this experience in other ways.

Two Focus Areas

LEUKOCARE is currently focusing on two core businesses – biopharmaceuticals and viral vectors, including live, infectious viruses used to transfect DNA or RNA into targeted cells. Newer biologics, such as bispecific antibodies and fusion proteins (e.g., an enzyme coupled to an Fc receptor), are even more likely to be unstable than traditional engineered proteins. All of these biologic drug substances present challenges that can be addressed using our SPS® platform. We also have extensive experience with the stabilization of live viruses and can provide solutions that enable stabilization for up to two years in liquid formulations. P

Ahmad Ghoniem
Business Development Manager, North America
tesa Labtec GmbH

Expanding Access to Oral Thin Film Technology

German CDMO tesa Labtec brings its years of experience in pharmaceutical thin film technology closer to clients in North America.

Rapid Expansion of the Oral Thin-Film Market

Thin-film drug delivery technologies enable the development of patient-centric drug formulations. For patients that have trouble swallowing, oral thin-film (OTF) drug delivery is an attractive alternative to traditional tablets, capsules and even syrups.

The OTF market is still in the early growth phase. As more formulators discover the benefits of the technology and regulatory authorities continue to expand requirements for patient centricity, the demand for OTF delivery solutions will increase.

Overcoming Formulation and Manufacturing Challenges

There are fundamental challenges in the development and manufacturing of OTF products that can only be overcome with extensive experience with this complex technology. tesa Labtec has focused on the development and production of film-based dosage forms for more than 25 years and has the expertise needed to provide solutions to our customers for even the most difficult APIs.

To overcome drug loading challenges, we have developed a proprietary approach that enables the loading of up to 150 mg of API on films small enough for oral delivery. We have also overcome issues with insufficient mucoadhesion and offer films that provide long-lasting formulations.

With respect to manufacturing, it is often necessary to achieve a balance between product performance and processability at commercial scale, which requires deep knowledge of both the technology and formulation, and are both areas of expertise at tesa Labtec. By running experiments at lab scale and in our pilot plant, we can identify optimal formulations and processing parameters that afford economic processes and high-performing products.

tesa Labtec has received approval from regulatory authorities in both the United States and Europe. We have expertise in managing the complexities of the European supply chain, from dealing with large numbers of SKUs to communicating in multiple languages.

Range of Proprietary Technologies

The dosage forms developed by tesa Labtec have been used in dietary supplements, medical devices and drug products. Our orodispersible Rapidfilm® technology is designed to meet the needs of patient groups that have difficulty swallowing by combining the convenience of a liquid with the stability and dosing accuracy of a tablet. Once placed on the tongue, Rapidfilm dissolves within seconds, and the API is swallowed with the saliva. A range of formulation alternatives is available depending on the specific target product profile, including fast-onset and slow-release forms and taste-masking solutions. Reformulation of existing oral products can typically be achieved using the same dose, providing a means for extending product life cycles.

tesa Labtec's Mucofilm® technology offers topical or transmucosal delivery. This mucoadhesive film is applied to the mucosa of the oral cavity, where it cannot be felt by the patient. The dosing of Mucofilm products can be as short as one minute or up to several hours– whatever is required for the specific product.

Mucofilm can be used to deliver an API unidirectionally for local treatment or bi-directionally to facilitate transmucosal delivery for systemic treatment. Transmucosal delivery avoids issues with first-pass metabolism and is therefore ideal for APIs and APIs that suffer from poor bioavailability. These OTFs can therefore often be formulated with lower doses.

tesa Labtec is a full-service CDMO for transdermal therapeutic systems and oral films, offering end-to-end solutions for all stages of drug development, including portfolio screening, development strategies, feasibility assessments, formulation development and clinical and commercial manufacturing and packaging.

One-Stop Shop

tesa Labtec is a full-service CDMO for transdermal therapeutic systems and oral films, offering end-to-end solutions for all stages of drug development, including portfolio screening, development strategies, feasibility assessments, formulation development and clinical and commercial manufacturing and packaging. We provide all of the regulatory support and analytical activities and testing required, including state-of-the-art ex vivo permeation studies.

As a wholly owned subsidiary of tesa SE, one of the world's leading manufacturers of technical adhesive tapes and self-adhesive systems, tesa Labtec has access to deep resources while maintaining the flexibility, agility and close collaborations associated with smaller firms. P

Erica Sosnowski
President
Sosna + Co.

Strategizing for International Business Development

Emerging pharma/biotech companies, having achieved their first two- or five-year plan milestones, often look to expand internationally. However, before making any moves, company CEOs should do their research and consult with an expert.

Optimizing Growth through Globalization

For emerging US-based pharma and biotech companies that have reached their initial milestones, business growth can best be achieved by expanding internationally. Emerging markets are particularly attractive, because they represent more than half of the world's population and a significant percentage of the global pharma market.

Start with a Market of Interest

While many companies are eager to establish a global footprint, the first step in a successful international strategy is to establish a strong presence in an initial – typically, domestic – market. Success in an initial market allows companies to overcome barriers to entry in secondary markets. Establishing internal processes, building an expert team, and generating cash flow in an initial market will increase the likelihood of a successful expansion abroad.

Many Ways to Expand

A successful global expansion strategy must focus on the competitive advantages of the company and the value proposition of the products or services in foreign markets.

There are numerous mechanisms for global expansion. Some companies choose to build brick-and-mortar edifices in a new market, while others choose to establish partnerships with domestic firms. The correct approach depends on the risk profile of the biopharma company, the regulatory environment in markets of interest, and the competitive landscape within the product category.

Four Key Considerations

When developing an appropriate globalization strategy, there are four key concepts to consider:

- Culture
- Quality and regulatory requirements
- Government policies
- The business plan

Regardless of whether you are a pharmaceutical company, biotech firm, contract research organization, contract development and manufacturing organization or testing lab – and whether you are partnering or going it alone – the results will depend on how you manage these four factors. Appropriate planning and proper execution with the right people drive success.

Understand the Culture

It is essential – but often undervalued – to understand the cultures of the markets you are considering. Cultural differences impact buying habits and, in the case of pharmaceuticals, prescription volume. Time and resources must be invested to ensure that the target market is appropriate for your products or services.

For American firms, Western European markets tend to offer the easiest entry, as there are many cultural similarities. Asian countries, on the other hand, present an entirely different cultural landscape. We recommend leveraging experienced professionals to navigate cultural complexities in foreign markets. Having a key influencer on the ground with a detailed implementation plan – regardless of the mechanism used for expansion – is essential.

Be Familiar with Regulatory Requirements

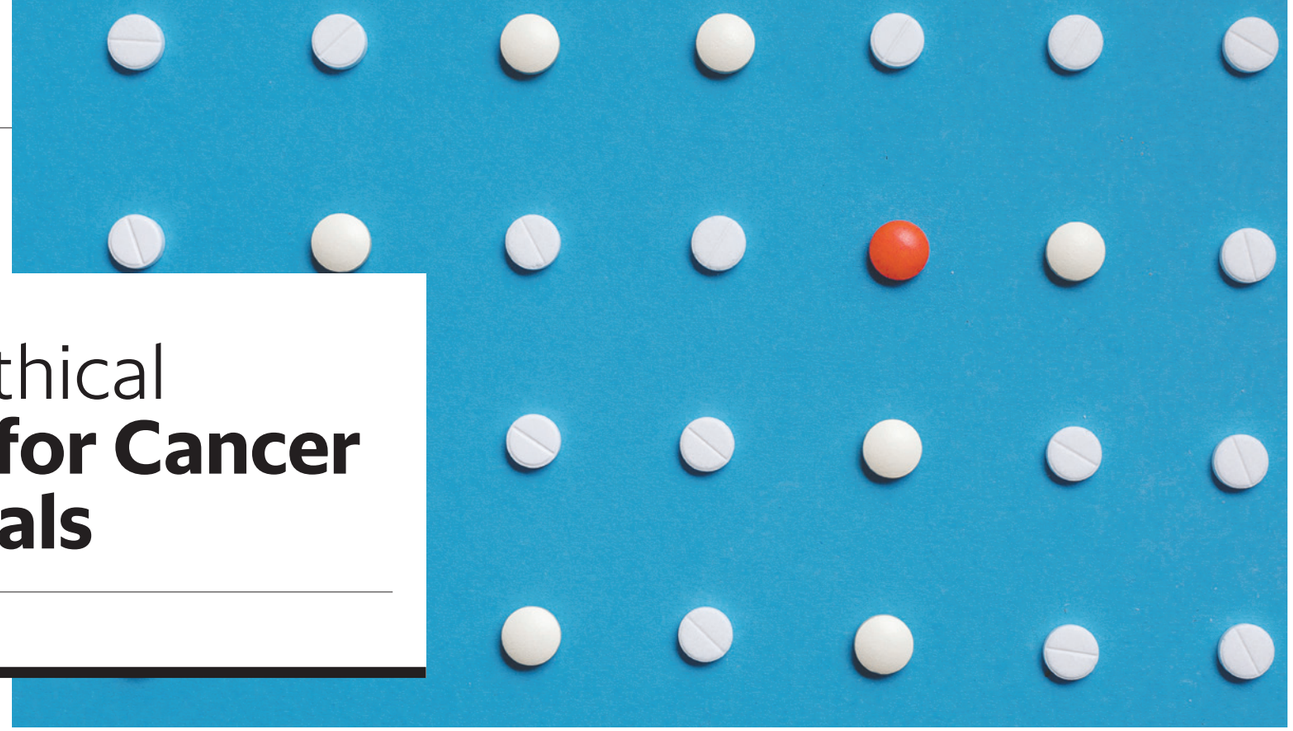
Every region/country has its own regulatory agencies and compliance requirements. There has been some degree of harmonization among U.S., European, and Japanese pharma regulations, and while many emerging markets are rapidly closing the gap, important differences remain. It is necessary to understand, in detail, the regulatory pathway of the target market. The most effective way to achieve this goal is to invest in human resources – consultants or external hires who have appropriate experience early in the process.

Build Government Relationships

Government policy can heavily influence the operations of foreign companies. It is necessary to understand those policies that impact foreign companies, especially those that protect the domestic biopharma industry to determine the best strategy for expansion. In addition to government finance programs, exchange rates, and permitting issues, there may also be standards that promote hiring domestically and discourage expatriates from establishing businesses. Building robust relationships with government representatives should begin at the earliest possible stage.

Have a Solid Business Foundation

If the proper cultural considerations are made, the regulatory pathway is understood, and government policies are supportive, the target market may still not be suitable for your product or service without a well-devised business plan. An understanding of market size, growth rate, penetration rate, intellectual property and trademark protection establishes the foundation of the business plan. There must be a clear sales benefit before making your international move. P



Updating Ethical Guidelines **for Cancer Clinical Trials**

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

Since the beginning of the modern era of clinical trials, double-blinded, placebo-controlled randomized controlled trials (RCTs) have represented the gold standard paradigm for the evaluation of the safety and efficacy of drugs. RCTs are powerful tools to reduce prominent sources of bias in clinical trials by randomly assigning participants to distinct groups; these groups each receive different treatments, which are compared with a measured response.

Blinding and Placebos in Clinical Trials

The simple model of an RCT involves an experimental group, given the novel treatment being evaluated, and a control group. There are a variety of ways in which the experiment–control relationship can be structured: comparing the new drug with a placebo (an inert substance with no pharmacologic activity), comparing it with the current standard of care, or comparing the new drug plus the current standard of care with the standard of care alone, among others.

Many RCTs are blinded, a practice in which information that may influence the participants and clinical researchers is withheld until after the completion of the trial. Blinding trials eliminate a range of sources of experimental bias, including the placebo effect, the observer effect and confirmation bias. Many trials require that study participants, caregivers, and researchers assessing clinical outcomes not know which intervention was given to each patient until after the outcome assessment or beyond.

As effective as blinded, placebo-controlled RCTs are in reducing experimental bias, they are not intrinsically ethical, and the decision to pursue this trial design must be made under deep consideration of factors including the disease indication, the acuteness of the medical need, relevant disease progression timelines, toxicity profiles and the effectiveness of existing treatments. By definition, blinded, placebo-controlled RCTs are only justified in situations where there is clinical equipoise -- legitimate uncertainty within the medical and research communities about the relative benefits of treatments. For many clinical trials exploring cancer treatments, this criterion is not met, and ethical treatment of trial participants requires conducting the trials using other models.

To help sponsor pharma and biopharma companies, contract research organizations (CROs), clinical logistics organizations (CLOs) and academic researchers to make the best ethical decisions in the design of clinical trials for development programs for small molecule or biologic drugs to treat hematological malignancies and oncological diseases, the U.S. Food and Drug Administration (FDA) issued a new guidance titled "Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products: Guidance for Industry" in August 2019.[1] As is typical for the FDA's guidance documents, the recommendations are nonbinding and are not legally enforceable, but rather depict that agency's current thinking about the topic and represent its assessment of overall best practices for these trials.

Ethical Issues with Placebos

In the guidance document, the FDA describe situations in which blinding and placebo controls are either impossible to effectively maintain in cancer clinical trials or inappropriate to the goal of providing ethically informed treatment to clinical trials participants.

Foremost among these considerations is the inappropriateness of using placebo controls for hematologic malignancies or oncological diseases, for which there is a standard effective therapy. As there is no ethnical rationalization for treating cancer patients with placebos and hence depriving the control group of the available effective treatment, active control trials must be conducted. Depending upon the nature of the experimental treatment, this could be an open-label trial comparing the experimental treatment with a standard therapy, or an add-on trial in which both groups receive the standard of care, with the experimental group also receiving the new therapy and the control group adding a placebo.

Ethical Issues with Blinding

Another source of ethical complications in cancer clinical trials involves the toxicity of the treatments and the potential for disease progression over the course of the trial. Because of the considerable toxicity profiles associated with many anticancer agents, true blinding may not be possible, because investigators may be able to infer the treatment a given patient received based on the adverse effects observed. Beyond this pragmatic concern, blinding in such cases may interfere with the ability to treat the patients appropriately. Patients may experience adverse effects from the investigational treatment that require therapeutic management, and those management decisions need to be definitively informed by specific knowledge of the treatment received by each patient, which requires unblinding, at least concerning the investigators and clinical evaluators.

Similarly, in cases where patients experience progression of the disease, maintaining blinding could prevent patients from receiving the appropriate subsequent therapy at the most appropriate time, preventing the patient from promptly receiving an approved therapy (if available) or enrolling in another clinical trial. Maintaining blinding of a clinical trial beyond the point of disease progression would prevent clinicians from making truly informed decisions about further treatment, to the clear disadvantage of the enrolled patients, and so blinding, if applied at all, should terminate at an appropriate time.

