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A NICE INSIGHT MAGAZINE

Q2 2018 VOLUME 4 NUMBER 2

THE NEXT-GENERATION ISSUE

THINKING A GENERATION AHEAD: CHALLENGES & DEVELOPMENT

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A NICE INSIGHT SUPPLEMENT

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→ A NOTE FROM THE EDITOR

GETTING NEXT-GENERATION THERAPIES INTO THE HANDS OF PATIENTS – THE INDUSTRY TAKES ON BIG CHALLENGES

→ BY **CYNTHIA A. CHALLENER, Ph.D.**, NICE INSIGHT

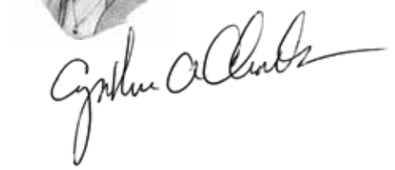
In this, our second issue of 2018, we explore the next-generation therapeutics that are demonstrating great potential to not only treat but to cure previously untreatable diseases. The industry faces numerous challenges to bring these novel medicines to market, and many innovative companies, from start-ups to established big pharma firms, are developing innovative technologies to overcome them.

Multiple advances are being made. These include improvements in screening processes to identify new candidates with better probabilities of commercial success, as well as enhanced expression systems for the production of complex drug substances and the design of modular, flexible equipment and facilities specifically for the production of next-generation biologics.

Our feature article focuses on these challenges to the discovery, development and manufacturing of next-generation therapeutics. Contributors in this issue provide thought-provoking discussions on topics of crucial importance to the successful realization of all biopharmaceuticals.

These thought leaders represent the entire gamut of service providers in the pharmaceutical industry. They tackle wide-ranging issues such as challenges in raw material management and security of supply, the development of oral peptide formulations, the importance of controlled nucleation during aseptic lyophilization, considerations when manufacturing in multi-product facilities and minimizing risk in direct-to-patient clinical trials.

We also hear from a range of biologics and specialty suppliers, learn about recent acquisitions and expansions made by CDMOs to better meet the needs of their global customers in locations across the U.S., Europe and Asia as well as the growing importance of integrated CDMOs that can support customers from gene to patient. P



M&A COLUMN

INSIDE MERGERS & ACQUISITIONS

Kevin Bottomley
Partner, Results Healthcare

Innovation and efficiency are both key to successful drug development and commercialization. In addition to internal investment in R&D, mergers and acquisitions and licensing deals are fundamental strategies for gaining access to novel therapeutic compounds and platform technologies that can expand pipeline portfolios and broaden market reach. These factors apply to both pharma companies and contract service providers.

GOOD FUNDAMENTALS

Pharmaceuticals have been, and continue to be, one of the most effective ways of managing disease and ailments which impact human health. A number of factors are driving current deal activity (including M&A, asset divestment, licensing and fund raising) in the pharmaceutical industry. First of all, the fundamentals are strong. The global population is growing, while the economic status of many people in emerging regions is consistently improving. As a result, more people can afford to pay for healthcare and are seeking access to advanced treatments.

Indeed, the pharmaceutical industry is massive. Healthcare spending represents approximately 10% of global GDP, which was estimated by the World Bank to be $75.848 trillion in 2016[1]. Drugs account for about 10-11% of overall healthcare costs, or approximately 0.5-1% of global GDP – that equates to $379-758 billion.[1] The healthcare industry is also attractive because pharmaceutical companies – and their contract service providers – operate outside normal economic cycles. Medical care is a necessity, independent of, and unphased by, the economic climate.

PHARMA FOCUSED ON BIOTECH ACQUISITIONS

Deals in the pharmaceutical industry are an important mechanism of acquiring innovation, business and efficiency, as such transactions are an essential activity for the majority of healthcare companies and their very senior personnel. In many cases, senior management may only be involved in a very few transactions throughout their career, so the advice and support of transaction specialists is essential to ensure a successful transaction.

Pharmaceutical M&A activity has remained strong over the past several years. In many cases, this activity is the result of companies seeking to broaden their pipeline portfolios. While many candidates continue to be developed in-house, pharmaceutical companies are turning to acquisitions of, and licensing deals with, biotech firms to gain access to next-generation technologies as well as innovative treatments.

CMOs/CDMOs ACQUIRING PHARMA ASSETS

Like the pharmaceutical industry, the contract services sector is growing at a healthy pace (upper single-digit growth across this industry). The same drivers that are leading pharmaceutical companies to seek new technologies from biotech companies have led to greater outsourcing activity. Current and future medicines require specialized technologies and manufacturing capabilities. Contract development and manufacturing organizations can offer a useful outsourced manufacturing option for the pharmaceutical company, which will have cost benefits. CDMOs can attract a broad base of customers by additionally offering advanced technologies and even developing their own proprietary modifications and offerings.

A second driver for growth is the concern of supply chain security. The significant level of outsourcing to firms in Asia (specifically China and India) that began approximately 10–15 years ago is trending in reverse. Some of the historical cost efficiencies have disappeared as the cost of manufacturing in Asia has increased, moving closer to Western levels. As a result, the greatest M&A activity in the CMO/CDMO space is taking place in the west, particularly by CDMOs based in the US and Europe looking for additional capacity and capabilities, especially in North America.

MEET RESULTS HEALTHCARE

Founded in 1991, Results Healthcare is a transaction advisory company. We provide our clients with support on both the sell and buy sides of transactions, including classical mergers and acquisitions, asset divestments and licensing deals. We also provide fundraising assistance. Our parent company Results International specializes in three important industry sectors – Marketing (Marcoms), Technology (Software) and Healthcare – with the Results Healthcare business accounting for approximately 50% of overall company revenues.

WHILE MANY CANDIDATES CONTINUE TO BE DEVELOPED IN-HOUSE, PHARMACEUTICAL COMPANIES ARE TURNING TO ACQUISITIONS OF, AND LICENSING DEALS WITH, BIOTECH FIRMS TO GAIN ACCESS TO NEXT-GENERATION TECHNOLOGIES AS WELL AS INNOVATIVE TREATMENTS.

With locations in New York and London, Results Healthcare supports clients largely in the U.S. and Europe, but also frequently works with companies in Asia and Latin America. Our people have diverse backgrounds in healthcare and a strong passion for the industry, combined with a deep understanding of the financial and legal aspects of executing deals. P