The FDA's Recommendations

In light of the above, the FDA makes a few clear recommendations for the use of placebos and blinding in clinical trials of cancer treatments. First, the agency suggests that, owing to the ethical issues discussed above, placebo-controlled clinical trial designs for cancer treatments are only appropriate in selected circumstances -- when the current standard of care is surveillance only or when the trial implements an add-on design.

Second, the FDA does not require or recommend patient-level blinding at the time of disease recurrence or progression, and explicitly recommends unblinding of the patient and investigator when disease recurrence or progression (objectively measured) occurs, unless there is no available alternative treatment. The agency further recommends patient- and investigator-level unblinding when a patient experiences an adverse effect likely related to the toxicity profile of the investigational treatment.

Finally, the FDA strongly suggests that sponsors provide a detailed plan in the relevant protocol for how blinding is to be maintained and the circumstances and timeline for unblinding, as well as to provide detailed justification for any decisions or elements of the trial design that are not in line with the agency's recommendations. P

REFERENCE

1. *Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products: Guidance for Industry.* U.S. Food and Drug Administration. Aug. 2019. Web.

ABOUT THE AUTHOR

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David is Scientific Editorial Director for That's Nice and the Pharma's Almanac content enterprise, responsible for directing and generating industry, scientific and research-based content, including client-owned strategic content. Before joining That's Nice, David served as a scientific editor for the multidisciplinary scientific journal Annals of the New York Academy of Sciences. He received a B.A. in Biology from New York University and a Ph.D. in Genetics and Development from Columbia University.

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Facilitating Pharmaceutical and Biotech Facility Acquisitions

With its extensive industry network, PharmaBioSource can connect pharma and biotech facility buyers with hidden opportunities.

More than a Life Science Advisory Firm

PharmaBioSource and PharmaBioSource Realty are committed to leveraging our broad experience in the Life Sciences sector to help our clients streamline their business activities. We provide a thorough and comprehensive suite of brokerage and pharma advisory services to help companies navigate any corporate need, from locating, acquiring and divesting prime manufacturing facilities and products to identifying M&A opportunities and investment risks and optimizing the supply chain. We have managed over 100 transactions on four continents that have included well over 15 million square feet of life sciences facilities and product and M&A deals worth over $5 billion.

Leveraging an Extensive Network

We recognize that pharmaceutical and biotech real estate transactions can be complex and time consuming. For companies looking to locate a future manufacturing facility to meet growing capacity needs, the team of Life Sciences consultants and licensed real estate brokers at PharmaBioSource leverages our extensive network of global connections to find the perfect fit. With our expert real estate and technical knowledge – as well as our in-depth industry experience – we help our clients navigate the intricacies of managing a Life Sciences real estate or M&A deal from start to finish with a smoother process, reduced timelines and less stress.

At PharmaBioSource, we have access to comprehensive databases of existing facilities and their specific capabilities; this means that we know which are currently available and which could be potential targets for transactions. Many times, the latter options are only uncovered through our network connections and are not disclosed industry-wide. As a result, we identify hidden opportunities for our clients that they would not find on their own. PharmaBioSource also provides valuation, benchmarking and negotiation support to ensure that our clients realize the best possible deals.

Three-Phase Process

The entire process occurs in three broad phases. During the target identification phase, many potential facilities (sometimes as many as 50–100) that generally fit the client's requirements are selected for further evaluation. Target profiling is then performed on those sites (usually about 10) that are determined to have the best fit. Target engagement then occurs with the few sites that appear most suitable to the client's needs. The first two phases, target engagement, due diligence and negotiations each take approximately three months, with the whole process typically taking 9–12 months from target identification to a successful transaction conclusion, though some transactions can happen much more quickly if everything aligns.

Finding the Right Facility for Flamma S.p.A.

Flamma S.p.A.'s recent acquisition of a small molecule active pharmaceutical ingredient (API) development and manufacturing site from Teva Pharmaceuticals is a prime example of the real estate transactions PharmaBioSource Realty routinely facilitates. Flamma is an Italian CDMO with many U.S. customers. The company was seeking a U.S. facility with R&D, kilo and small-scale production capabilities to better serve these clients. The company had been looking for a new location for over one year, but had not had success at finding the right site.

PharmaBioSource was aware of Flamma's desire for a U.S. site and, in March 2019, discovered the availability of Teva's leased 40,000-ft² Chemical Synthesis Center located just outside of Philadelphia. The site includes R&D laboratories, kilo lab suites and a cGMP pilot plant for small-scale clinical and commercial manufacture of small molecule APIs – exactly what Flamma was looking for.

More than a Facility Finder

In addition to finding the Teva site for Flamma, PharmaBioSource Realty provided support throughout the due diligence and negotiation stages of the deal, which was signed July 1, 2019, acting as a mediator and identifying a compromise that satisfied Flamma, Teva and the landlord.

Because Flamma's presence in the United States before the acquisition entailed an office in Boston with just one employee, PharmaBioSource also provided start-up and logistics services to assist the company in occupying the Pennsylvania site. The security system required reactivation, IT services needed to be established, an environmental consultant had to be brought on board to handle permitting issues and financial incentives were solicited from the local and state economic development agencies.

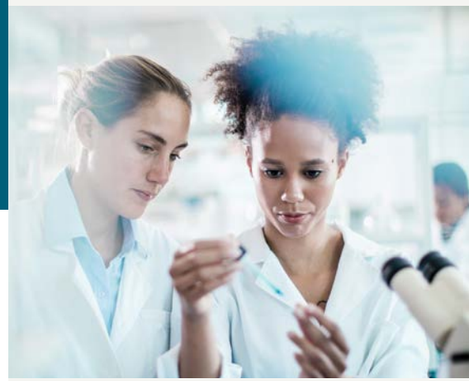
These post-transactional services and more, such as management of renovation projects, can all be provided by PharmaBioSource to companies following a real estate purchase if they have limited resources and require additional support. P

BioVectra Inc. to be sold to H.I.G. Capital

On September 10, 2019, Mallinckrodt plc, a global biopharmaceutical company, announced it has entered into a definitive agreement to sell its wholly owned subsidiary BioVectra Inc. to an affiliate of H.I.G. Capital, a leading global private equity investment firm, for approximately $250 million. This total includes $175 million of fixed consideration, comprised of an upfront payment of $135 million and a long-term note for $40 million, and contingent payments of up to $75 million, enabling Mallinckrodt to capture future BioVectra growth potential. The transaction is expected to close in the fourth quarter of 2019, subject to customary closing conditions.

> **We are excited to support BioVectra's exceptional leadership and highly dedicated employees," said Mike Gallagher, Managing Director at H.I.G. Capital.** "BioVectra demonstrates a tremendous ability to generate robust organic growth and utilizes a broad set of technical capabilities to deliver outstanding service and quality," he continued. "They are completing major capital expenditure programs to significantly expand capacity and the company is well positioned to capitalize on growing demand for their services.

BioVectra



About BioVectra

BioVectra is a CDMO that serves global pharmaceutical and biotech companies with full-service cGMP outsourcing solutions for intermediates and active pharmaceutical ingredients. An innovative and reliable service partner with a strong regulatory history, BioVectra has over 45 years of experience specializing in:

+ cGMP microbial fermentation
+ Complex chemistry – high-potency APIs
+ Biologics
+ Formulation development

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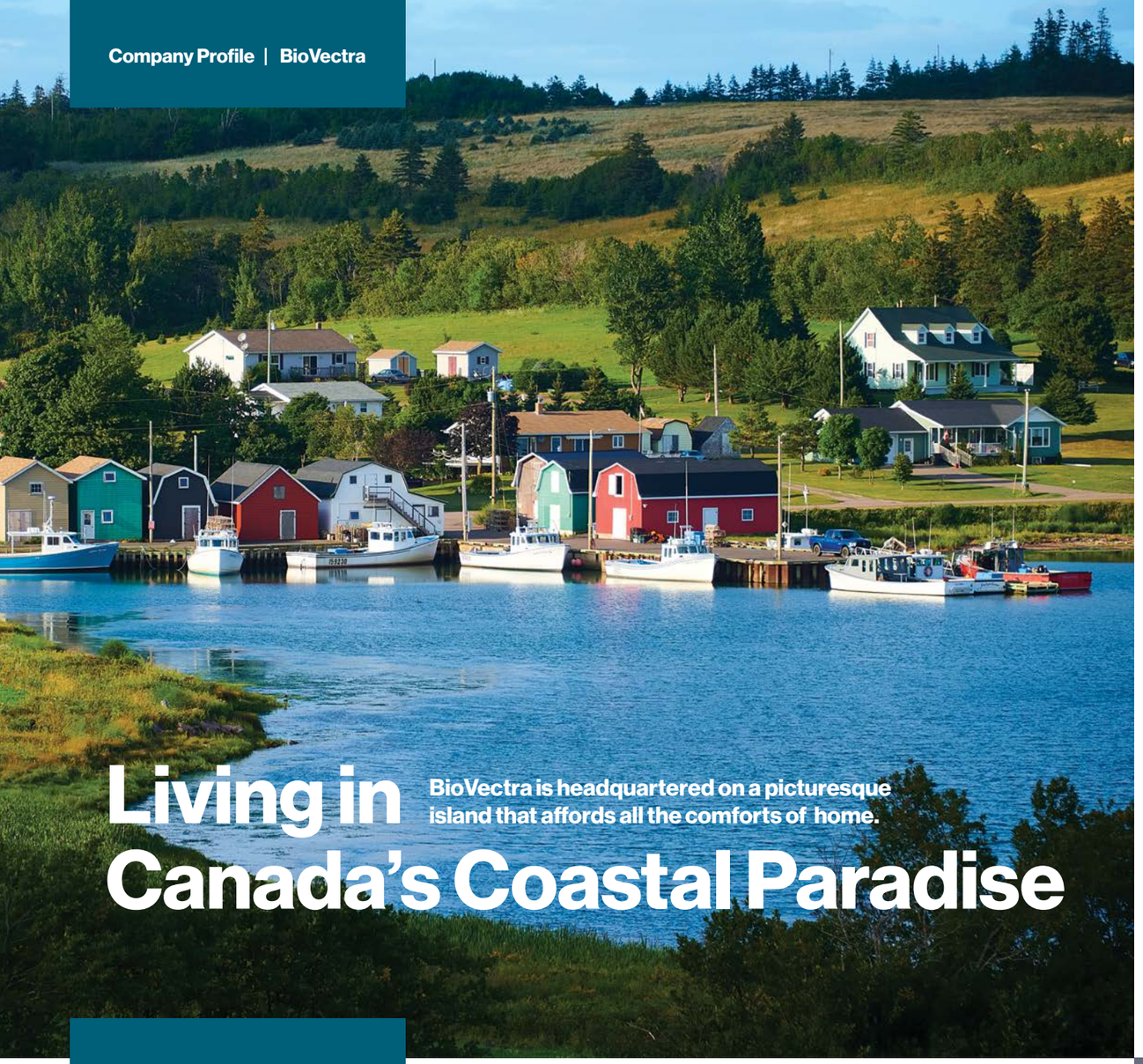

Living in Canada's Coastal Paradise

BioVectra is headquartered on a picturesque island that affords all the comforts of home.

Canada's Atlantic Region

BioVectra has two locations in this region, one in Charlottetown, Prince Edward Island, and one in Windsor, Nova Scotia. They are a full-service contract development and manufacturing organization (CDMO) that specializes in microbial fermentation, complex chemistry, high potency APIs, biologics, process and analytical development and drug development, serving pharmaceutical and biotech companies with cGMP outsourcing solutions for intermediates and active pharmaceutical ingredients (APIs).

Charlottetown Welcomes You!

JOIN OUR FAMILY

THE ANNUAL GRAN FONDO RACE...

takes over the island as cyclists enjoy the ride through an iconic landscape.

FRESH SEAFOOD

You can't miss fresh seafood and a cold beer at Richard's, a beloved local eatery.

Prince Edward Island is famous for its access to miles of beach.

These photographs depict some of the natural beauty and idyllic charm of Prince Edward Island and illustrate what makes Prince Edward Island such an wonderful place to both live and work.

FRESH AIR

Enjoy fresh air and greenery as far as the eye can see.

Picturesque sunsets set the scene nightly.

To learn more about BioVectra and our current opportunities, or start your journey, visit **www.biovectra.com/careers**.

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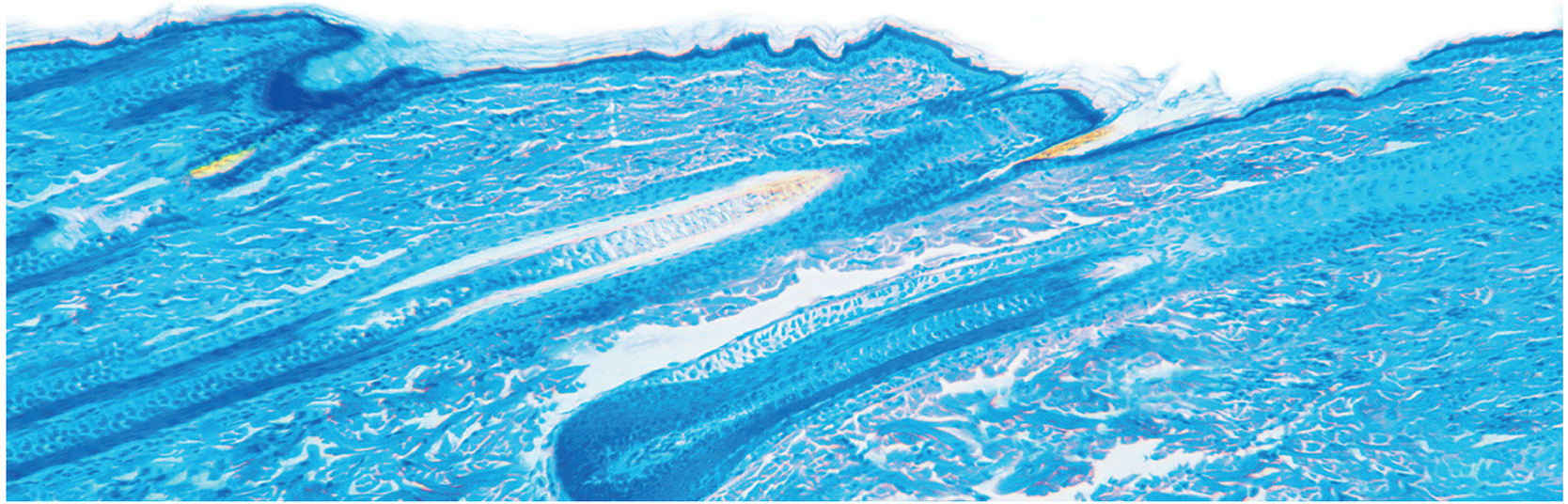
iPSCS: MOVING FROM DRUG TESTING TO NOVEL CELL THERAPIES

→ BY **CENK SUMEN, Ph.D.**, STEMSON THERAPEUTICS



Technology for the manufacture and differentiation of induced pluripotent stem cells (iPSCs) is advancing rapidly. Model organoids and other materials produced from iPSCs are already being used to screen potential drug candidates for safety. Soon, cell therapies for the treatment of a wide variety of diseases will make it to the clinic.

AN ALTERNATIVE TO EMBRYONIC STEM CELLS

During fetal development in mammals, pluripotent stem cells differentiate into the many types of cells required to form the organs and tissues. Embryonic stem cells (ESCs) have been used in drug development in the past. There are currently more than 10 clinical trials underway evaluating treatments developed using ESCs. In addition, HEK293 cells, which are the workhorse cells for gene therapy manufacturing, are derived from embryonic cells taken from a female fetus after an elective abortion in Holland in 1973.

Recently, however, there has been significant controversy surrounding the use of discarded fetal tissue. Therefore, the focus has switched to iPSCs, which are derived from adult cells programmed back to the pluripotent condition. While iPSCs are not identical to embryonic stem cells, they have the ability to replicate indefinitely and can be used to generate mature populations of many different types of cells.

IPSCS IN DRUG DISCOVERY AND DEVELOPMENT

Access to human iPSCs (hiPSCs) has presented opportunities to improve the drug discovery and development process. Using hiPSCs for large-scale cell-based safety and efficacy allows for screening at the level of a population – an approach referred to as "clinical trials in a dish" (CTiD).[1] Such screening can lead to selection of drug candidates with a much higher likelihood of success, reducing development time and cost. Using patient-derived hiPSCs to develop models that represent their actual diseases can also facilitate orphan drug development, particularly for monogenic rare hereditary diseases, by compensating for the lack of predictive *in vitro* human models for drug discovery.[2] Several drug candidates using iPSCs for screening are in clinical trials.

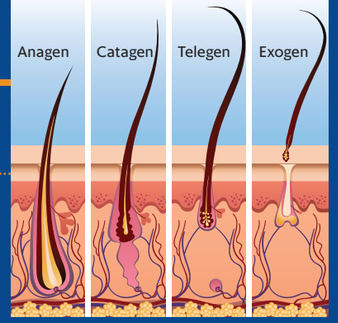
THERAPEUTIC APPLICATIONS

Differentiated cells derived from hiPSCs also have the potential to be used as therapies to treat diseases such as cardiovascular, neurological and metabolic disorders and to repair damaged cartilage, spinal, motor neuron and eye tissues resulting from genetic causes or injury. Targets for iPSC-derived therapies include any diseases or disorders for which there are no other viable treatments and where there is a need to create functioning tissue.

Five companies are leading the development of iPSC-based therapies. Semma Therapeutics, which is being acquired by Vertex Pharmaceuticals, is developing a treatment for type I diabetes comprising cells derived from iPSCs that behave like pancreatic cells. BlueRock Therapeutics, which was recently purchased by Bayer, is targeting Parkinson's disease and heart failure. Cynata Therapeutics Limited is developing an iPSC-derived treatment for graft-versus-host disease (GvHD), a complication that occurs after bone marrow transplants. Fate Therapeutics is using iPSC-derived NK and T cells to treat cancer and immune disorders; launching, in 2019, the first ever U.S. clinical trial of an iPSC-derived cell therapy product. At Stemson Therapeutics, we are developing a treatment for hair loss involving generation of *de novo* hair follicles.

Cynata and Fujifilm completed a phase I clinical trial in GvHD in December 2018 using mesenchymal stem cells (MSCs) derived from iPSCs, reporting positive results. The company plans to advance its Cymerus™ MSCs into phase II trials for GvHD and critical limb ischemia.[3] The Japanese firm Healios K.K. is currently preparing, in collaboration with Sumitomo Dainippon Pharma, for a clinical trial using allogeneic iPSC-based retinal cells for the treatment of age-related macular degeneration.[4] Other trials for AMD[5] and the use of iPSC-derived treatments targeting ischemic cardiomyopathy,[6] Parkinson's disease,[7] solid tumors[8] and spinal cord injury[9] have been approved.

Developing an iPSC-Based Treatment for Hair Loss



According to the American Hair Loss Association, 85% of men and 40% of women will experience visible hair loss (alopecia) by the age of 50,[15] with the most common form being androgenetic alopecia (male or female pattern baldness).[16] While most hair loss is genetic, some is due to autoimmune diseases, treatment with chemotherapy, radiation and certain other medications and as the result of scalp trauma (e.g., burns, surgery).

Hair follicles are formed during early fetal growth, and no new follicles are generated after birth.[15] Over 1 million follicles exist on the body, with one hundred thousand located on the scalp. The living part of hair is located at the bottom of the follicle surrounding the dermal papilla (DP) and is referred to as the bulb. Cells in the bulb divide much faster than any other cells in the body — every 23–72 hours. Hair growth follows a cycle of four stages: growth (anagen), regression (catagen), resting (telogen) and shedding (exogen) at any one time.

The DP produce molecular signals that initiate the proliferating progenitor cells into the anagen phase. Melanocytes provide pigment to the hair shaft during anagen. The follicle enters the catagen phase when the DP down-regulates production of molecular signals.

Hair loss follows damage, depletion or disruption of the DP and proliferating progenitor cells in the bulb because there is no way to regenerate them. In pattern baldness sufferers, various modulatory agents, such as androgens, prolactin and thyroid hormones, are believed to lengthen the telogen phase and disrupt the transition to anagen.

Current hair treatments, including transplantation, hair loss medications, follicle stimulus injections and the use of hair pieces and wigs, do not satisfactorily remedy hair loss conditions.

Stemson Therapeutics is taking a novel approach to hair loss treatment. The company formed in April 2018 to commercialize technology developed by scientists at Sanford Burnham Prebys (SBP) Medical Discovery Institute.

Rather than attempting to revive damaged, dying or shrinking hair follicles, we generate *de novo* follicles using iPSCs designed to grow new DP. Cells are harvested from an individual and used to generate iPSCs that are then differentiated into folliculogenic cells (FCs). The FCs are transplanted into the individual at target sites using technology designed to ensure that the cells anchor effectively under the skin and yield healthy hair follicles.

This approach is attractive because it enables the production of an unlimited supply of new folliculogenic cells that can be used to address hair loss resulting from many different causes. We are also exploring the possibility of establishing a bank of appropriate iPSC cells that would allow the development of allogeneic solutions for further scalability and superior economics.

TARGETS FOR IPSC-DERIVED THERAPIES INCLUDE ANY DISEASES OR DISORDERS FOR WHICH **THERE ARE NO OTHER VIABLE TREATMENTS AND WHERE THERE IS A NEED TO CREATE FUNCTIONING TISSUE.**

AUTOLOGOUS OR ALLOGENEIC?

A key question that developers of iPSC-based therapies must address is whether to focus on autologous (patient-derived) or allogeneic (donor) products. Some companies prefer to rely on preprogrammed iPSCs or outsource this part of the development effort, because reprogramming somatic cells to generate iPSCs is a complex and time-consuming process, and they may not wish to invest in in-house resources and expertise.

Autologous treatments do not have the potential for immune rejection, because they are derived from cells taken from the individual patient. Allogeneic products typically require coadministration of immunosuppressants, but they avoid the need to address logistic, supply chain and manufacturing challenges associated with processing individual patient samples.

Several academic and industry researchers are tackling the issue of immune rejection. Gene editing is being used to delete the genes that cause immune rejection responses and insert genes to protect the iPSC-derived cellular therapies from NK cells, which can recognize "missing self" and kill such targets. Current approaches are cumbersome, and the process can take up to a year to complete. However, it is still in development and shows great promise.

In Japan, the government has invested approximately $250 million in the establishment of iPSC banks for use in the development of regenerative therapies.[10] The cell donors were chosen by considering immune compatibility and overall should be compatible with 70% of the Japanese population. Similar efforts to establish iPSC banks are underway in the United States and other countries.

OTHER KEY QUESTIONS

Another significant challenge to overcome is the need to confirm that, once iPSCs are differentiated into the target cell type, they are committed to that phenotype and do not revert back to the pluripotent stage, creating the potential for differentiation into other cell types. In addition, differentiation should be as complete as possible to ensure that no differentiation-competent iPSCs remain. Furthermore, the potential for the generated target cells to exhibit other phenotypes must be determined for each particular therapy.

The source tissue must also be selected carefully. Skin biopsies, blood, hair follicles and waste material such as urine can all be used as the source of somatic cells from which iPSCs can be generated. However, the source tissue for iPSCs intended for the generation of cellular therapies (rather than drug screening) should be as mutation-free as possible. Skin cells are the least attractive, because they are constantly exposed to ultraviolet radiation; bone marrow tissue is the most protected from radiation and carries a lower mutational load.

There are also manufacturing issues that must be addressed. Unlike T cells, which can be expanded many orders of magnitude without significant loss of potency, iPSCs cannot be expanded too many times without losing their pluripotency. Because it is essential to achieve as close to 100% conversion to the derived cell type as possible, consistent, GMP-compliant processes must be developed and appropriate markers and methods identified and developed to effectively define the results. It is crucial that the leading companies developing the first iPSC-derived therapies set the standard for drug safety.

Ideally, such processes will be best achieved in centralized facilities using automated closed systems. The entire process – from the initial collection of the patient sample to production of the iPSCs – must be standardized. While no automated solution is yet on the market, there will eventually be devices into which purified samples are placed and from which iPSCs are generated after one to two weeks. Using plastic flatware to manufacture therapies will also become obsolete; bioreactors designed to support suspension and adherent culture of stem cell therapies are already on the market, and this technology is rapidly advancing.

Working in a nascent field with few established regulatory requirements can also create hurdles. These challenges are overcome through close cooperation among all stakeholders. Organizations such as the American Society of Gene and Cell Therapy bring together clinicians, hospital administrators, caregivers, academics, insurers, industry researchers and regulatory experts for honest discussions focused on identifying optimal solutions. We all have the same end goal: to get new therapies to as many patients as possible.

TREMENDOUS MARKET POTENTIAL

Estimates of the value of the global iPSC market vary significantly, but one thing the market research firms do agree on is that the market is expanding at a healthy rate. The Business Research Company estimates the global iPSC market, including iPSCs and related services, was valued at about $1.98 billion in 2018 and will increase at a CAGR of 9.2% through 2022, reaching $2.82 billion.[11] BCC Research pegged the CAGR at 11.6% from 2017 through 2021, with the market value reaching $3.6 billion at the end of the period.[12]

Leading producers of iPSCs include FUJIFILM Cellular Dynamics, which is headquartered in Madison, Wisconsin, Europe-based Ncardia (formed through the merger of Axiogenesis and Pluriomics in 2017) and Sumitomo Dainippon Pharma in Japan. Commercial applications for iPSCs' academic research, drug development and discovery, cellular therapies, toxicology screening and stem cell biobanking.

A notable recent development was the opening of Sumitomo Dainippon's $340-million SMaRT (Sumitomo Dainippon Manufacturing Plant for Regenerative Medicine & Cell Therapy) facility in Osaka, Japan in March 2018.[13] The plant is the first to offer iPSCs for commercial applications. Cells have been available for research purposes from the National Institutes of Health's Center for Regenerative Medicine and WiCell's Stem Cell Bank, among others. The SMaRT plant will use iPSCs produced at Kyoto University's Center for iPS Cell Research and Application (CiRA).

Meanwhile, the iCone (iPSC-derived Cortical neurons) Consortium comprising of MaSTherCell SA (CDMO dedicated to industrialization and production of Cell and Gene Therapies), Ncardia, the Pierre Vanderhaeghen Lab at the Université Libre de Bruxelles and the "Laboratoire de Chimie Analytique Pharmaceutique" led by Philippe Hubert at Université de Liège reported in September 2019 achieved initial success with a new 3-D mid- and large-scale process for the production of human iPSC-derived cortical neurons in stirred-tank bioreactors using the Eppendorf DASbox® bioreactor platform.[14] P

REFERENCES

1. Fermini, Bernard, Shawn T. Coyne and Kevin P. Coyne. "Clinical Trials in a Dish: A Perspective on the Coming Revolution in Drug Development." *SLAS DISCOVERY: Advancing Life Sciences R&D,* 23: 765–776 (2018).
2. "Application of iPSC Technology in Orphan Drug Development." Centogene. 28 May 2019. Web.
3. *Cynata Completes Clinical Study Report for Phase 1 Trial of CYP-001 in GvHD.* Cynata Therapeutics Limited. 18 Dec. 2018. Web.
4. "Pipeline in the Field of iPSC Regenerative Medicine." Healios K.K. n.d. Web.
5. Begley, Sharon. "Macular degeneration trial will be first human test in U.S. of Nobel-winning stem cell technique." *STAT.* 16 Jan. 2019. Web.
6. Cyranoski, David. "'Reprogrammed' stem cells approved to mend human hearts for the first time." *Nature.* 19 May 2018. Web.
7. *Announcement of physician-initiated clinical trials for Parkinson's disease.* Kyoto University. 30 Jul. 2018. Web.
8. *Fate Therapeutics Announces FDA Clearance of Landmark IND for FT500 iPSC-derived, Off-the-Shelf NK Cell Cancer Immunotherapy.* Fate Therapeutics. 30 Nov. 2018. Web.
9. Offord, Catherine. "Japan Approves iPS Cell Therapy Trial for Spinal Cord Injury." *The Scientist.* 18 Feb. 2019. Web.
10. Zimmer, Katarina. "Increasing Number of iPS Cell Therapies Tested in Clinical Trials." *The Scientist.* 28 Nov. 2018. Web.
11. *Induced Pluripotent Stem Cell (iPSC) Global Market Report 2019.* Rep. The Business Research Company. Oct. 2019. Web.
12. *Burgeoning iPSC Global Market to Strike Double-Digit Growth (11.6% CAGR).* BCC Research, 24 Jul. 2017. Web.
13. Daley, Jim. "World's First Commercial iPSC Cell Plant Opens in Japan." *The Scientist.* 23 Mar. 2018. Web.
14. *iCone Consortium hits major milestone in developing an industrial process for large-scale production of hiPSC-derived cortical neurons.* Ncardia. 18 Sep. 2019. Web.
15. "Hair Loss." American Hair Loss Association. n.d. Web.
16. McElwee, Kevin J. "Types of Hair Loss." American Hair Loss Association. n.d. Web.