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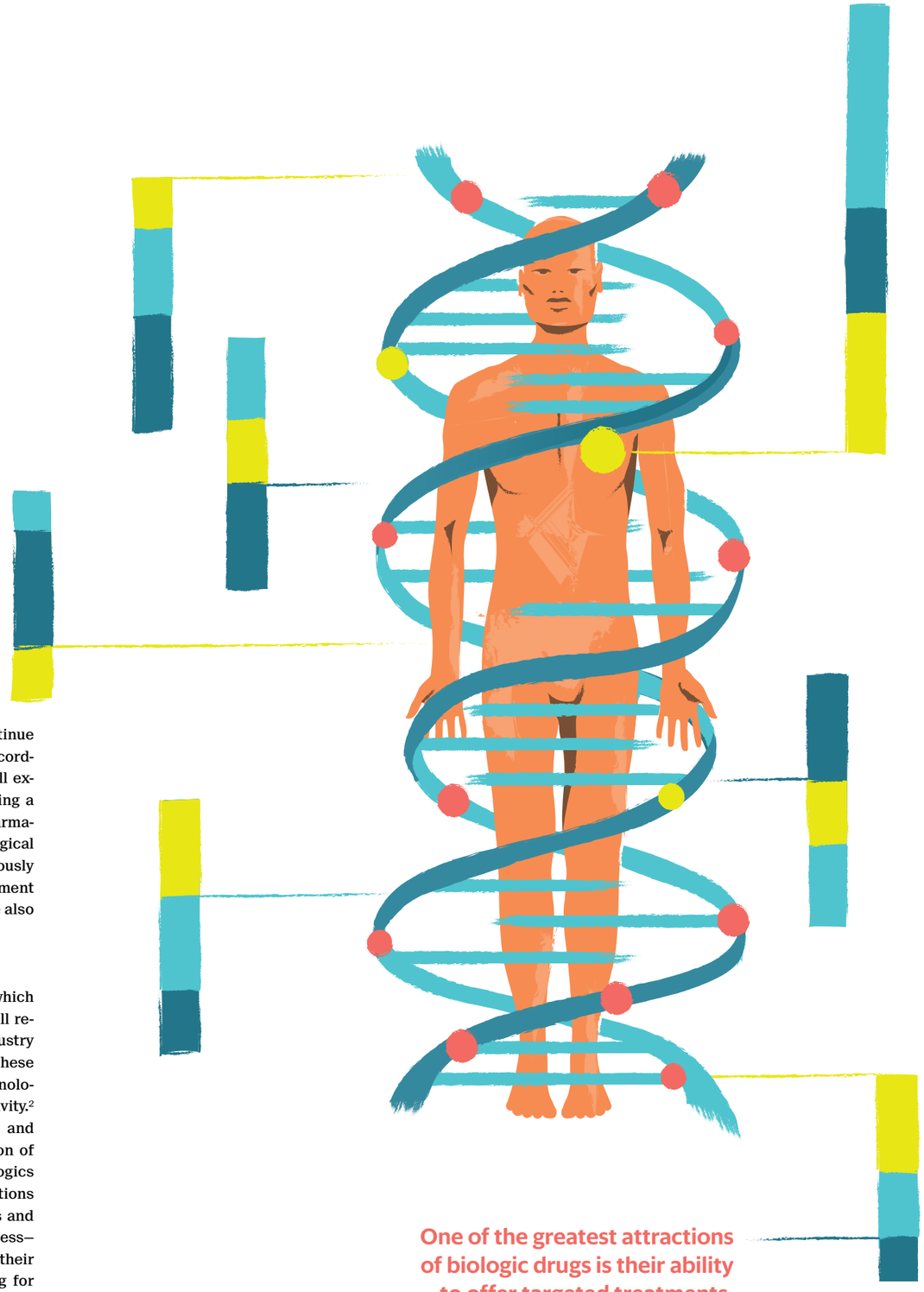
CHANGES IN THE BIOPHARMA INDUSTRY: FROM MINOR TO MAJOR EVOLUTION

By **Nigel Walker**, Nice Insight



The biopharmaceutical industry continues to grow rapidly. Targeted biologics are helping treat previously untreatable diseases. New technologies such as gene editing are leading to the development of even more advanced, targeted medicines. The application of artificial intelligence is helping to reduce costs and increase efficiencies across the entire biopharmaceutical value chain. Real-world evidence and digital technologies are creating new medical solutions that will change the way diseases are detected, treated and prevented.

Continued Healthy Growth

The market for biologic drugs is predicted to continue its strong growth over the next several years. According to Mordor Intelligence, the global market will expand at a CAGR of 8.5% from 2018-2023, reaching a value of $341.16 billion by 2023.[1] Because biopharmaceuticals can theoretically modulate any physiological pathway that is well understood and treat previously untreatable diseases, significant further development of biologics is anticipated. Patent expirations are also creating opportunities for biosimilars.

Improved Efficiency and Productivity

Reducing costs and increasing the speed at which new drugs are developed and commercialized will remain a top issue for the biopharmaceutical industry going forward. Manufacturers are achieving these goals through the implementation of new technologies that allow greater efficiency and productivity.[2] For instance, the construction of multi-product and flexible manufacturing facilities and the adoption of single-use technologies are both increasing. Biologics producers are also constantly seeking new solutions to increase the titer and yield of their processes and implementing autorotation, monitoring and process–control technologies to improve the efficiency of their operations. Interest in continuous bioprocessing for both upstream and downstream operations continues to grow as well.

Robotic and cognitive automation (RCA) is also being used to streamline resources across the clinical trial value chain, according to Deloitte.[3] According to the firm, RCA has the potential to accelerate clinical trial site selection, support site initiation and improve site monitoring. Separately, natural language generation (NLG) will be employed to automate safety and efficacy sections of dossier submissions.

More Targeted Therapies

One of the greatest attractions of biologic drugs is their ability to offer targeted treatments. This ability ties in well with the growing interest in the development of treatments for rare diseases. With low development costs and high market value, rare disease therapeutics are attractive. To date, however, treatments for less than 1% of the world's population have been developed.[4] The pipeline of rare disease drugs is full, with many new biologic candidates developed as the result of breakthroughs in gene therapy, nucleic acid therapy and gene editing.

Numerous biotech startups are working on nucleic acid therapeutics, including DNA delivery, DNA modification (gene editing, gene therapy) and modified RNA/mRNA technology companies. Gene therapy is exciting because it has the potential to cure diseases that are considered chronic conditions that would require ongoing, long-term pharmaceutical care in a single treatment. Gene editing – notably CRISPR-Cas9 technology – is playing a key role in the advancement of many different gene and cell therapies. Rapid gene sequencing and next-generation sequencing machines are also enabling the development of new drugs, the use of genetic markers and genetic background information to select treatments and true precision medicine.[4]

Cell therapies will also have a tremendous impact on the biopharmaceutical industry in the years to come, as many new treatments progress through late-stage clinical trials and receive market approvals. Both major biopharma firms and emerging biotech companies are investing in CAR T-cell targeted therapies, particularly for the treatment of oncology indications.

Rapid advances in immunotherapy treatment are also taking place, many with the goal of preventing diseases.[5] While most of the drugs under development today are focused on the treatment of cancers, companies are also investigating their application for the targeted treatment and prevention of other chronic conditions like diabetes, cardiovascular diseases, Parkinson's and multiple sclerosis.

One of the greatest attractions of biologic drugs is their ability to offer targeted treatments.

Electroceuticals and Implantables

Electrical management of the body using bioelectronics and electroceuticals has the potential to impact the way many diseases will be treated in the future.[4] Galvani Bioelectronics, the joint venture between GSK and Google, is one company developing miniature devices designed to change nerve electrical signals. Investments in the brain machine interface (BMI) and smart implantables (enabled by extreme miniaturization of electronics) for targeted drug delivery when needed (via monitoring using sensor technology) are also increasing. Digitally-enabled pharmaceutical drug/device combinations that serve as closed-loop systems for automatic dosing could potentially change hospital and subacute care. Such devices could also allow consumers to detect disease states much earlier and thus receive more effective treatment before a disease progresses.

Using Real-World Evidence

Access to real-world evidence (RWE) may dramatically impact new drug development and facilitate clinical trial setup.[3] Using data in new ways may also have the potential to move treatment to the pre-disease state.[6] Data obtained from genetic mapping can be linked to observations of disease characteristics, leading to the identification of new diagnostic markers. When combined with clinical lab results, real-time data generated from wearables and other mobile technologies, behavioral data from social media sites and data on how patients on existing drugs are responding, genetic information can expand the applicability of precision medicine and, perhaps, even enable predictive medicine.

Applying Artificial Intelligence

Artificial intelligence (AI) can be used to analyze large sets of pharmaceutical data – whether research results, manufacturing process information, preclinical study data, clinical trial results or patient treatment responses – and thus has potential to impact all aspects of drug discovery, development and commercialization. Perhaps most significantly it may help reduce the cost of R&D activities by driving greater efficiency.[6] For instance, AI can help identify patterns and links across large sets of data to rapidly identify potential drug targets. When combined with high-throughput technologies and cloud-based data-sharing platforms, R&D is accelerated through both greater productivity and increased collaboration.

Leveraging Digital Technologies

Traditional biopharmaceutical companies are facing real competition from players outside the industry with expertise in digital technologies.[6] Technology companies like Apple and Alphabet (the parent of Google), along with wellness firms and other nontraditional organizations with access to consumer data, an understanding of consumer behaviors and advanced digital and big data technologies, are positioned to compete or partner with biopharma companies in the development of new digital medicines.[6] Collaborations, in particular, have the potential to address real issues in the biopharma industry, such as chronic disease management/treatment, patient adherence and clinical trial design and implementation.

Some companies are already taking action, including Sanofi with Verily Life Sciences, the life sciences unit of Alphabet, and Novo Nordisk with IBM Watson Health.[6] The former two companies agreed in 2016 to invest $500 million in the development of diabetes solutions that combined devices, software and medicines.[5] Another example is device maker Medtronic's collaboration with technology company Qualcomm for the development of a continuous glucose monitoring system that provides patients and providers with information that they can act upon.

Key Trends Impact

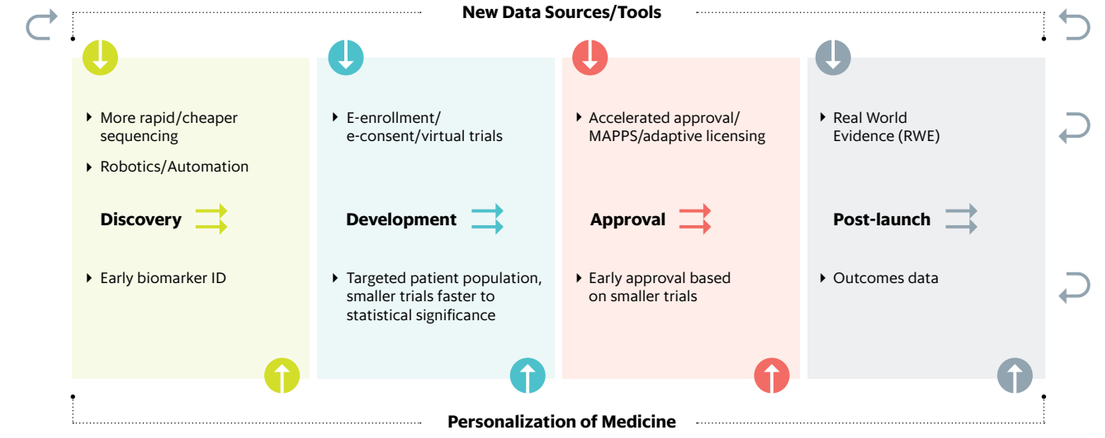
The table evaluates the potential impact of selected trends across four therapeutic areas: oncology, neurology, diabetes and cardiovascular diseases.

KEY Expected Strong Impact (P) Prevention (D) Diagnosis (R) Real Cure

		Enabler	Oncology			Neurology			Diabetes			Cardiovascular		
New Therapies	**Genetics**	Gene editing, genotyping, genetic profiling and mapping, gene therapy			R	P	D		P				D	
	Cellular programming	Stem cell therapies			R			R			R			
Advances in technology	**3D printing**	3D printed models, organs, cells					D					P	D	
	Nanotechnology	Nanobots, nanoparticles, nanochips		D						D		P	D	
	Bionics	Artificial organs, implants, prosthetics, assistive devices, exoskeletons							P	D				R
	Predictive analytics	Artificial intelligence, big data analytics		D		P						P	D	
Consumerization of health	**Patient access to data and technology**	Wearable monitoring devices, apps, gamification and digital medicine							P	D		P	D	

SOURCE KPMG Analysis, 2016. Note: These examples are not exhaustive. They are selected to demonstrate the underlying key developments behind the second shift.

Improving R&D's ROI



SOURCE Beyond Borders – Biotechnology Report 2017. Ernst & Young. 2017.

Gene therapy is exciting because it has the potential to cure diseases that are considered chronic conditions that would require ongoing, long-term pharmaceutical care in a single treatment.

Faster Pace of Innovation

Regardless of whether new innovations are coming from traditional big biopharmaceutical firms, startups established in a garage or nontraditional technology companies, they are coming at a faster pace than ever before.[3] Patients with access to greater data and the use of AI and augmented virtual reality are leading to new innovations, many of which facilitate the development of personalized medicines.[7] Disruptive digital technologies are being adopted and implemented that will dramatically change the way drug discovery, clinical trials and patient management are performed. Rapid advances in genetics, gene editing, cell and gene therapies, electroceuticals and smart implantables are already changing the way diseases are treated.[3] Predictive medicine and the use of increasingly targeted therapies will enable safer and more effective early treatment and, ultimately, disease prevention.[5] P