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ACHIEVING RAPID SUCCESS WITH A FLEXIBLE, CLIENT-CENTRIC APPROACH

→ BY **DANIEL P. SLONE**, SAMSUNG BIOLOGICS

By considering evolving client needs across operations Samsung BioLogics has rapidly become a leading biopharmaceutical CDMO.

PROVIDING FULLY INTEGRATED SOLUTIONS

Samsung BioLogics began as a large-scale contract manufacturing company – shortly after opening in 2011, we recognized the growing need in the industry for product development support and analytical testing services. Contract development services were added in 2017, and a variety of analytical testing capabilities have recently been integrated into our comprehensive offering. Today, we are a full end-to-end CDMO providing cell line development through commercial manufacturing of drug substance and product, all from a single location.

With these integrated services, Samsung BioLogics offers a faster and better path to IND filings and successful BLAs to clients worldwide. We provide phase-appropriate solutions guided by our track record of approvals and our technical operational model, supporting clients from the idea stage to the commercial product – all from an integrated campus.

EXPANDING MANUFACTURING CAPABILITIES

In just eight years, Samsung BioLogics has designed, constructed and validated three manufacturing facilities. Plant 1 is an industry-standard facility with a total capacity of 30,000 L (6 X 5,000 L). Plant 2 has a total capacity of 152,000 L (10 X 15,000 L + 2 X 1,000 L) and incorporates minor engineering changes for improved efficiencies and processing capacity. With a total capacity of 180,000L (12 X 15,000L), Plant 3 is the largest single biopharmaceutical plant in the world and leverages all of the lessons learned through the operation of the two previous plants to achieve tremendous efficiencies.

These three plants are world-class facilities with bioreactors ranging from small to large scale and an innovative operating system that can address the diverse needs of our customers across the globe. Unique backup systems for our cleaning utilities ensure constant access to key utilities through limited to no shut-down periods. Additionally, all media can be heat-treated using the high-temperature/short-time systems installed in each plant.

Our process development labs were designed using the same concepts as our large-scale operations, ensuring the effectiveness of our scale-down models. Currently, clinical manufacturing can be performed in 1000-L stainless steel reactors, and a second unit containing two 1000-L single-use bioreactors will be operational by Q2 2020.

We now also have the ability to perform N-1 perfusion using an alternating tangential flow (ATF) device (3,000 L) in Plant 3. With the ATF system, we can effectively achieve higher cell culture densities (up to 10-fold) while retaining high cell viabilities (>98%) at the seed stage (N-1). Inoculation of the production bioreactors (15,000 L) then allows us to achieve peak cell densities within shorter culture durations, improving productivity and reducing production times.

Perhaps most notably, a fourth facility is in the planning stage. We are currently evaluating potential market developments and new technologies before selecting the best design and equipment options.

INCREASING COMPLEMENTARY SERVICES

In addition to development and manufacturing services, Samsung BioLogics has added – and will continue to add – key analytical services to help clients address major industry roadblocks for biologic drug production.

For both existing and new customers with marketed products, we offer standalone QC/QA testing services. We will also be bringing a new biological safety testing lab online, which will offer viral contamination, mycoplasma, endotoxin and sterility testing. Outsourcing analytical services can often be subject to delays in contracting and scheduling, which may become a bottleneck of the project. Through the opening of our in-house laboratory, we are able to provide faster turnaround on testing service and monitor analytical issues. Samsung BioLogics is also moving quickly to add master cell banking and other supportive services to meet the growing needs of clients.

FOCUS ON CLIENT SATISFACTION

We operate under a client satisfaction model in which consideration of client needs drives business activities. Our focus is on understanding our customers' requirements and finding ways to close any gaps that cause issues in biopharmaceutical manufacturing. One example of this customer-centric approach is our end-to-end practice of project management.

GOING FORWARD, SAMSUNG BIOLOGICS WILL CONTINUE TO STRENGTHEN OUR PRESENCE IN THE RAPIDLY GROWING GLOBAL BIOPHARMACEUTICAL MARKET **BY UTILIZING OUR WORLD-CLASS PLANT DESIGN AND OPERATIONAL TECHNOLOGY.**

The dedicated project manager and project team assigned on day-one stay with a project throughout its lifetime, ensuring the development of strong relationships and retention of process knowledge.

CREATING UNIQUE CONTRACT TERMS

Being part of the larger Samsung group enhances our customer satisfaction model, since we can tap into the broader organization and bring its capabilities and offerings to our clients – for example, leveraging Samsung engineering expertise in the design of our manufacturing facilities.

Samsung's broader financial resources also allow us to create flexible, client-centric deals that maximize value creation for our clients. These innovative deals provide certainty of stable and reliable supply through the various development stages with optimized cost-effectiveness at commercialization through the implementation of creative commercial terms, and protecting clients if products fail to advance.

ESTABLISHING A LEADERSHIP POSITION

Our success at achieving client satisfaction has been recognized for three consecutive years with CMO Leadership Awards (presented by Life Science Leader) for all six core categories: capabilities, compatibility, expertise, quality, reliability and service.

Going forward, Samsung BioLogics will continue to strengthen our presence in the rapidly growing global biopharmaceutical market by utilizing our world-class plant design and operational technology, which maximizes production efficiency and ensures stable supply of the highest quality products to patients worldwide.

In addition to our aggressive short-term plans to build a fourth plant in South Korea, we are evaluating options to establish a facility outside of the country to further expand our footprint. We will also continue to expand our development and testing services, adding capabilities that complement our manufacturing expertise and capacities with the goal of providing the most comprehensive, integrated, single source of client-focused support for biopharmaceutical research, development and production. P

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Dan Slone is a recognized industry expert with a demonstrated history of ~30 years working in biotechnology manufacturing and bioprocess. As a head of DS manufacturing for Samsung BioLogics, Dan is responsible for the overall operations and performance of upstream and downstream production. The responsibility of this position also includes ensuring leadership of GMP compliance in manufacturing operations, as well as regulatory site inspections in producing drug substances.

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SOLVING THE INDUSTRY'S CAPACITY UTILIZATION PROBLEM

→ BY **TIM TYSON,** TRIRX PHARMACEUTICAL SERVICES

THE PHARMACEUTICAL INDUSTRY MUST LEARN FROM OTHER SECTORS, **SUCH AS THE CONSUMER PRODUCTS INDUSTRY, THAT HAVE ACHIEVED HIGH CAPACITY UTILIZATION RATES AND LEAN MANUFACTURING SOLUTIONS.**

With capacity utilization in the pharmaceutical industry at a surprisingly low rate, drug makers are rationalizing facilities and contract supply networks to gain efficiencies and reduce cost. The new contract development and manufacturing organization (CDMO) TriRx Pharmaceutical Services was formed to help pharma customers reach their goals by providing integrated contract development and manufacturing services across the full development and manufacturing continuum, supported by exceptional service.

THE CAPACITY UTILIZATION CONUNDRUM

The pharmaceutical industry currently faces a significant issue: poor capacity utilization rates. Compared with the consumer products industry, where true capacity utilization rates are maintained above 85%, utilization of existing pharmaceutical manufacturing capacity across the entire industry network hovers near 30–35%.

The actual utilization rate is difficult to definitively determine, because companies calculate capacity utilization in different ways on the basis of individual criteria and assumptions. Truly, capacity utilization should be calculated based on the full potential capacity of a plant, which includes all of the possible shifts and operating lines running 24/7 (or at least 24/5), because the equipment is available for use every hour of each day.

Unfortunately, 100% utilization is most typically determined based on the current state of operations. A company running two shifts, five days per week will consider that full capacity, rather than running three shifts, five or seven days per week.

By taking this approach, many manufacturers choose to expand capacity when doing so is not required. In general, companies establish a capacity utilization rate, above which they deem it essential to add additional capacity. If the assumptions used to determine that utilization rate are inaccurate, investment in additional equipment and facilities can occur when those expenditures are not yet needed. A facility running two shifts per week can add another five to eight operators and run an additional shift rather than invest in a new process line, saving significant CapEx, accelerating the rate of expansion and preventing underutilization.

THE DEMAND FOR GREATER EFFICIENCY

Another factor contributing to the present low capacity utilization rate in the pharmaceutical industry is the high level of inefficiency of many facilities and processes. In general, the batch approach to manufacturing is inefficient, because it requires a very large footprint and expensive equipment, much of which sits idle while specific unit operations are completed.

Many older pharmaceutical production processes also tend to be inefficient, because, at the time they were initially designed, the main driver was speed and the need for boosting efficiency and productivity was not as critical. Manufacturing processes often deliver the desired product at 70% yield or less. Most small molecule production requires multiple steps, so poor yields are magnified throughout the entire process. Increasing the yield to 80–90% enables the manufacturer to obtain more product with the same equipment over the same time period. Utilization of Lean and Six Sigma tools can have a tremendous impact on efficiency and productivity improvements and can significantly increase capacity utilization.

Increasing productivity should be considered for all activities in a pharmaceutical production facility, from raw material testing to packaging. Each process should be comprehensively mapped, and then each step/unit operation/activity must be challenged to clearly understand what is restricting the ability to increase efficiency and productivity. If the packaging process is found to be critical, for example, then capacity could be increased by adding a second packaging line or limiting a piece of equipment and running them in parallel. The overall result would be increased capacity for the entire process, with investment and expansion only where it is actually needed.

ACHIEVING COST IMPROVEMENT

Annual revenues for the global pharmaceutical industry are approximately $1 trillion. The cost of goods (COGS) for the entire industry averages approximately U.S. $250 billion – about 25% of revenues. The potential opportunity to reduce COGS by implementing efficiency and productivity improvements is

Technologies of the Future

There are a number of advanced technologies that are beginning to enable leaner, more cost-efficient pharmaceutical manufacturing. Continuous processes, 3-D printing and modular facilities are a few primary examples.

Continuous processing is being adopted by industry leaders for both small molecule and biologic drug substance and drug product manufacturing. Continuous processes operate at an optimum steady state and are continuously monitored and adjusted to provide consistent, high-quality products at high yields. They are highly automated, reducing human intervention and risks for operator errors and product contamination. Additionally, they have smaller physical and environmental footprints.

3D printing has broad applications and is developing rapidly in pharmaceutical manufacturing processes, and it is a key technology for organ manufacturing in the regenerative medicine market.

Modular facilities will make it possible to rapidly and cost-effectively establish a local manufacturing presence, even in areas with little infrastructure. The modular approach will also allow replication of manufacturing processes, ensuring that products produced in different locations are identical. Construction of such systems is possible at considerably less time and cost than traditional facilities, and the individual components can be shipped to a site and rapidly assembled, with reduced onsite construction safety risks compared with conventional construction. The overall result is reduced cost and time to market. Incorporation of continuous processing also simplifies scale-up, because the same setup can be used for R&D, clinical and commercial manufacturing.

Ultimately, manufacturers must make investments focused on outcomes. Greenfield facilities should be constructed as factories of the future, leveraging all of the available efficiency and productivity tools and technologies. If designed, constructed and managed correctly, such facilities would be able to achieve 80% capacity utilization from the outset.

3D PRINTING HAS BROAD APPLICATIONS AND IS DEVELOPING RAPIDLY IN THE PHARMACEUTICAL MANUFACTURING PROCESSES AND **IS KEY TO ORGAN MANUFACTURING IN THE REGENERATIVE MEDICINE MARKET.**

somewhere in the neighborhood of 10% – which could reduce COGS by about $100 billion per year!

Reducing COGS in this manner will enable pharmaceutical companies to be more cost competitive and to realize a fair profit.

The pharmaceutical industry must learn from other sectors, such as the consumer products industry, that have achieved high capacity utilization rates and lean manufacturing solutions. Manufacturers must take the best practices demonstrated in these other production environments and translate them into effective solutions for the pharmaceutical business. Investment in Lean Six Sigma tools, application of automation process control and robotics and utilization of new technologies will yield significantly increased efficiencies and productivity.

NEED FOR DELIVERY PERFORMANCE

The need to improve capacity utilization and increase productivity and efficiency are particularly important for CDMOs. Customers want delivery on time and in full at a fair price. They also want their products to comply with regulatory requirements. Accomplishing these goals requires excellent process control, such that all processes are reliable, repeatable and sustainable. Only under these conditions is it possible to commit to and meet a schedule and ensure optimal delivery 100% of the time.

Unfortunately, few CDMOs are successful in this respect. While many pharmaceutical companies choose to partner with and rely heavily on service providers, they often say that their reliance on CDMOs is among the biggest challenges of their business. When outsourcing partners do not deliver on time and in full, the sponsor firm's supply chain is put at risk. Fortunately, CDMOs perform well most of the time. When they do not, however, it can be a major problem.

SUPPLIER CONSOLIDATION

The industry's low capacity utilization rate also impacts the types of CDMOs with whom pharma companies want to partner. Innovator companies are often focused on rationalizing their manufacturing networks to increase their internal capacity utilization, and doing so creates a need to outsource some products. Rather than add to their complex supply networks, however, sponsors are also looking to rationalize their suppliers.

Most large pharma companies have approximately 500 suppliers. Many want to reduce that number to between 75 and 100 in order to reduce the time, cost and resources needed to manage their outsourcing partners.

CDMOs that can manufacture both drug substances and drug products, including a wide range of dosage forms (e.g., liquid, solid, inhalation, sterile) for both small molecule and biologic formulations are therefore receiving significant attention. These integrated, global CDMOs can help sponsor firms sustain their rationalization efforts by producing a wide range of products and delivering them to every major market in the world.

BUILDING A BETTER CDMO

TriRx Pharmaceutical Services was founded to meet the need for integrated CDMOs that can consistently and reliably deliver. We have established a company with the expert staff, facilities, equipment, capabilities and experience necessary to function as the manufacturing arm of sponsor organizations.

Unlike CDMOs that are owned by private equity firms with short-term goals, we recognize that pharmaceutical manufacturing is a long-term business that requires long-term investment and commitment. We also recognize that quality is critical and are willing to invest in the people, processes and equipment needed to meet or exceed regulatory requirements in all of the markets that we serve.