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

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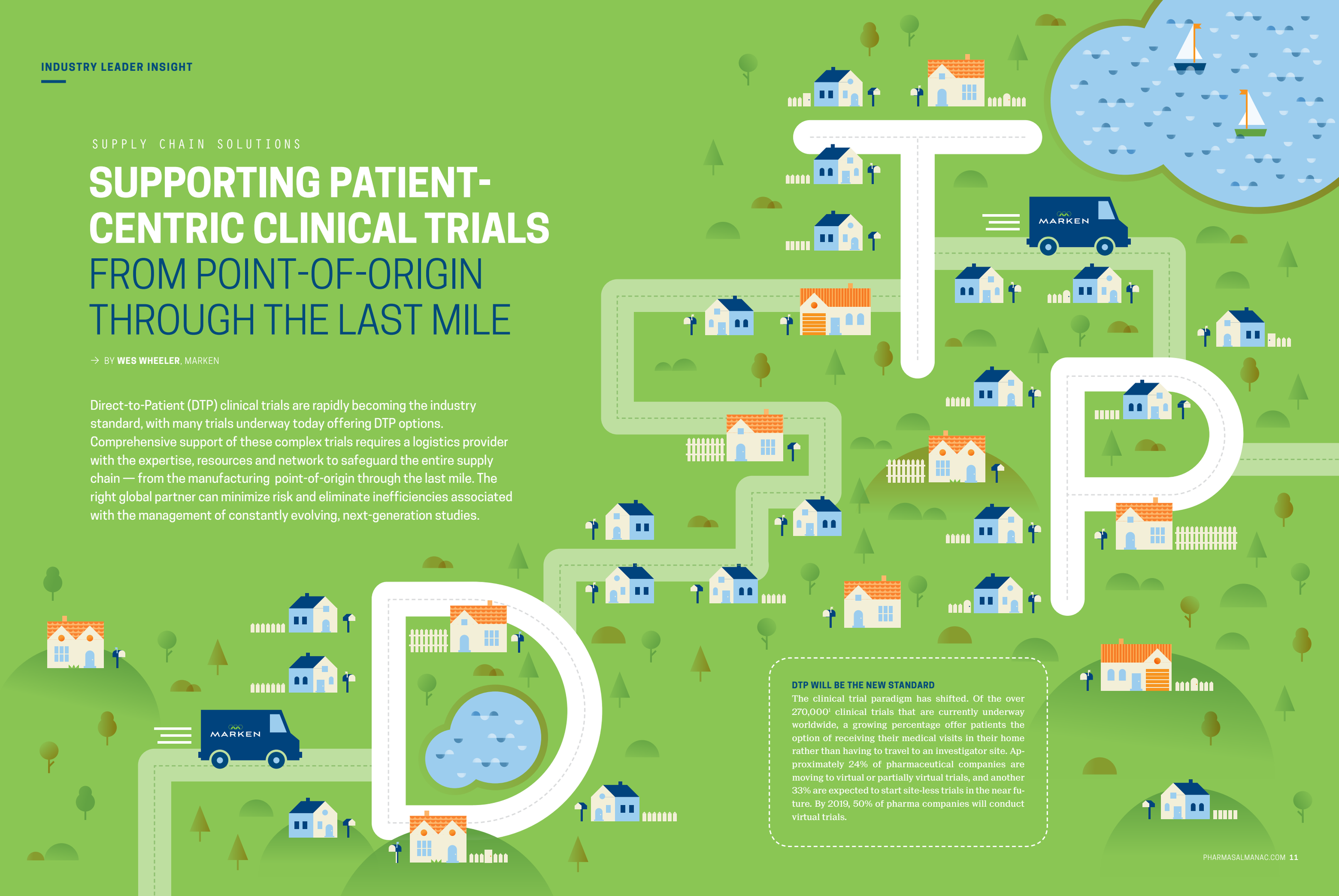
SUPPLY CHAIN SOLUTIONS

SUPPORTING PATIENT-CENTRIC CLINICAL TRIALS FROM POINT-OF-ORIGIN THROUGH THE LAST MILE

→ BY **WES WHEELER**, MARKEN

Direct-to-Patient (DTP) clinical trials are rapidly becoming the industry standard, with many trials underway today offering DTP options. Comprehensive support of these complex trials requires a logistics provider with the expertise, resources and network to safeguard the entire supply chain — from the manufacturing point-of-origin through the last mile. The right global partner can minimize risk and eliminate inefficiencies associated with the management of constantly evolving, next-generation studies.



DTP WILL BE THE NEW STANDARD

The clinical trial paradigm has shifted. Of the over 270,000[1] clinical trials that are currently underway worldwide, a growing percentage offer patients the option of receiving their medical visits in their home rather than having to travel to an investigator site. Approximately 24% of pharmaceutical companies are moving to virtual or partially virtual trials, and another 33% are expected to start site-less trials in the near future. By 2019, 50% of pharma companies will conduct virtual trials.

The growth of Direct-to-Patient/Direct-from-Patient (DTP/DFP) supply chain services in recent years has been a response to the focus on patient-centric trials and medicines. These services allow clinical trial materials to be delivered directly to a patient's home and biological samples picked up with minimal interruption to a patient's lifestyle. Offering a DTP option enables pharmaceutical companies to increase recruitment rates, particularly for trials where many patients live in remote locations or are too ill to visit a doctor's office. For instance, for the hundreds of cell and gene therapies in development, DTP services often predominate because these treatments are very personalized and often target late-stage cancer patients. DTP services can also increase patient compliance, which in turn prevents the loss of trial participants.

In this new era of clinical logistics, however, the supply chain may be one of the most vital links between the manufacturer and patient. For any clinical trial, it is critical that patient privacy and protection be maintained at all times, and this becomes a challenge when the supply chain reaches the home. No one can know which patients are receiving the investigated drug, the comparator or placebo. Marken has demonstrated its ability to effectively manage drug product delivery and biological sample pickup to/from patient homes and has resolved the patient privacy issue. Pharmaceutical companies are becoming comfortable with the DTP service, and eventually we believe the majority of clinical studies will be conducted in this manner.

INCREASING EFFICIENCY WITH UNIQUE DROP-OFF SERVICE

As the clinical trial industry moves toward more personalized treatments, Marken is ensuring its services evolve for these more complex and specialized trials. DTP services are the fastest-growing part of our business. We currently manage over 1600 DTP shipments per month in 51 countries, and that number continues to steadily increase. As the clinical logistics subsidiary of UPS®, we are able to leverage the UPS network to improve the efficiency of our DTP services.

IN THIS NEW ERA OF CLINICAL LOGISTICS, THE SUPPLY CHAIN WILL BE THE ONLY LINK BETWEEN THE MANUFACTURER AND PATIENT.

MARKEN'S TOTAL SERVICE OFFERING

Our hybrid service introduced in 2017 is one example where we combine our expertise and capabilities in managing deliveries over the last mile with UPS airline and ground operations. Our ability to use UPS aircraft in conjunction with commercial airlines has dramatically reduced the cost and improved the quality of our services.

In February 2018 in direct response to the exponential growth of home-based clinical trials in the past few years, we launched another unique new service that in this case makes use of the nearly 5,000 The UPS Store® locations across the United States. Nurses and drivers are now able to drop off clinical trial samples at the nearest The UPS Store® instead of needing to find the next available commercial flight at the closest airport – a cumbersome, expensive and often frustrating process.

Approximately 84% of the U.S. population lives within 10 miles of a The UPS Store® location in the United States. All locations have the capability to handle pre-packed, pre-paid shipments at all temperature ranges, including ambient, refrigerated and even frozen samples that require dry ice. In addition, The UPS Store® locations offer UPS Next Day Air® service and early morning delivery to the central and regional labs – as early as 6 AM in some cases – from many origins, which can reduce delivery times by 6–12 hours.

Marken will manage the booking of shipments with UPS in order to ensure protocol compliance, patient data blinding and data encryption as required for clinical trials.

REMOVING THE MIDDLEMAN WITH A NEW HOME HEALTH SERVICE

In addition to offering our new drop-off service, Marken is developing a global home-based nursing network to supplement our existing DTP/DFP services. This new service will allow Marken to streamline the compliant delivery of clinical trial materials to patients' homes and collect biologic samples in accordance with client's clinical protocols.

Currently, Marken works with three nursing providers and a separate group of specially trained drivers who must follow the same protocol and good distribution practices (GDP) requirements. Instead of having two people arrive at a patient's home, the new service will allow nurses, who will manage the entire patient visit. Marken is building its own nursing network that will offer clients new services that may include intravenous infusion, blood draws including safety lab samples, biologic sampling such as pharyngeal and oral mucosal swabs as well as the clinical assessment of vital signs and other mobile-based electronic data collection.