We are building TriRx via the acquisition of high-quality facilities with long histories of making quality products, extensive track records with respect to compliance and delivery and transparent cost structures. As each new facility is acquired, it is integrated into a single, cohesive company through the implementation of standardized systems, processes and procedures.

WITHIN FIVE YEARS, TRIRX WILL COMPRISE SIX TO 10 FACILITIES COVERING DRUG SUBSTANCE AND DRUG PRODUCT **FOR SMALL AND LARGE MOLECULE PRODUCTS IN ALL RELEVANT DOSAGE FORMS.**

Our team of pharmaceutical industry executives have served as both contract service providers and customers. They have held a range of positions, from working on the plant floor to the executive suite. Our diverse staff ensures that TriRx has a deep and multifaceted understanding of our evolving customers needs. Our goal is to be recognized as a CDMO that consistently meets those requirements and to be viewed by pharma companies as a critical component of their supply chains.

AGGRESSIVE GROWTH PLANS

Headquartered approximately 50 miles outside of New York City in Norwalk, Connecticut, TriRx is building a network of facilities with state-of-the-art laboratory, manufacturing, packaging and warehousing capabilities.

Our first manufacturing site (Huntsville, Alabama) is a best-in-class facility for the production of liquids (solutions, suspensions and colloidal dispersions), creams, ointments and lotions. It is a proven industry leader in liquid and semisolid manufacturing and packaging that is also capable of handling controlled substances (CII – CV), with vault and cage storage on site. The facility is serialization-ready, with Optel Line Equipment and TraceLink Level 4 Solution online.

Currently, TriRx is exploring other potential acquisition in the solid dosage, large molecule, sterile processing and animal health spaces. Negotiations are underway for facilities in each of these areas, and we expect to close on two of the four deals within the next six months.

Within five years, TriRx will comprise six to 10 facilities covering drug substance and drug product for small and large molecule products in all relevant dosage forms. By that time, we project that we will be generating revenues approaching $500 million annually. P

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Tim Tyson
Chairman and Chief Executive Officer, TriRx Pharmaceutical Services

Tim Tyson is a world-renowned pharmaceutical industry leader. In his 35-plus year career, he has negotiated complex multi-billion-dollar mergers and acquisitions, led major turnarounds that have fueled growth and value, and, most significantly, has been instrumental in bringing more than 50 life-saving and life-improving medicines to market. Prior to establishing TriRx, Mr. Tyson served as Chairman and CEO of Avara Pharmaceutical Services, Chairman and CEO of Aptuit, and CEO of Valeant Pharmaceuticals International. He is a graduate of the United States Military Academy at West Point and received his M.B.A. and M.P.A. from Jacksonville State University.

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SUPPORTING CUSTOMERS WITH AN INTEGRATED FERMENTATION OFFERING

→ BY **GIOVANNI CELESTE,** OLON GROUP

Demand for microbial fermentation services is increasing, but there are few contract manufacturers with an intense focus and expertise in this important bioprocessing technology. Olon S.p.A. offers truly integrated fermentation process development and manufacturing capabilities, including downstream chemical modification, purification and spray drying.

GROWING INTEREST IN MICROBIAL FERMENTATION

Demand for microbial fermentation services is increasing as pharmaceutical manufacturers realize the economic benefits of producing many types of bioactive molecules using this technology. One market research firm estimates the overall value of the market for chemicals produced by fermentation was $58.68 billion in 2018, with pharmaceutical products accounting for approximately 20% of the market,[1] while another pegs the value of the market for microbial-produced biopharmaceuticals at $100 billion in 2017 and expanding at a CAGR of 6%.[2] The contract pharmaceutical fermentation services market is predicted to expand at a similar rate of 5.9% through 2026, reaching a value greater than $4.0 billion.[3]

For the production of many smaller biologics, microbial fermentation can have cost and time advantages over mammalian cell culture, providing shorter development timelines and reduced variability. Commonly used Chinese hamster ovary cells are not able to practically and economically produce some biomolecules currently of interest, such as single-domain antibodies and peptibodies.

Using fermentation for the manufacture of longer-chain peptides (30–40 amino acids) is economically advantageous compared with traditional solid-state chemical synthesis. In 2018, more than 100 peptide therapeutics were available globally, with over 100 additional peptides in late-stage clinical development and more than 200 at the preclinical stage.[4] The increasing interest in peptide therapeutics is a key driver of growth for the pharmaceutical fermentation market.

Microbial fermentation provides a sustainable alternative for the production of natural products (with limited natural availability) and therapeutic peptides. Leveraging microbial fermentation can allow reduction of the use of limited natural resources, producing purer products and reducing the environment impact.

EXPANDING FERMENTATION EXPERTISE AND CAPACITY

Olon is a world-leading advanced intermediates, proteins, enzymes, peptides and small molecule active pharmaceutical ingredient (API) contract development and manufacturing organization (CDMO) and generics supplier, with headquarters in Italy and manufacturing sites around the world.

It has been the strategic plan of the company to build an integrated offering through a combination of acquisitions and organic growth. Our first step was taken in 2016, when we purchased Italian API producer Infa Group (2 manufacturing sites in Italy and 1 in Spain). That move was followed by the acquisition of the Chemical Division of U.S. CDMO/contract research organization (CRO) Ricerca Biosciences, which added new early-phase CDMO capabilities and expertise while providing additional access to the American market.

Continuing the expansion of our global footprint, in 2018, we acquired from Sandoz-Novartis a microbial fermentation and chemical synthesis API manufacturing facility in Mahad, India. That purchase was followed by the acquisition of Capua BioServices S.p.A., one of the larger provider of beta-lactam–free fermentation services in the world, in early 2019. We have already initiated construction of a new GMP manufacturing plant for the manufacture of multiple products up to commercial scale at this site. Having finalized our 3-year development plan, we are now evaluating opportunities to formally enter the biopharmaceutical market.

Olon has a breadth of capabilities for API manufacturing. The acquisition of Capua Bioservices has expanded not only our fermentation capacity, but our knowledge and expertise in the development of efficient, cost-effective fermentation processes.

We have a total fermentation capacity of 4.500 m^3, based on 65 fermenters spread between two manufacturing locations in Italy, and an additional 400 m^3 in fermentation capacity at our site in India. We offer dedicated solutions for peptides, proteins, enzymes and specialty small molecules for clients in Europe as well as the United States, using a variety of microbes, including, but not limited to, yeast (*Saccharomyces cerevisiae, Pichia pastoris*), bacteria (*Escherichia coli, Bacillus, Streptomyces*) and fungi (*Aspergillus, Trichoderma*).

INTEGRATED SERVICES

Olon's pharmaceutical services, including fermentation, are managed by a dedicated commercial team, while a separate commercial team handles the non-pharma business, named Food+ (food, feed and additives). We have dedicated manufacturing areas and equipment for pharmaceutical products (including HPC), and our sites operate according to cGMP guidelines and are annually audited by the U.S. FDA, the EMA and other global regulatory authorities.

Our involvement in the food industry is key differentiator for Olon. We have experience implementing quality systems and manufacturing products according to both GMP guidelines and food manufacturing regulations. As a result, we are highly flexible and can provide support – and unique solutions – to producers of products that fall into the gray area between food and pharma.

Our extensive experience in microbial fermentation is combined with the highly flexible design of our process development lab, pilot plant and commercial manufacturing units. We are able to implement different processes and different types of unit operations and even multiple processes in parallel. Based on the experience gained in the last years, we have also increased our flexibility in how we support our customers.

Olon's highly experienced R&D team delivers solutions to critical and complex projects at each development phase, from familiarization and proof of concept to robust commercial-scale production. We have strong expertise in strain development/improvement and the optimization of fermentation and downstream processes, including purification and chemical modification. Our ability to provide fermentation and chemical modification within one company provides tremendous value for our customers by eliminating the need for technology transfer.

The acquisition of Capua also provided access to state-of-the-art spray-drying capabilities within a facility opened in 2018. With this technology, Olon is able to offer customers an economically attractive alternative to lyophilization, crystallization and micronization. Spray drying allows the production of stable formulations of dry powder proteins, peptides, monoclonal antibodies and can often enhance the bioavailability of poorly soluble compounds. It also enables precise engineering of particle size and the embedding of microencapsulation technology.

FIVE STRONG PILLARS

The CDMO Division of the Olon Group has implemented a Five Strong Pillars approach to ensure that we consistently meet or exceed our customers' expectations. The Pillars include quality on time in full (QOTIF), supporting customers from R&D to commercial, a strong team-based project management culture, security of project information and cost management.

Underlying and supporting all of our development and manufacturing activities is our financial stability and commitment to be a long-term partner for our customers. We are interested in being strategic partners with our customers and are committed to forming long-term, risk-sharing, win–win relationships. Customers also know that we maintain the confidentiality of each project without compromise.

Our pharma-focused commercial team is backed by an excellent group of highly experienced scientists, project managers and engineers. These talented people make up our dedicated project teams, which follow each project from the day they are introduced to Olon until they are completed and we have met all customer expectations. This approach fosters excellent communication and the building of strong relationships. P

REFERENCES

1. *Fermentation Chemicals Market Size, Share & Trends Analysis Report By Product (Alcohols, Enzymes), By Application (Industrial, Plastic, Pharmaceutical), By Region, And Segment Forecasts, 2019 – 2025.* Rep. Grand View Research. Apr. 2019. Web.

2. *Biopharmaceutical Fermentation Systems Market to be Worth US$ 17.8 Billion by 2026, Says TMR.* Transparency Market Research. 19 Jul. 2018. Web.

3. Jha, Shambhu Nath. "Growing Usage of Fermentation Techniques for Developing Active Pharmaceutical Ingredients expected to drive the Revenue Growth of the Contract Pharmaceutical Fermentation Services Market over 2018–2026. *The Guardian Tribune*. 15 Mar. 2019. Web.

4. *Global Peptide Therapeutics Market, Dosage, Price & Clinical Trials Insight 2024 - 101 Marketed Drugs with a $50 Billion Opportunity.* Research and Markets. 6 Sep. 2018. Web.

ABOUT THE AUTHOR

Giovanni Celeste
Senior Vice President of Sales & Marketing, Olon Group

Giovanni Celeste is the Senior Vice President of Sales & Marketing of Olon Group. He has more than 20 years experience in the pharmaceutical industry and healthcare business. He joined Olon in 2004 in the Sales & Marketing Dept. and has continued to contribute to the company's strong internal growth. He currently supervises the global commercial activities of the Group for both CDMO and Generics. Prior to Olon, Mr. Celeste served in other Italian APIs manufacture, Dipharma, as Area Manager. Mr. Celeste holds a Master Degree in Economics from the University of Pisa, Italy.

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CREATING A GLOBAL CDMO FOCUSED ON QUALITY, INNOVATION AND HAPPINESS

→ BY **ASLAM MALIK,** SK PHARMTECO

SK holdings, the holding firm of SK Group, has combined its three contract pharmaceutical manufacturing businesses SK biotek Korea, SK biotek Ireland and AMPAC Fine Chemicals to form SK pharmteco, a global, integrated contract development and manufacturing organization (CDMO) based in California.

NATURAL PROGRESSION TO SK PHARMTECO

SK is a successful South Korean conglomerate known for its leadership in oil and gas, telecommunications, information technology and other industries. This position has been achieved through organic growth and acquisition under the guidance of SK holdings. The company entered the pharmaceutical contract manufacturing business in the 1990s with the establishment of SK biotek, and that business has grown into a global CDMO that now operates under the consolidated SK pharmteco umbrella.

SK biotek initially expanded organically to include two sites in South Korea, focusing on its continuous processing and engineering capabilities. In 2017, SK biotek acquired the Bristol-Myers Squibb commercial launch facility located in Swords, Ireland, which was rechristened as SK biotek Ireland.

Meanwhile, in the 1980s in Sacramento, California, defense company Aerojet was developing specialty capabilities in energetic chemistry and engineering for the production of rocket fuels. The company later developed a side business by leveraging its expertise in engineering and chemistry to begin production of cancer drugs for the National Cancer Institute, Walter Reed Medical Center and others. When the aerospace business declined in the 1990s, Aerojet began to grow its fine chemicals business branded as Aerojet Fine Chemicals, which was divested to American Pacific Corporation (AMPAC) in 2005 and rebranded as AMPAC Fine Chemicals.

The AMPAC Fine Chemicals business grew rapidly, and in 2014, it was acquired by the large private equity firm H.I.G. Capital. This led to significant investment in infrastructure and capabilities, allowing the company to further strengthen its position in the CDMO industry. In 2018, AMPAC Fine Chemicals management sought a strategic investor to drive further growth. SK was identified as an ideal strategic growth partner.

SK biotek and AMPAC Fine Chemicals had developed a good relationship over the previous two decades, and the two companies shared expertise as pioneers in applying continuous manufacturing to the pharmaceutical industry. In addition, SK was looking to add CDMO capabilities in the United States. The deal between SK and AMPAC Fine Chemicals closed in September 2018.

One year later, SK established SK pharmteco, which will serve as the parent company for AMPAC Fine Chemicals, SK biotek Korea and SK biotek Ireland. The new company has six production plants, one analytical testing facility and a vast array of enabling technologies. The move not only allows SK to streamline the corporate structure, maximize synergies and efficiency, but also forms a strong foundation upon which we will grow our global CDMO business.

MAINTAINING IDENTITY AND CULTURE

Each of the three companies coming together to form SK pharmteco has its own established culture, identity and reputation in the marketplace. SK pharmteco implemented a strategy wherein each entity will retain its name, culture, processes, and structure. By retaining the individual company names, we avoid the need to update existing filings, a time-consuming and costly process for our customers. Maintaining existing company structures and employees also means that customers will be able to work with familiar people and continue to build on existing relationships.

Synergies will be achieved by implementing best practices across the enterprise. We will be able to leverage our global footprint to provide increased value to our customers. This can be achieved by producing registered starting materials and advanced intermediates at a lower cost in our plants in South Korea and supplied to the U.S. and European facilities for API manufacturing. Additionally, tax benefits may be achieved by performing final manufacturing steps at SK biotek Ireland.

Overall, this approach will enable SK pharmteco to capitalize on the true value of each company and its people. At the same time, customers from all organizations are provided with access to new ideas, technologies, opportunities and global capacity.

COMMITMENT TO SAFETY AND QUALITY

A commitment to Safety and Quality is what has made SK biotek Ireland, SK biotek Korea and AMPAC Fine Chemicals successful. All three companies have an excellent track record of compliance and transparency with regulatory agencies.

AMPAC Fine Chemicals has opened its manufacturing facility as a training ground for FDA auditors. Initially, a dozen auditors were brought to the Rancho Cordova facility for training; for the most recent visit in 2019, 40 auditors (including national experts) were involved. In this manner, we are sharing our experience in cGMP manufacturing with the agency.

WITH THE THREE COMPANIES WORKING TOGETHER, CUSTOMERS OF SK PHARMTECO CAN HAVE THEIR REGISTERED RAW MATERIAL PRODUCED COST-EFFECTIVELY IN KOREA, PURIFIED AND THEN CONVERTED TO AN ADVANCED INTERMEDIATE IN THE UNITED STATES, AND THEN TRANSFORMED INTO THE API IN IRELAND TO LEVERAGE TAX BENEFITS.

SHARING BEST PRACTICES

With the foundation of safety and quality, the first step is to identify the strengths and weaknesses of each company. To do so, we have formed expert teams that comprise representatives from each site, who are typically the heads of business segments. For instance, the research and development (R&D) team consists of the heads of R&D for SK biotek Ireland, SK biotek Korea and AMPAC Fine Chemicals and is led by an experienced executive.

In addition to R&D, committees are focused on Safety, Health and Environmental; Supply Chain & Logistics; Quality; Operational Excellence; and Project Management. Each committee is actively comparing systems, practices and procedures to identify strengths from each site that can be leveraged by the others, as well as any weaknesses at each site that can be improved.

WE BELIEVE THAT THE HAPPINESS OF ALL STAKEHOLDERS WILL LEAD TO MAXIMUM SUCCESS, AND BY FOCUSING ON CREATING HAPPINESS, **WE WILL BECOME A HIGHLY VALUED OUTSOURCING PARTNER RECOGNIZED BY PHARMACEUTICAL AND BIOPHARMACEUTICAL COMPANIES AROUND THE WORLD.**

INTEGRATED SUPPLY CHAIN

A key benefit for SK pharmteco is the fact that the three founding companies share many technologies while also providing complementary capabilities.

All three companies produce high-quality products. SK biotek focuses on registered starting materials, key building blocks, and advanced intermediates. AMPAC Fine Chemicals specializes in advanced intermediates and APIs. SK biotek Ireland also produces APIs and provides a tax advantaged manufacturing location. As a result, SK pharmteco supports the entire supply chain, from registered starting materials to final API.

On the technology side, both SK biotek Korea and AMPAC Fine Chemicals have developed expertise in different aspects of continuous processing, in part the result of each company having emerged from a larger organization with extensive experience in manufacturing. One of AMPAC's particular areas of expertise is Simulated Moving Bed (SMB) chromatography – a technology used for the cGMP purification of complex molecules and separation of chiral materials. Presently, AMPAC Fine Chemicals is the only U.S. CDMO offering this capability at commercial scale.

Other areas of expertise include energetic chemistries, production of highly potent APIs and intermediates, particle engineering, continuous manufacturing (low temperature, hydrogenations, high pressure, etc.) and controlled substance manufacturing.

With the three companies working together, customers of SK pharmteco can have their registered starting material produced cost-effectively in Korea, purified and then converted to an advanced intermediate in the United States, and then transformed into the API in Ireland to leverage tax benefits.

We also have flexibility as regards available capacity. SK pharmteco currently has a total of more than 1,000 m^3 of cGMP capacity, a number that will be continually expanding. With six different manufacturing sites located in the United States, Europe and Asia, we can accommodate a range of customer needs regarding quantity, timing and location.

To support our consolidated offering, we have integrated the marketing and business development teams into a single group that is part of SK pharmteco. By taking this approach, we are able to show potential customers the true value proposition that we offer. As such, business development will be a global enterprise, while execution will take place on the local level.

PROVIDING SOLUTIONS

Each of the three companies coming together under SK pharmteco has unique and specialized expertise and, going forward, SK pharmteco will remain a specialized CDMO.

We will be creating Centers of Excellence in the technology areas where we have extremely deep knowledge and capabilities. These areas – which notably include continuous processing – offer tremendous opportunities for enhancing our ability to be a comprehensive technology solutions provider. We will – through acquisitions and organic growth, develop and acquire additional technology platforms to overcome complex manufacturing challenges. Ultimately, the SK pharmteco name will be widely recognized to stand for safety, quality, reliability and engineered chemical solutions.

FOCUSED ON HAPPINESS

SK is focused on the happiness of its employees, neighbors, customers and shareholders – our main mission is to be a company that truly cares.

Happy employees reward the company with dedication, superior performance and a commitment to safety and quality. Happy neighbors welcome the company into the community. Happy customers bring repeat business and help the company grow and happy shareholders continue to invest, fueling even more growth.

By focusing on happiness, we have established a business that runs efficiently, grows rapidly and helps get life-changing and lifesaving medicines to patients quickly.

This belief is reflected in the SK logo, which is a butterfly that represents the "wings of happiness." At SK pharmteco, we are living this philosophy. We believe that the happiness of all stakeholders will lead to maximum success, and, by focusing on creating happiness, we will become a highly valued CDMO partner recognized by pharmaceutical and biopharmaceutical companies around the world. P

ABOUT THE AUTHOR

Aslam Malik, Ph.D.
Chief Executive Officer, SK pharmteco

Dr. Malik serves as the CEO of SK pharmteco, a U.S.-based CDMO with global headquarters in Sacramento, CA and operations in Korea, Ireland and the United States. Pharmteco is the recent combination of SK biotek Korea, SK biotek Ireland and AMPAC Fine Chemicals. Prior to the establishment of SK pharmteco, Dr. Malik served as the President and CEO of AMPAC Fine Chemicals. Dr. Malik holds a doctorate degree in organic chemistry from the University of California at San Diego, a Master's degree in organic chemistry from San Diego State University and a Bachelor's degree in chemistry and physics from St. Xavier's College in India.

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Kevin McLean
Quality and Technical Manager – Americas
SGD Pharma

Alternative Vial Designs to Reduce Lyo-Breakage Risk

Even at low frequency occurrence, glass vial breakage during a lyophilization cycle is a serious issue. Traditional molded glass vials are heavier and more resistant to breakage, however still not ideal. An optimized molded vial design provides lyo-breakage protection without sacrificing acceptable thermodynamic performance.

Rising Demand for Lyophilization

Within the parenteral route of administration, lyophilized products are increasing in application. In many biologic therapies for example, lyophilization is used to extend shelf life because the product is not stable in liquid form. With biologics accounting for approximately one-third of all new drug approvals and over 50% of drugs in the clinical pipeline, the demand for lyophilization is expected to increase.[1]

The Challenge of Glass Breakage During Lyophilization

Lyo-breakage is generally not a routine occurrence; however, even at a persistent low frequency it can have significant cost and operational impacts. There is the obvious cost of lost product in the broken doses and doses potentially contaminated by the breakage, but there are also other, less obvious costs. Lyophilization of injectable drugs is a lengthy process, performed in costly equipment and under tightly controlled environmental and thermo-mechanical conditions; any product-loss, or time-loss due to clean-ups, typically means significant cost-lost. If the broken dose is cytotoxic or an otherwise a dangerous substance, there is an even greater risk to safety.

Lyophilization is a demanding process on the primary container. There can be significant side-load force during vial transfer in/out of the lyophilizer; dramatic temperature cycles range from ambient to cryogenic; phase changes involvie all three states-of-matter; and finally, there are significant vertical-load forces during stopper closure. Lyo-breakage can occur when individual, or combined, mechanical load, thermal shock, and/or drug product expansion forces concentrate at an otherwise insignificant flaw in a vial.

While the mechanism of lyo-breakage is not fully known and has been largely attributed to thermal stress, current studies suggest a primary source of failure is the expansion force of the drug product during freezing.[2]

Alternative Lyo Vial Options

Regardless of the exact cause for lyo-breakage, it seems logical that stronger vials may lead to a reduced likelihood of occurrence. For low volume fills, the traditional vial-of-choice has been thin-walled glass vials with squared-off shoulders and base, cylindrical sidewalls and flattened bases to promote heat transfer. However, for larger fills (20ml – 100ml), molded serum vials as described in ISO-8362-4, and having a much heavier wall, are frequently used.

Recognizing there was an intermediate design, which could be optimized for lyophilization, SGD Pharma developed the EasyLyo vial range. EasyLyo vials combine the strength and chemical durability of molded vials with the geometry and visual characteristics of thin-walled vials.

Technical studies of breakage rates and heat-transfer capability in lyo have shown favorable results for EasyLyo vials. They tested at five-to-ten times stronger than thin-walled vials with respect to side-load and vertical-load fractures. In lyo-breakage tests, using a worst-case formulation and cycle designed to break vials, EasyLyo vials performed better than both traditional thin-walled vials *and* standard molded vials, despite being 33% lighter than the standard molded vials! In heat-transfer studies, the flat base, squared-off shoulder and heel, and uniform sidewall thickness of the EasyLyo vials yielded performance results within 5% of the traditional thin-walled vials.

Outside of lyophilization applications, manufacturers of liquid fills have found another advantage. They have avoided some glass delamination concerns by switching to 5ml and 20ml EasyLyo vials, which are the same size as the thin-walled vials they were using, and – because the body diameters were the same – there was no need for major changes on the filling line and labeling remained the same.

EasyLyo vials are available an ISO 20mm standard neck finish in clear, or amber, USP/EP Type I glass. Nominal fills range from 5ml to 100ml and for either lyophilized or liquid fills, EasyLyo 20ml, 25ml and 50ml vials are available in a ready-to-use (RTU) format, trademarked under SGD Pharma *Sterinity* tradename and utilizing the Ompi EZ-Fill platform. Due to the uniformity and improved cosmetic nature of the EasyLyo sidewall, these vials offer better inspectability compared to standard molded vials.

The EasyLyo product line reflects the SGD Pharma mission to supply high-quality, reliable and innovative glass primary packaging for pharmaceutical and biotech manufacturers. P

References

1. *Lyophilization Services for Biopharmaceuticals Market, 2027.* Research and Markets. 11 Jan. 2018. Web.

2. Machak, D.R. and G.L. Smay. "Failure of Glass Tubing Vials during Lyophilization." *PDA J. Pharm. Sci. Technol.* 73: 30–38 (2019).

GLOBAL COMPLIANCE

How does your company manage to provide local services/support while still efficiently managing global compliance?

Alcami aims to be "Connected at Every Level," and our compliance and quality team members work every day to help us deliver that vision. Like all cGMP companies in the CDMO industry, we host many external and internal audits every year. Our risk-based approach promotes the internal review of activities across all systems, processes and facilities, while concurrently managing a high volume of external audits, which can range from paper assessments to full-scale mock pre-approval inspections. Alcami's corporate regulatory and compliance team works in concert with site-based quality, compliance and leadership teams to support these audits and maintain a constant state of inspection readiness. Operational resource talent pools are leveraged across the Alcami network to tackle opportunities and potential concerns with a holistic approach.

Joseph Payne,
Vice President,
Regulatory Affairs &
Compliance, Alcami

RxGen is a preclinical contract research organization with global reach that offers specialized nonhuman primate models in ophthalmic, CNS and other prevalent disease conditions, with broad experience in small molecule, biologics and gene therapy candidate evaluation. RxGen partners to achieve the development objectives of sponsors in North America, Europe and Asia and complies with international animal research, regulatory and shipping guidelines, and all of those that apply within respective regions.

RxGen's commitment to efficiently conducting resource-intensive research with the objective of improving the lives of patients is inherently a heavily social activity, built on positive relationships maintained at a local level within immediate communication and execution time frames. This includes the physical communities in which RxGen directly works and our emulating the qualities of local-level connectivity in our engagement with clients at distant sites, allowing RxGen to act as an extension of their labs. Our mission is to drive substantial gains in R&D productivity in serving the diverse needs of the biomedical research community globally. Critical to that capability is bringing immediate, firsthand know-how to demands that are specific to a given project and location — an expertise we have achieved through working long and effectively within local and global compliance standards and managing the logistical dependencies associated with multi-site science.

Matthew Lawrence,
Chief Executive Officer and
Chief Scientific Officer, RxGen

Isofol is currently advancing lead developmental candidate arfolitixorin in a global phase III clinical study in patients with metastatic colorectal cancer treated in the first line. With trial sites in the United States, Canada and Europe, we have to be keenly aware of maintaining global compliance throughout the process of designing and executing the trial. We have worked closely with regulatory agencies, as well as top oncology experts from each of these regions, to ensure that we have accounted for as many potential concerns as possible, including regulatory differences and variances in existing standard of care, to make sure that this process is as smooth as possible. We also have regular dialogue with individual trial sites in local regions to ensure that all their trial planning, enrollment and execution needs are met.

Anders Rabbe,
Chief Executive Officer,
Isofol Medical

Catalent provides customized regulatory services for customers utilizing our contract development and manufacturing services. Compliance is interwoven into the regulatory support we provide. Whether Catalent authors applicable sections of a customer's dossier or supports its generation, the customer provides us the applicable sections of the dossier for review and comment prior to submission, ensuring that the regulatory documentation accurately reflects the development history, Catalent's manufacturing process and applicable Health Authority requirements. Regulatory affairs specialists also review proposed changes to assess which products are affected and the type of regulatory reporting that will be required for the change, prior to it being implemented.

We have regulatory affairs experts in various regions to help evaluate the impact of any regulatory changes for the jurisdiction in which a product is registered. Our CDMO regulatory affairs organization stays current with regulatory requirements through the experience of supporting numerous customers. Additionally, we have a dedicated regulatory intelligence team, which shares information throughout Catalent, so we can transform the information into actionable plans to mitigate risk. It is to our advantage to be well informed so we can identify opportunities and optimize product development to deliver successful outcomes for customers and the patients we all serve.

Veda K. Walcott,
Vice President, Global Regulatory Affairs & Compliance,
Catalent

As the world of pharmaceuticals rapidly advances, it is more important than ever to manage both local services and global compliance. We are developing a corrective eye drop for presbyopia, also known as age-related farsightedness, which affects more than 1.8 billion people globally. Our goal is to bring a convenient and on-demand solution to these people in our local community and other regions of the world.

We have designed a strategic path forward to navigate the local and global regulatory and compliance landscape. More than 115 million people in the United States are affected by presbyopia, and that number will increase to over 130 million in the next 10 years. We want to bring a pharmaceutical solution to these people, and that's why it's incredibly important for us to understand the U.S. market and regulatory path. After successfully completing phase IIa studies locally in Israel, we started testing our product candidate in a phase IIb clinical study across several states in the United States.