The new services will integrate with Marken's proprietary Maestro™ operating system for comprehensive shipment tracking from booking through delivery. Our existing 24/7 Patient Communications Center (PCC) in Philadelphia will also be offered to enhance DTP services. Nurses will also be able to drop bio sample boxes at nearby The UPS Store® locations for direct shipment to the central laboratory.

MAKING THE PROCESS EASIER FOR PATIENTS AND CLIENTS

Challenges to DTP/DFP clinical trials remain, and Marken is committed to effectively managing and constantly improving services to address these challenges. Efforts are ongoing to reduce the cost of in-home services; the combination of home nursing and logistics services is not inexpensive compared to traditional trials in which patients visit a doctor's office. We need to continue to reduce the costs and make DTP/DFP services more efficient.

Data protection is an evolving issue, as discussed above. As FDA reviews larger numbers of DTP/DFP trials, we expect that regulatory requirements will be introduced to ensure data protection. One possibility is a requirement that logistics software be subjected to additional legislation. We are prepared if this happens.

Marken is also focused on making the DTP/DFP process as easy as possible for our clients and their patients. We have invested in highly trained drivers who are capable of following clinical trial protocols. Our Viseo smartphone application allows patients to see when the driver is arriving, his/her certification number and when their shipment has been finished; they can also rank their driver, which allows Marken to keep track of performance. This type of real-time driver traceability can translate into improved patient expectations and confidence with DTP trials and reduce the number of rescheduled deliveries and delays.

DIRECT-TO-PATIENT (DTP) CLINICAL TRIALS, ONCE A FORECASTED TREND, ARE RAPIDLY BECOMING THE INDUSTRY STANDARD.

Marken also continues to expand its physical network. In December 2017, we opened our sixth location in India (Ahmedabad), and in Q1 2018 we opened an additional kit building facility in Shanghai, China and a new operational hub in Stuttgart, Germany.

Currently, we are working with various vendors to develop a branded and patented "smart box" that will contain a GPS device and be patient-friendly and easy to handle. We also have plans for further technology development to ensure tighter control and end-to-end visibility, variations of GPS trackers, new devices that communicate by Bluetooth or other means and smart packaging solutions. These advances will enable Marken to further minimize the risks associated with the clinical supply chain.

THE MOST IMPORTANT LINK

The market, patient pool and technology available in supply chain solutions and clinical trials have shifted. Streamlined logistics and simplified patient-centric services are the key to success for the complex clinical trial industry. As the independent, clinical subsidiary of UPS, we are working closely with the company to find additional ways to leverage the UPS network.

Marken has actively managed supply chain solutions for DTP trials since the 2012 inception of the DTP service and was the first to introduce DTP services. We continue to anticipate the future needs of our clients and their patients. We recognize that the supply chain is the most important link in today's clinical trials and are committed to covering trial materials to the last mile without putting them, the trial or patients at risk. With our growing experience in DTP/DFP trials, coupled with our history of high-touch, personalized service and our UPS network, we will be able to reach populations in remote geographies and home-based clinical trials with an unwavering commitment to patient safety and privacy. P

CASE STUDY: MAKING A DIFFERENCE WITH PERSONALIZED SERVICE

Personalized, high-touch services can make the difference between the success and failure of a clinical trial. As one example, a small child from Scotland enrolled in a phase II, multicenter, multinational study for a rare disorder characterized by progressive neurological damage was traveling to Pakistan for the holidays. The family's trip involved multiple flights, stops and cities over the course of a month, many in countries with complex customs requirements for the importation of Investigational Medicinal Product (IMP). The study's dosing schedule requires that patients receive daily infusions, which can be conducted in a home environment (after an initial hospitalization).

The time window for the placement of the shipments defined by the study protocol was tight and had to perfectly align with the family's travel schedule. Additionally, the child could not be infused until the study sponsor received confirmation of the IMPs integrity after handover in the form of Marken's trusted logger data.

Marken responded to this challenge by developing personalized solutions that simplified the delivery and network of care for the child. Marken team members maintained constant communication with the sponsor regarding shipment data and infusions. Marken ensured the integrity of the study's IMP through the use of customized packaging solutions, utilizing the fastest and most secure lanes possible to minimize waiting time, and offered detailed monitoring of shipments via Marken's Global Control Center. Advanced packaging solutions and the latest tracking and reporting technology ensured complete end-to-end visibility and security of the shipment through to the last mile.

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Chief Executive Officer, Marken

Wes Wheeler joined Marken in 2011 to transform the company, which has grown to 47 locations in 26 countries throughout the world. Wes joined the pharmaceutical industry in 1989 with Glaxo (now GlaxoSmithKline) and has served as CEO/President at four different companies for the last 15 years. Prior to 1989, he worked for 12 years as an engineer for Exxon (now ExxonMobil). Wes holds a bachelor of science degree in mechanical engineering from Worcester Polytechnic Institute and a masters in business administration with an emphasis in finance.

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Managing Director at Castleford Capital and Executive in Residence at Revelstoke Capital Partners

Taking Middle-Market CROs and CDMOs to the Next Level

Small CDMOs and CROs that have achieved profits in the $5 to $20 million USD range often need assistance moving to the next level. Investment firms like Castleford Capital that focus on lower-middle-market companies in this sector have the capital, relationships and operational resources needed by executives to enable further growth.

Industry Trends Underscore Need for Growth Investment

Numerous trends in the pharmaceutical contract services industry are impacting the ability of smaller contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs) to expand their market share.

While pharmaceutical companies continue to shed manufacturing assets to optimize costs, the main driver for outsourcing to CDMOs is the need to access specialized capabilities that accelerate the commercialization of complex drug candidates. Demand for CDMOs with biologics development and manufacturing expertise is particularly strong. Growth in the generics and biosimilars markets is also fueling demand for CDMOs as many of these firms rely on outsourced manufacturing.

Long-term strategic partnerships with CDMOs that can best enable biopharma firms to get their products to market in a timely fashion are of growing importance. Middle-market CDMOs that can support multiple projects across a broad range of biomolecules with a wide array of manufacturing and delivery technologies create additional value for their customers and potential acquirers.

Many of the same factors affecting CDMOs are similar for CROs. Drug development continues to be increasingly complex as new drugs are significantly more challenging to develop than previously. Regulations on development are very complicated and process oriented requiring specialization. Regulators and payers increasingly look for real-world data, which leads to an emphasis on predictive modeling and analytics. Regulatory and data expertise combined with specialized technologies are differentiators for CROs and CDMOs to capture customers and grow.

> Pharmaceutical development is a very attractive area for both strategic and financial investors due to the expanding market size and a fragmented marketplace.

Globalization Drives Service-Sector M&A

Pharmaceutical development is a very attractive area for both strategic and financial investors due to the expanding market size and a fragmented marketplace. Pharma is a global industry. Large pharma companies want to deal with CROs/CDMOs that can support them in their ever-expanding footprint. Through consolidation, today's larger CROs and CDMOs have acquired international scale to meet the needs of their top-tier customer base. Smaller firms that have developed specialized expertise, created innovative processes and spent the effort to create the right institutional governance are attractive targets for these acquisitive consolidators.

Many Benefits of Investment

Castleford Capital looks to back management teams of lower-middle-market firms ($5 to $20 million USD in profits) with the capital and resources they need to grow their business. Many growth-stage firms need to amplify their management team on the commercial side and often require additional capital to expand both organically and through the acquisition of technologies and capabilities. Growing firms generally need the insight and necessary tools to bring institutional governance to a level that enables them to go public, become targets for strategic consolidators or receive investments from larger sponsors.

Why Castleford Capital

Leveraging the twenty-year advisory and investment career of its founder, Castleford Capital provides management teams with the capital, relationships and operational resources that empower leadership to attain new levels of growth. By aligning with Revelstoke Capital Partners, Castleford has the backing of a leading healthcare private equity firm that has raised approximately $1.0 billion of equity in the last five years, an experienced top-tier team of investment professionals, access to junior resources and vast sources of debt financing. Invested companies are able to draw on executive relationships from ten invested platforms, a pool of operating partners and industry experts who are able to serve on advisory or scientific boards.

Castleford and Revelstoke invest primarily in the pharmaceutical and healthcare services markets. The capital they provide and the resources at their disposal are specifically oriented to the specialized needs of companies in pharma and healthcare. Castleford focuses on lower-middle-market companies including CROs, CDMOs, PBMs, pharmacy services, RCM and other tech-enabled healthcare solutions. P

Karen Fallen
Vice President, Business Unit Head of Clinical Development & Manufacturing
Lonza Pharma & Biotech

Addressing Development Challenges for Complex Biologic Drug Candidates

Biologic drugs are increasingly complex, creating numerous difficulties for biopharmaceutical companies from higher candidate failure rates to expression and manufacturing challenges. As a full-service contract development and manufacturing organization (CDMO), Lonza has the tools, techniques, capabilities and flexible capacity to help our customers overcome these hurdles and reduce the time for projects to move from development through commercial launch.

Selecting Candidates with Potential for Success

Biotherapeutics identified as potential drug candidates are increasingly complex. As drug makers focus on addressing unmet therapeutic needs, they are studying new and unexplored disease states and novel mechanisms of action. At the same time, payers and patients expect new drugs brought to market to be more effective and provide "clinical cost effectiveness." This greater complexity and higher bar for approval make the development of manufacturable, safe and efficacious medicines more difficult, increasing the risk of candidate failure.

It has become crucial for biopharma companies to reduce the risks associated with development projects by selecting biomolecules and their expression systems with the greatest likelihood of reaching the commercialization stage. Lonza has created Developability Assessment, a suite of services designed to help our customers gain a better understanding of which candidates have the greatest chances for clinical success and ease of manufacture. This service assesses structural stability, post-translational modifications and potential immunogenicity, among other factors.

Most recently, we introduced a protein sequence variant analysis service. While some variants can be minor, others can impact efficacy and safety. Traditionally, studies to identify variants are performed during phase II/III trials, but finding the existence of a problematic variant at this stage presents real challenges. With our new service, protein sequence variant analysis can be performed at the preclinical stage, when the cell line is being selected, which enables early, proactive detection of variants.

> At Lonza, we are constantly looking to reduce the development timeline, giving our customers more control over their projects.

Many Hurdles in Biologic Drug Development

Drug companies are under growing pressure to reduce the time it takes to go from DNA to IND. Projects must be implemented as quickly as possible while minimizing risk and ensuring the development of safe and efficacious medicines. As projects progress through development to the clinic and on to commercialization, access to manufacturing capacity at the right scale when it is needed can also be a real challenge which increases supply chain complexity.

Expression and Manufacturing Solutions for Next-Gen Biologics

Next-generation biologics with the greatest potential include cancer immunotherapies such as checkpoint inhibitors and cancer vaccines. Next-generation biologics, for example, antibody-drug conjugates (ADCs), bispecific antibodies and novel scaffolds can offer improved efficacy and safety. All of these biomolecules are structurally complicated and typically operate via complex mechanisms of action.

Facilitating Biologic Drug Development

Selection of an appropriate contract development and manufacturing organization (CDMO) can help alleviate the challenges of developing and manufacturing complex, next-generation biologic drugs. At Lonza, we are constantly looking to reduce the development timeline, giving our customers more control over their projects. We look for opportunities to introduce automation and find efficiencies by doing work in parallel or in nontraditional sequences. We have experience with many products with Breakthrough designation, including the commercial manufacture of ten products.

We are also committed to having the right capacity available when it is needed. We are continually expanding capacity around the world to improve our flexibility. Recent examples include the acquisition of a facility near San Francisco, CA with 1000L and 2000L bioreactors and the expansion of our facility in Singapore with the addition of 2000L disposable bioreactors.

We have 35 years of experience developing biomolecules from early phase to commercialization. Our teams are able to anticipate potential problems and build in contingencies to avoid them. If problems arise, they are addressed rapidly to keep projects on track. Our regulatory team has broad experience; over the last five years we have supported 60+ IND filings and more than 10 marketing authorizations. We participate in regulatory agency meetings with customers and can help them implement the most effective regulatory strategies striving for right-first-time success. P

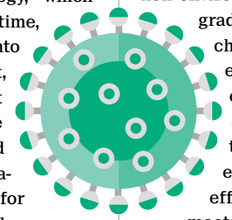
Thomas Page, Ph.D.
VP of Engineering and Asset Development
Fujifilm Diosynth Biotechnologies

Flexible, Mobile, Modular: High-Containment Viral Vector Center of Excellence

Next-generation viral vector and gene therapy manufacturing facilities must be sufficiently flexible to work with a range of viral technologies, cell-culture processes, downstream unit operations and fill/finish systems over a wide range of scales – and do so under high-containment conditions. Fujifilm Diosynth Biotechnologies has mobile, modular multiproduct facilities that can support product development to commercial production activates from the earliest stages of cell-line identification to drug product manufacturing.

University Beginnings

The Fujifilm Diosynth Biotechnologies (FDB) site in Texas was originally established as the National Center for Therapeutics Manufacturing (NCTM). The site was based on the concept of mobile cleanroom (MCR) technology, which was a new concept at the time, and ultimately developed into an early-phase, multiproduct, flexible, responsive contract manufacturing facility. The original site was expanded with the addition of two facilities, one (Building 100) for efficient monoclonal antibody production and the other (Building 200) for viral and gene therapy products. The latter facility is a multiproduct, multi-class manufacturing site based on third-generation MCR technology. FDB acquired the site, including all three production buildings, in December 2014.



Flexible Yet Customized Solutions

Next-generation MCR technology provides a high level of flexibility in conjunction with high containment and rigorous segregation and control, allowing FDB to process multiple products that fall into several classes simultaneously. The modular nature of MCR technology also affords the ability to design production operations on multiple scales to meet the varying needs of clients as projects move from development to commercialization.

Rather than treat facilities as stick-built structures, mobile cleanrooms are intrinsically designed as pieces of equipment that are standardized and configurable. All of the critical components in MCRs are based on the same design concepts and use the same technologies (i.e., single-use bioreactors), reducing risk and opening fascinating opportunities.

By modifying the configuration of standard components, we are able to provide clients with a customized production environment in terms of the room grade, pressure cascade, air exchange rates, fresh/recirculated air distribution, etc. These custom configurations are designed following an extensive risk assessment to ensure that the environment efficiently and appropriately meets the needs of the project, with no over- or under-engineering.