Elad Kedar,
Chief Executive Officer,
Orasis Pharmaceuticals

Q: How does your company manage to provide local services/support **while still efficiently managing global compliance?**

As a global life science business with a complex supply chain, 59 manufacturing sites and operations in 66 countries, MilliporeSigma is structured to meet local regulations efficiently and compliantly. Adding to this complexity is a broad and deep portfolio of more than 300,000 products, which naturally implies a high number of regulations with which to comply in the various regions of the world.

MilliporeSigma's Quality & Regulatory Management organization enables the business to commercialize or market our products globally in an increasingly stricter and ever-changing regulatory environment. The key here is to be in close contact with local authorities and to have a deep understanding and knowledge of local regulations.

How do we do this? We have a wide regulatory and trade compliance network in more than 40 countries where we need to understand local regulatory requirements and then optimize processes according to these requirements. Our regulatory colleagues are based in the respective countries, speaking the local language, are experienced with local compliance/regulatory requirements and foster collaboration with local authorities.

All around the world, we have harmonized regulatory processes that are scalable and can be customized according to the local requirements. One example is our safety data sheets, which we use to communicate product hazards and appropriate measures to manage risks during transport, storage and handling. We offer more than 25 million safety data sheets in various language combinations for following local regulations.

We are setting industry standards through subject matter expertise and fostering collaborative and fruitful dialogue with local authorities, ensuring that we implement new regulatory requirements early for compliance.

Robert Nass,
Head of Quality & Regulatory Management, MilliporeSigma

"ROUNDTABLE"

Christian Krautkramer,
Senior Counsel & Head of Ethics and Compliance for Life Sciences, GE Healthcare

EVERY COMPANY WITH A LARGE, GLOBAL FOOTPRINT IS FACING INCREASING COMPLEXITY IN LOCAL RULES AND REGULATIONS.

That's why it is important for our legal and compliance teams, including our lawyers, medical affairs, pharmacovigilance, regulatory, quality and other compliance professionals, to build relationships based on trust with the commercial and manufacturing teams. These close collaborations help to spot potential risks early on and speed changes in laws or business practices to the experts who can help guide decisions to mitigate big concerns.

At Lonza, we take compliance very seriously, as we consider it as a key factor for sustainable success. We promote a culture of full transparency and continuous improvement. Compliance is monitored and acted on through various means and across the different levels of the organization. This includes elements such as three-tier Quality Councils (site, business segment, senior management), well-established escalation paths, and tailored Quality/Compliance-related key performance indicators, as well as local and corporate audits. Globally coordinated Quality Alerts serve to share learnings across the network, and the global follow-up of regulatory inspections supports us in preventing (re-)occurrences. We stay current with the ever-changing regulatory landscape by means of global regulatory intelligence, which serves as input for adapting our quality management system (global, local) accordingly. The Global Technical Functions and Global GMP Compliance directly support sites based on individual needs (e.g., inspection readiness support).

Claudia Stampfli,
Head of Global GMP Compliance, Lonza

At Check-Cap, we have leveraged the strong experience of our team and local medical resources in Israel for the development and optimization of our product, the C-Scan system. We initially tested the technology in the local population through clinical trials in Israel and advanced a clear path toward commercialization of the C-Scan system in international markets.

With a global vision in mind and the goal of reducing the global incidence of colorectal cancer, our experienced team always carefully assures compliance to both local and international regulatory standards and has initiated multiple discussions with local and global regulatory agencies, including the European Union, the Israeli Ministry of Health, and the U.S. FDA. Following approval of the C-Scan system in Israel and the CE Mark in Europe, our team focused efforts for the clinical trials in the United States while continuing to harness local resources for the acquisition of additional data to guide further optimization of the C-Scan system. Additionally, our company has strategically established a collaboration with a global leader in medical technology manufacturing, GE Healthcare, to assure the capability to scale up production and distribution of the C-Scan system, while assuring adherence to regulatory and safety standards in various markets worldwide.

Alex Ovadia,
Chief Executive Officer, Check-Cap

CRB actively collaborates with global professional organizations, such as the International Society for Pharmaceutical Engineering (ISPE) and Biophorum Operations Group (BPOG), and has been very instrumental in the development of several ISPE Baseline® Guides and six of the eight phorums of BPOG. Our subject matter experts' passion for technical excellence, combined with their experience in the execution of international projects, allows them to have an exceptional understanding of global compliance. This knowledge is shared with our various centers of excellence through internal workshops and summits, giving us a deep bench of resources with global experience.

Our local project teams include at least one subject matter expert with experience in the specific technology to be used and knowledge of the compliance requirements of the country where the project will be executed and/or the products will be sold. Our subject matter experts also participate in various reviews dictated by our quality program to ensure that compliance requirements are incorporated into the design of the project in a timely manner.

Daniel G. Lachapelle,
PE, Regional Leader, CRB

REGULATORY HARMONIZATION

What do you identify as the greatest advances that have been achieved in recent years with respect to harmonization of pharmaceutical regulations?

One of the more significant advances for the industry was the Mutual Recognition Agreement (MRA) between the FDA and the EU. That agreement allowed FDA and EU inspectors to utilize inspection reports and additional information generated by the other party. To accept an EU member country into the MRA, the FDA conducted a capability assessment of that country's inspectorate. In September 2015, three FDA district offices were visited by EU officials to assess the FDA's capabilities. As of July 11 2019, all 28 member countries have been deemed capable inspectorates and have entered into the MRA.

The MRA will undoubtedly lead to greater efficiencies for both regulatory agencies through information exchange and coordination of inspections. The agencies will be able to focus on inspecting organizations that present a higher risk to public health. While both authorities can inspect an organization at any time, the anticipated benefit to industry includes a reduction in duplicate inspections. We have already noticed several differences in our multinational on-site inspections and pre-inspection activities. This is a welcome change, and we look forward to the continuing progress in mutual recognition between the regulators governing the pharmaceutical space.

Joseph Payne,
Vice President, Regulatory Affairs & Compliance, Alcami

As a Belgian biotech company running global clinical trials advancing treatments intended to reach multiple major world markets, synchronizing regulatory bodies, including the U.S. Food and Drug Administration (FDA), the EMA and Belgium's Federal Agency for Medicines and Health Products (FAMHP), is of the utmost importance to our business. A major advancement in recent years is increased harmonization between these agencies, especially on rapid regulatory approval of production and process updates with therapies tested globally.

A good example of such harmonization is the simultaneous approval by both the FDA and FAMHP to use our new proprietary OptimAb manufacturing process for our NKG2D-based CAR-T cell therapies CYAD-01 and CYAD-02. This dual approval allows smooth transition of this innovation from the laboratory to the clinic to ensure that we offer the most advanced solution to patients involved in our clinical trials worldwide. Synchronizing global regulators ultimately benefits the patient by allowing innovative companies to provide clinical trial sites around the world with the most up-to-date products.

Filippo Petti,
Chief Executive Officer, Celyad

MilliporeSigma welcomes the harmonization of regulations, which makes it easier to operate as a global life science business. On the other hand, we still see different local interpretations of global regulations, which can make things more complicated for our worldwide supply chain.

A few examples of harmonization that we recognize as great achievements:

- Mutual recognition agreement between the European Union and the United States for medicines, now fully operational for human medicines as of 11 July 2019, following a transition phase. This will reduce the amount of inspections as it allows the authorities to rely on each other's GMP system.
- Medical Device Single Audit Program (MDSAP): Authorities participating in the program are the World Health Organization, the U.S. FDA and authorities from Australia, Brazil, Canada, Japan and the EU. It allows a MDSAP-recognized auditing organization to conduct a single regulatory audit of a medical device manufacturer, satisfying the requirements of the regulatory authorities participating in the program.
- EXCiPACT™ Certification: This certification was developed in partnership with the International Pharmaceutical Excipients Council, with input coming from academic fields, industry and the U.S. FDA. MilliporeSigma played a vital role in shaping this program to define and standardize GMPs and good distribution practice (GDP) for excipients. EXCiPACT™ certification grants an independent, one-stop "seal of approval" by third-party auditors. With EXCiPACT™ certification, a single audit will be all it takes to prove that an excipient complies with current GMP and GDP requirements. This certification for manufacturers, suppliers and distributors of pharmaceutical excipients minimizes risks to customers and helps to reduce the burden of audits and thus costs.
- REACH (registration, evaluation, authorization and restriction of chemicals) in the EU is one of the most advanced regulations of the world, which recently reached a milestone with wave 3. This regulation provides a standard regulatory framework for Europe, which will lead the way for further global regulations.
- PIC/S: The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme are two international instruments between countries and pharmaceutical inspection authorities. This non-binding, informal cooperative arrangement between regulatory authorities in the GMP field of medicinal products for human or veterinary use is open to any authority having a comparable GMP inspection system. Currently, there are 52 active state members.

Robert Nass,
Head of Quality & Regulatory Management, MilliporeSigma

International agencies, such as the World Health Organization (WHO) or the International Organization for Standardization (ISO), have developed important initiatives over the years to advance global harmonized medical device regulations. The ISO has published a set of voluntary international standards, extensively adopted both at regional and national levels, in relation to product development, manufacturing, quality assurance and control to provide the different governments with a technical base for health, safety and environmental requirements. The WHO has similarly published international guides to help member states develop internationally compatible regulations. At Check-Cap, we are constantly monitoring and adopting these initiatives and guidelines to ensure that our product is being held to the highest standards in terms of patient safety, product quality and global compliance and to ensure that patients from multiple countries can access and benefit from our C-Scan technology.

Alex Ovadia,
Chief Executive Officer, Check-Cap

Q: What do you identify as the greatest advances that have been achieved in recent years **with respect to harmonization of pharmaceutical regulations?**

Our ability to leverage data and work done in one jurisdiction to support regulatory approval in another and to bring lifesaving biotherapeutics to market faster is certainly a big step forward. Regulatory agencies worldwide seem to use technology to enhance speed in moving drugs from application to approval. They also seem to be more receptive than ever to industry input, especially where they have a lack of internal expertise, such as new regulations around use of artificial intelligence as either a manufacturing or clinical enhancement. Hopefully, regulators will continue this momentum of cross-agency collaboration.

Christian Krautkramer,
Senior Counsel & Head of Ethics and Compliance for Life Sciences, GE Healthcare

I consider the recent full implementation of the mutual recognition agreement (MRA) between the European Union and the United States as a very positive development. This covers inspections of manufacturing sites for certain human medicines (e.g., APIs, pharmaceuticals in various dosage forms, biotechnology-derived biological products) in their respective territories. From an industry perspective, we expect a reduction in the number of regulatory inspections with the same scope, which allows us to free up resources for continuous improvement activities. The impact will primarily be in the area of surveillance and general GMP inspections, and we hope the MRA work will continue to include additional inspection types (i.e., application-related inspections) and additional product categories (e.g., ATMPs (advanced therapy medicinal products)) in the near future.

Claudia Stampfli,
Head of Global GMP Compliance, Lonza

For our ongoing phase III clinical trial, we are having all manufacturing of drug candidate arfolitixorin completed by Recipharm, a major European contract manufacturer of pharmaceuticals. The drug product is then shipped to our distributor with several storage facilitates to ensure that all active trial sites have arfolitixorin throughout the phase III trial. It may sound simple, but one of the most impactful recent advances with respect to harmonization of pharmaceutical regulations for shipping, import/export and customs has been the digital revolution. Having the ability to schedule, register and log shipments of arfolitixorin electronically with the required officials has significantly reduced small errors that could otherwise delay the process. We look forward to integrating digital communications and electronic records to further improve these coordinated activities.

Anders Rabbe,
Chief Executive Officer, Isofol Medical

The progressive harmonization of animal welfare standards and regulatory definitions of good laboratory practices (GLP) have been key to RxGen's ability to grow and thrive in this era of rapid biomedical advances and strong stakeholder interests in research quality. With the combination of standards into a global set of practices, specific local political/regulatory jurisdictions carry reduced importance, streamlining the creation and operation within broadly applicable standard operating procedures and setting the stage for greater scientific reproducibility and animal welfare.

Matthew Lawrence,
Chief Executive Officer and Chief Scientific Officer, RxGen

Speed and ease of communication have resulted in real global participation. Formal and informal groups are easily developed across the industry to facilitate open communication and knowledge sharing. Communication tools are readily available to enable this participation, and the result is real harmonization of pharmaceutical regulations.

Scientific consensus on innovative advancements can be reached quicker due to the ability to easily communicate on a global scale and the willingness of regulatory and industry experts to openly share information. Harmonized guidelines are more readily adopted when the community has the opportunity to participate during the development of technical documents.

Daniel G. Lachapelle,
PE, Regional Leader, CRB

The harmonization of Module 3 – CMC sections by the International Council on Harmonization (ICH), has allowed a global submission approach that reduces regional submission variations, reduces regulatory authoring timelines and reduces post-market life cycle management activities. The implementation of the electronic common technical document (eCTD) is also a great achievement, as electronic submissions decrease authoring, review and publication time. The ICH and global Ministry of Health agencies are continuing to build Quality-by-Design principles to allow the identification of established conditions and continue to reduce the impact of post-market life cycle changes. These harmonization activities contribute to the pharmaceutical manufacturer's ability to continue to meet global demand throughout the product life cycle.

Veda K. Walcott,
Vice President, Global Regulatory Affairs & Compliance, Catalent

The harmonization of pharmaceutical regulations has become increasingly important to bring together the pharmaceutical industry and regulatory authorities. It is essential that biopharma professionals between nations can share reliable information with one another for the timely advancement of life-changing technology. For example, the development of our phase IIa and phase IIb trials was made possible through harmonization of clinical trial regulations. In our phase IIa trials, we tested our CSF-1 eye drop on more than 70 individuals, mainly in Israel.

This is a multi-center, double-masked trial enrolling 150 participants with presbyopia to evaluate the efficacy and safety of CSF-1. The harmonization of pharmaceutical regulations has made it possible to efficiently transition our studies from Israel to the United States. Additionally, Orasis was granted an accelerated FDA approval process thanks to prior established global research and clinical experience of ingredients in our eye drop. Our regulatory pathway is a 505(B)(2) abbreviated pathway, allowing us faster access to the market without compromising safety. The harmonization of research from scientists and clinicians across the globe has helped fast-track the development of our product for people living with presbyopia.

Elad Kedar,
Chief Executive Officer, Orasis Pharmaceuticals

Vladas Bumelis, Ph.D.
Chairman of the Board
Northway Biotechpharma

Northway Biotechpharma Celebrates 15 Years of Growth and Success

Northway Biotechpharma, a leading biopharmaceutical contract development and manufacturing organization (CDMO), celebrated its 15th anniversary on July 16, 2019. As a midsized CDMO, Northway Biotechpharma is able to provide flexibility and responsiveness backed by a strong foundation in science and technology.