High Level of Containment

Viral vectors are designed to infect different human cellular targets. A very high level of containment is required for the manufacture of these products. With state-of-the-art layered, redundant segregation and layered controls for containment – graded zoning and unidirectional flows, segregated HVAC zoning and pressurization, local engineering controls and captive equipment to avoid open work, transactional controls and local waste management – next-generation cleanrooms are an ideal solution.

The Neutral State

Another important feature of our MCRs is the ability to ensure neutral conditions prior to the start and following the completion of each client project. Each MCR is equipped with a vaporized hydrogen peroxide (VHP) system that allows sanitization of the entire room and all of the equipment. While some in the industry feel that this approach is a conservative one, at Fujifilm Diosynth Biotechnologies we believe that this capability is critical to achieving success in advanced therapy manufacturing.

Platform Technologies Under Development

Having established advanced facilities for next-generation therapy production, FDB is now focusing on the development of advanced tools for cell culture and downstream processing. We are not only developing technologies that will allow products typically produced using adherent cells to be manufactured using suspension cell culture, but also are installing 2000L bioreactors. With these additions, we are able to perform suspension cell culture, both fed-batch and perfusion, from the 100L to 2000L scales. We also continue to offer adherent manufacturing services.

Center of Excellence

The Texas site is being developed as a Center of Excellence for Advanced Therapies development and manufacturing. Fujifilm Diosynth Biotechnologies possesses robust capabilities in process development through late-phase and commercial manufacturing and from cell-line development through final product filling. We are excited to work with clients to accelerate their CMC timelines. P

Gustavo Mahler
President and CEO
AGC Biologics

Meeting Biopharma Contract Manufacturing Needs with a Flexible Global Network

As biologic drugs become more complex and sophisticated, biopharmaceutical companies increasingly need the support of contract development and manufacturing organizations (CDMOs) with advanced capabilities and technology platforms that are consistently implemented across scales and geographies. With multiple sites around the globe, AGC Biologics has the flexibility and expertise needed to meet the ever-changing demands of this rapidly evolving sector.

Demand for contract development and manufacturing services in the biopharmaceutical sector is rising around the world, as growing numbers of biologic drugs – from antibodies to next-generation cell and gene therapies – continue to achieve success in the clinic and move toward commercialization. Expansion of the biosimilar and follow-on biologics markets, particularly in Asia and also in South America, is also fueling the need for support from CDMOs that can provide cost-effective, accelerated development and commercialization pathways.

Careful Convergence

To help reduce project costs and timelines, biopharmaceutical companies are looking for CDMO partners with established global networks of facilities and advanced technical capabilities that use the same technology platforms across locations and development phases. In response to this need, AGC Biologics was formed. The name reflects aspects of each of the brands brought together to form the company and the reputations they have earned in the marketplace.

The convergence and integration of Asahi Glass Company (AGC) Bioscience, Biomeva GmbH and CMC Biologics have generated a CDMO with deep industry expertise in both mammalian cell culture and microbial fermentation methods for the scale-up and cGMP manufacture of protein-based therapeutics, from preclinical to commercial production. With global heads of Quality, Project Management, Business Development and all other key activities, AGC Biologics ensures that the same systems, technologies and management practices are implemented at all sites. As a result, transfer and scale-up of projects as they move from early to late-phase or expand to meet demand in new geographies can occur seamlessly within our global network.

AGC Biologics has made significant investments to align our development groups and technology platforms across all regions for both upstream and downstream processing. Importantly, AGC Biologics has deployed unique technologies that enable acceleration of development timelines, getting customer projects from the DNA stage to IND filing in less than 14 months. We work side by side with our customers to bring their products to market as quickly as possible. That includes rare-disease treatments and personalized medicines, to more traditional antibodies and products with accelerated approval pathways.

Customer Support from Early Phase to Commercial

For customers with phase III and commercial products, access to flexible capacity is essential. AGC Biologics meets that need with our Bioreactor 6Pack™ manufacturing platform consisting of six x 2000L bioreactors. Customers can begin with production in one bioreactor and scale up as needed, in response to real demand. We also employ a number of solutions designed to enable rapid development and validation. The combination of flexible capacity that grows as needed and the ability to work on accelerated pathways makes it viable for our customers to get their high-quality treatments to patients as quickly as possible.

Continual Investment

Ongoing investment in facilities and capabilities is a key component of our strategy for growth at AGC Biologics. In early March 2018, we announced the addition of a 2000L single-use bioreactor (SUB) as part of a production expansion project at our Berkeley, California facility. Capacity at this site has tripled in the last three years and now offers cell culture manufacturing from 100L to 3000L in both SUB and stainless-steel bioreactors to support early-phase projects.

Later that same month, we announced the addition of a new building complex that will house the company's global headquarters in Bothell, Washington. Spanning more than 150,000 square feet, the addition will be located next to the existing AGC Biologics facility and house Process Development labs and Corporate Administrative offices, as well as provide expansion space for additional manufacturing capacity. It will also include a new R&D center dedicated to novel manufacturing technologies for faster development of therapeutic proteins.

These investments underscore our commitment to meet the growing needs of our customers for both mammalian and microbial development and manufacturing services. They will also enable us to further integrate the development, manufacturing and commercial functions at our global headquarters and reinforce the effectiveness of our extensive global network. P

Tony Listro
Vice President
Foster Delivery Science

Leveraging Hot Melt Extrusion for Solubility and Continuous Manufacturing

Hot melt extrusion (HME) technology has become a key solution to adding absorption for enhanced solubility. HME is also a continuous process, which has been encouraged by the FDA.[1] Companies lacking in this particular expertise are encouraged to seek out a firm with proven authority in the space, such as Foster Delivery Science.

Foster Delivery Science operates out of a 32,000-square-foot GMP manufacturing facility. The plant was constructed in 2015 and took about 16 months to become fully commissioned and qualified. By the first quarter of 2017, the plant was operational and producing clinical supply batches. Foster Delivery Science was born out of Foster Corporation, which was founded in 1989 with a focus on serving the healthcare industry with custom biomedical polymers. Due to our leadership position in this market, Foster's customers began requesting drug/polymer blending about 15 years ago. Pharmaceutical companies learned of this capability and began making similar requests. Foster Delivery Science became a subsidiary of Foster Corporation to better meet this need. At Foster Delivery Science, we are focused on polymer-based drug delivery technologies requiring HME and are dedicated to innovating polymer and process technologies required for drug delivery applications.

> Cryogenic milling is key for blending polymers and APIs in order to minimize particle separation.

To top our own constantly improving standards, Foster Delivery Science is continually upgrading. Most recently, we added cryogenic milling capability. Cryogenic milling is key for blending polymers and APIs in order to minimize particle separation. We are a polymer-focused company, and although polymers do not mill easily – for example, implant polymers that are used for drug delivery such as ethylene-vinyl acetate (EVA) and thermoplastic polyurethane (TPU) polymers – we've found success cryogenic milling both polymer types. To better our processes and create solutions, we turn to cryogenic milling as an initial step, prior to combining the polymer with the drug. We then melt-blend the drug in a twin-screw extrusion step; this is followed by a single screw-step necessary for the shaping involved in drug delivery implant production.