The company focuses on understanding its customers and meeting their specific needs without binding them to one single approach. It is able to react rapidly to unexpected project changes, adjusting timelines, capacities and other activities to meet its customers' evolving needs. On average, Northway Biotechpharma has 25–30 development projects underway each year, ranging from gene cloning to final drug product manufacturing.

The entire history of Northway Biotechpharma is important and has made an impact on what we are today and helped establish the values we live by: leadership, openness to change, creativity, strategic discipline and excellent execution are the keys to our success.

History of Rapid Growth

Founded in 2004 as a CDMO providing support for branded biologics and biosimilars, Northway Biotechpharma – then just Biotechpharma – began operating in rented space for product development and small-scale GMP manufacturing activities. During the past 15 years, the company has become a full-service CDMO with capabilities in cell line development, process development and optimization and mid-volume GMP manufacturing of biologic drug substances and drug products – both branded biopharmaceuticals and biosimilars.

Strong Customer Focus

Throughout its first 15 years, Northway Biotechpharma has focused on providing its customers with the highest level of quality and service. Today, the track record of performance and high level of trust that the CDMO has established with its customers result in frequent recommendations and an increasing number of customers. Northway Biotechpharma is deeply invested in providing high quality, world-class CDMO services and long-term partnerships based on its blend of experience and openly collaborative project teams.

Ongoing Commitment to Reinvestment

The commitment to Northway Biotechpharma's customers is also reflected in the company's ongoing willingness to reinvest and enhance its services and capabilities. Recent management changes, new branding and new capacity are enabling Northway Biotechpharma to further advance its mission of becoming a single-source CDMO able to support its worldwide customers with a full range of development and manufacturing services from the clinic to the market.

Exciting Future Ahead

The entire history of Northway Biotechpharma is important and has made an impact on what we are today and helped establish the values we live by: leadership, openness to change, creativity, strategic discipline and excellent execution are the keys to our success.

Giedrius Žunda, CEO of Northway Biotechpharma, added, "I see a great opportunity to leverage the company's vertically integrated business model and to lead its talented employees to deliver increased value for shareholders. I am excited to lead this organization to its next stage of evolution."

About Northway Biotechpharma

Northway Biotechpharma is a contract development and manufacturing organization (CDMO) supporting worldwide customers. Its highly experienced biochemistry, biology and bioprocess engineering staff can deliver projects at any stage, from cell line construction and process development to cGMP production of biopharmaceutical products. High-quality performance and on-time delivery are guaranteed by a team of highly qualified and experienced researchers, engineers, technologists and management professionals.

Northway Biotechpharma is headquartered in the EU member state of Lithuania, a fast-growing biotech hub with a state-subsidized university system that supports a highly-educated scientific workforce.

Our global teams based in the US and Europe are exceptionally well-versed in all aspects of the biopharmaceutical value chain, from cell line development to commercial production and aseptic fill-finish. We continually invest in expansion at our modern facilities, located just 20 minutes from Vilnius Airport, which makes us easily accessible via multiple daily flights from many European hubs. We are deeply invested in providing high quality, world-class CDMO services and long-term partnerships based on our blend of experience and openly collaborative project teams. P

▶ 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.

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

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Charlotte, NC 28209

Established from humble beginnings in Durban, South Africa, and with a 160 year heritage, **Aspen Pharmacare** has grown into a leading specialty and branded multinational pharmaceutical company. Aspen Pharmacare's manufacturing capabilities are scaleable to demand and cover a wide variety of product types including injectables, oral solid dose, liquids, semi-solids, steriles, biologicals and active pharmaceutical ingredients. The company operates 23 manufacturing facilities across 15 sites.

www.aspenpharma.com
+1 27 31 580 8600
9 Rydall Vale Park, Douglas Saunders Drive
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Axial Biotherapeutics is a clinical stage biopharmaceutical company harnessing the gut-brain axis to develop novel Central Nervous System (CNS) Therapeutics to improve the quality of life for people with CNS diseases and disorders. Axial's scientific co-founder, Sarkis K. Mazmanian, Ph.D., and researchers from the California Institute of Technology (Caltech) discovered a novel, causal link between the gut microbiome and Parkinson's Disease (PD) and Autism Spectrum Disorder (ASD).

axialbiotherapeutics.com
+1 781 701 8468
9 Fourth Avenue
Waltham, MA 024511

BioVectra is a North American CDMO specializing in microbial fermentation, complex chemistry, high potency APIs, process and analytical development, and drug development. With over 45 years of experience, BioVectra provides cGMP outsourcing solutions for intermediates and APIs, which have been used in the treatment of a myriad of life-threatening diseases.

www.biovectra.com
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Boyle Transportation is a specialized trucking firm providing exceptional quality, safety, and security to select clients in life sciences and defense. By combining expertise in highly regulated and valuable military cargo with rigorous quality and temperature protocols, Boyle Transportation is now widely regarded as the premier provider of end-to-end, secure cool and cold chain truckload services for pharmaceutical shippers in the U.S. and in/out of Canada.

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15 Riverhurst Road
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Castleford Capital invests in growing pharmaceutical development and tech-enabled healthcare services companies. Castleford backs management teams with capital, relationships and operational resources that empower company leadership to attain new levels of growth. Castleford focuses on lower middle-market companies including CROs, CDMOs, PBMs, pharmacy services, RCM and tech-enabled healthcare solutions.

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300 Park Avenue, 12th Floor
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CRB is a full-service network of engineers, architects, constructors and consultants assisting advanced technology organizations in the planning, design, construction and operational support of facilities across the globe. CRB serves clients in biotechnology, pharmaceuticals, science and technology, food, nutraceuticals and consumer products, providing support across the full project lifecycle.

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ClostraBio's world-leading scientific team has made key discoveries that highlight the importance of the intestinal microbiota in regulating allergic sensitization to food. The company is committed to a deeper understanding of the role of intestinal microbes in gut barrier function and determining the mechanisms of barrier protection. ClostraBio is breaking new ground in treatments that restore this protective intestinal barrier function in individuals where it is compromised.

www.clostrabio.com
1452 E 53rd Street
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Established in 1994, **Doppel** is today recognized as one of Europe's leading experts in contract R&D and manufacturing. It has start-of-the-art facilities and highest scientific capabilities to service its international pharmaceutical and nutritional clients. The company is committed to applying its innovative technologies, deep knowledge and broad experience to develop products of the highest quality for its customers worldwide.

www.doppel.it
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Evolve Biologics is a new kind of biologics company. We're built around a next-generation technology for bringing critical therapeutics to the people who need them. We believe our patented next-generation technology, PlasmaCap EBA™, is the first major advancement in the field since the 1940s. We believe it will help us deliver critical plasma-derived therapeutics at higher levels of purity, efficiency, and quality than conventional methods can.

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420 Ambassador Drive
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Grifols provides CDMO services for bulk recombinant proteins produced by microbial and mammalian expression systems for use in diagnostics, therapeutics and vaccines. Based in the San Francisco Bay Area, they have three decades of process development and GMP manufacturing experience, and they support long-term relationships through expertise, quality, and reliability.

www.grifols.com
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Grifols Partnership is a business to business contract development and manufacturing platform for sterile solutions (small molecules) and lipid emulsions with over 75 years of experience in producing high-quality intravenous solutions for the pharmaceutical industry worldwide.

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Haig Barrett Inc. facilitates the optimization of innovation, technology, culture and products to stimulate the growth and profitability of organizations. Its senior expert consultants multiply the force of clients' teams by offering the data-driven insights and expertise needed to grow your business faster.

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Leukocare is a privately owned, product-focused, clinical-stage biotechnology company founded in 2003 and headquartered in Martinsried/Munich, Germany. Leukocare AG is dedicated to providing processes and services that consistently meet or exceed the requirements and expectations of our customers through the application of a certified Quality Management System in accordance to EN ISO 13485.

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Northway Biotechpharma is a CDMO supporting clients worldwide. They offer fully integrated services, thus saving clients valuable time and money as a real one-stop solution. In state-of-the-art R&D/process development and manufacturing facilities, Northway Biotechpharma performs different projects at any stage, starting from cell line construction and process development up to cGMP production of biopharmaceutical products. Northway Biotechpharma has expertise in development and GMP compliant manufacturing of biotechnological drug substances as well as drug products.

www.biotechpharma.lt
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Mokslininku str. 4
LT-08412 Vilnius, Lithuania

Q3 2019 COMPANY PROFILES

Olon S.p.A. is one of the largest European developers and manufacturers, supplying APIs to pharmaceutical industries worldwide for both generic and CDMO markets. Their mission is to be a world leader in the manufacturing and sales of advanced intermediates and active pharmaceutical ingredients (APIs) for human and animal health, and food companies.

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PharmaBioSource is a life sciences advisory and consulting firm specializing in global facilities and product transactions for pharmaceutical, biotech, and Life Sciences companies. They also consult with healthcare investors to support life sciences investment due diligence and risk analysis. PharmaBioSource offers an extensive collection of expert pharma advisory services and solutions that are designed to help your company make strategic decisions and improve how you do business.

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Piramal Pharma Solutions is the contract development and manufacturing arm of Piramal Healthcare, a part of Piramal Enterprises Limited. Piramal Pharma Solutions provides a comprehensive range of services across all phases of the drug life cycle, including drug discovery and development, manufacturing and packaging of clinical trial supplies, and delivering commercial volumes of APIs and finished dosage products.

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Established in 2011 and headquartered in Incheon, South Korea, **Samsung BioLogics** is a world class CDMO offering state-of-the-art development, manufacturing, and laboratory testing services. With a flawless regulatory record, the highest capacity, and the fastest throughout, Samsung BioLogics is the most qualified CDMO as chosen by our clients and is uniquely able to support the development and manufacturing of biologics product at every stage of the process while meeting the evolving needs of pharmaceutical companies worldwide.

www.samsungbiologics.com
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Servier provides fully integrated manufacturing and supply chain services for small molecules & drug product, from development and clinical supply up to commercial launch. Servier possesses 11 state-of-the-art facilities, a proven track record in chemical synthesis, pharmaceutical formulation, development and manufacturing, and a complete range of services offering full flexibility. Services include process and analytical development, pilot production and industrial scale production, and regulatory dossiers, in collaboration with the Servier network.

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SGD Pharma is a leading provider of glass pharmaceutical packaging, with five ISO 15378 certified manufacturing plants throughout Europe and Asia. SGD Pharma offers a broad range of sizes and finishes in Type I, II or III, amber and clear glass molded vials and bottles, as well as innovative added-value products and services, including RTU sterile molded glass vials, internal siliconization and protective plastic coatings.

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SK pharmteco is a U.S.-based Contract Manufacturing Organization (CMO) that consolidates the operations of AMPAC Fine Chemicals and SK biotek Korea and Ireland. The company has global manufacturing facilities with demonstrated capabilities in process development, scale-up, and cGMP-compliant commercial production of active pharmaceutical ingredients and registered intermediates for pharmaceutical and biotechnology customers worldwide.

+1 916 355 1000
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At **Sosna & Co.,** clients come first. We leverage our global network to make impactful connections for our business partners. As every business faces unique challenges, we work closely with our client to create customized solutions.

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www.stemsontx.com
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Teewinot Life Sciences is a global leader in the biosynthetic development and production of cannabinoids and their derivatives for consumer and pharmaceutical products. The company is leveraging a unique integrated biocatalytic and chemical synthesis platform, that allows the production of an unprecedented range of cannabinoids and cannabinoid NCEs from bench to cGMP manufacturing.

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TriRx Pharmaceutical Services is a global contract development and manufacturing organization (CDMO) serving the biopharmaceutical market. Headquartered approximately 50 miles outside of New York City in Norwalk, Connecticut, we operate facilities providing state-of-the-art laboratory, manufacturing, packaging and warehousing capabilities.

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Thermo Fisher Scientific is the world leader in serving science, with revenues of more than $24 billion and approximately 70,000 employees globally. Our mission is to enable our customers to make the world healthier, cleaner and safer. We help our customers accelerate life sciences research, solve complex analytical challenges, improve patient diagnostics, deliver medicines to market and increase laboratory productivity.

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UPM Pharmaceuticals Formulating Your Future™

UPM Pharmaceuticals is a Bristol, Tennessee–based, independent drug-development and contract manufacturer serving the pharmaceutical and biotechnology industries. The company provides pharmaceutical drug development services — including formulation development, cGMP manufacturing, analytical methods development and stability testing — from concept to commercialization. UPM's focus is on drug development for dosages with oral routes of administration, in solid dosage forms such as capsules and tablets, and semisolid creams and ointments.

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VETTER

Vetter is a global contract development and manufacturing organization (CDMO) headquartered in Ravensburg, Germany, with production facilities in Germany and the United States. The company has long-term experience offering services ranging from early development support, including clinical manufacturing, to commercial supply and various packaging solutions for vials, syringes, and cartridges.

www.vetter-pharma.com
+49 (0) 751 3700 0
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Germany

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Q3 2019 COMPANY PROFILES

YOURWAY THE BIOPHARMA SERVICES COMPANY

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

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- Lonza
- MilliporeSigma
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2019 Biologics Market Report & CDMO Pricing Study

Optimize Your CDMO Positioning & Pricing

To consistently be top of mind, placed on shortlists and winning business from companies seeking a biologics CDMO, you need to know the latest market trends, your competitive arena, and how you match up on pricing and other benchmarks. You can get all of this in our Biologics Market Report & CDMO Pricing Study.

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TEL +1 212 366 4455

Nigel Walker
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Guy Tiene
Business Director, Partner
E: guy@thatsnice.com

Core Deliverables of This Market Report

+ Data collection from 100 biopharmaceutical CDMOs
+ One-on-one interviews (primary data) from KOLs representing CDMOs
+ Pricing on all common line items for mammalian and microbial innovator drug substance projects
+ Low, median and high pricing data
+ Regional break down for North America, Europe and Asia
+ Analysis of the data gathered from interviews

Answers to Key Questions About the Pricing Study

+ Respondents had an average of 22 years of experience in commercial production
+ CDMOs that responded reported an average of five active commercial projects in house
+ Pricing data came only from responses from CDMOs – no data derived from buyers (innovators)

Over 1,500 Hours of Data Collection & Analysis

+ Report Page Count: 200+
+ Data From 30 Key Opinion Leaders
+ Data Collection on 100 Biologics CDMOs
+ Data Collection: February–July 2019

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