More than a Solubilization Strategy

We pride ourselves on our niche expertise. HME is our core drug delivery technology. We leverage our proficiency in this technology, not only as a solubilization strategy but also as a means to create various dosage forms. Our extensive work in extrusion is also applied to other drug delivery techniques – we have GMP processes in place to produce a pellet or a powder through extrusion and milling, or to create a rod and monofilaments, films, tubes and profile shapes. Another example of how we elevate our capabilities is in twin-screw extrusion, which is highly modular, as both the barrels and screws are programmable.

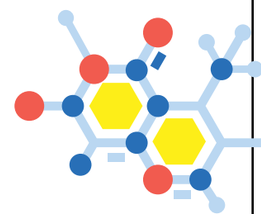
At Foster Delivery Science, we take a very pragmatic approach to developing processes centered on our client's valuable API. As we are backed by Foster Corporation, we benefit from the best of both worlds – we enjoy the flexibility and nimbleness that comes from being a small company, as well as the resources present in our sister organization. This backing has helped Foster Delivery Science to grow organically, always motivated to build on our prior successes.

Clinical to Commercial

We take pride in our work, which begins with our client's clinical supply programs. We are able to fully support these programs as they progress through to commercial and are trusted with a client's valuable project from the very beginning of formulation to whenever the drug goes off the market.

Ultimately, extrusion itself is a part of a continuous manufacturing process. It can be bookended by API continuous manufacturing on one end and, on the other, by the tableting or the insertion of the implant into an applicator or a final packaging. When a client walks through our door, they know continuous manufacturing is possible – batches are not required. As continuous manufacturing is an initiative that is constantly being pushed by the FDA, this adds another layer to why our clients are already at an advantage when working with us in this process.

As extrusion experts, we are confident that, when a client begins formulation development, we are supplying a product that is going to be accepted for approval. P



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Hannes Teissl
VP Biologics
Polpharma Biologics

Building a Biologics Business from the Ground Up

Building a biologics business from the ground up provides tremendous flexibility but requires the right business strategy. Polpharma has attracted world-recognized leaders to build and manage all key biologics funcions at its new, state-of-the-art facilities, which are located in Poland and in the Netherlands, ideally situated to serve the global markets. Backed by a strong branded small-molecule business, Polpharma has silently established a fully integrated in-house value chain for biologics and is now reaching out to potential clients that can benefit from its end-to-end contract development and manufacturing services.

Startup Benefits with Deep Resources

Polpharma, a privately owned regional leader, employs more than 7,500 people and generates revenues of $1 billion annually from the sale of small-molecule pharmaceuticals and APIs, largely in Central and Eastern Europe.

Polpharma entered the biologics space in 2012 and has since grown through the establishment of technical capabilities and global assets. We have brought together a diverse team of world-class veterans with local talent from the Polish biopharmaceutical industry to work in one of the most modern biotechnology centers in Europe. The success of the branded generics business of Polpharma has enabled the funding of our activities in the biologics space. As a result, Polpharma Biologics has the nimbleness and flexibility of a start-up paired with the access to resources of an established company.

Technical Control

Polpharma Biologics retains full control of all technical elements of the business and has built competencies in all aspects of biologics development and manufacturing from cell-line development to clinical and commercial production.

For our in-house biosimilar candidates, we bring molecules to the approval stage and then find the best commercialization partners. This approach allows us to work on biosimilars that fit our capabilities without the need to focus on a single therapeutic area or justify sales in particular markets. In addition, we have developed a strategic offering for contract development and manufacturing services to global industry partners based on our established competencies.

Covering the Entire Spectrum

Our modern biotechnology center in Gdansk consists of a comprehensive R&D platform and GMP production capabilities, including 2 X 1000L single-use systems with cell culture capacity for clinical and smaller commercial volumes. Our microbial fermentation capability will be fully operational in May 2018 and will be used to produce our first biosimilar candidate. It will also be available for client projects. By Q1 of 2019, a flexible fill/finish line to produce vials, prefilled syringes and lyophilized products will be operational. As a result, at this facility, Polpharma will have all of the technologies needed to support projects from development through clinical and small-scale commercial manufacturing.

With our acquisition of Bioceros in 2016, Polpharma brought in-house a well-established cell-line development platform technology, making us a truly integrated one-stop shop. Access to this proprietary technology allows us to generate and optimize cell lines in terms of yield and productivity plus apply our comprehensive modulation toolbox for the development of processes that require fingerprint-like biosimilarity – a unique combination of capabilities.

Our large-scale commercial production site near Warsaw will come onstream in 2020. This facility will mainly serve as a contract development and manufacturing site with mammalian and fill/finish technologies. We believe that this Polpharma Biologics plant will serve as an attractive option for clients that want top-of-the-line quality, on-time delivery and access to state-of-the-art technologies combined with a maximum of attention and focus, and we can meet that need.

Polpharma Biologics has immediately available capacity intended to support external clients at any stage of the development process. We are very flexible in terms of work packages and scope and are happy to work on integrated, end-to-end solutions or just on one aspect of the development cycle. Customers looking for a strategic manufacturing alliance are invited to join us as partner for the Warsaw facility so that our modular expansion is in alignment with their needs. P

Peter Boeddeker
Director of Quality Management
Baxter BioPharma Solutions

Using a Risk-Based Approach to Manufacturing in a Multi-Product Facility

Manufacturing in multi-product facilities affords numerous advantages, but also presents significant challenges. At its Halle/Westfalen, Germany, plant, Baxter BioPharma Solutions has implemented a risk-based approach to addressing those challenges, providing customers with the benefits of multi-product manufacturing.

Multiple Advantages

The biopharmaceutical industry is continually challenged to reduce costs and time needed to produce advanced drug products. Drug manufacturers are consequently pursuing numerous approaches to achieving gains in efficiency and productivity.

Manufacturing in a multi-product facility offers one approach to reaching greater efficiencies and quicker time to market. Multi-product facilities offer manufacturing flexibility combined with efficiency and cost reductions. In such plants, the equipment is continuously used rather than being operated intermittently, leading to improved capacity utilization. Equipment is typically better maintained because it does not sit idle for extended periods of time. Perhaps the most important advantage is the consistency of processes on standardized equipment instead of having to build dedicated manufacturing facilities. With respect to cost benefits, one multi-product facility can replace multiple dedicated facilities, eliminating the need to invest in duplicate equipment, utilities, etc. Personnel requirements are also reduced, as is the need for auditing, inspections and compliance activities.

The Cross-Contamination Challenge

The greatest challenge in multi-product facilities is the prevention of cross-contamination. The facility itself, including product and non-product contact surfaces, is viewed as a potential source of contamination; therefore, facility, equipment design and cleaning are critical areas of focus. It is of particular concern when highly potent, cytotoxic active pharmaceutical ingredients are involved. Cross-contamination can occur if the same equipment is used to manufacture different products and is not subject to adequate cleaning. It can also occur from human interactions with open processes, which means it is essential in a multi-product facility to demonstrate that no cross-contamination occurs in order to maintain the highest quality and safety of all drug products.

The European Medicines Agency (EMA) has published guidelines for setting health-based exposure limits for use in risk identification in the manufacture of drug products in multi-product facilities.

The FDA also offers guidance on how to identify and understand risks for cross-contamination and implementation of appropriate control strategies.

Handling Oncology Drugs

Baxter BioPharma Solutions' Halle, Germany fill/finish facility has a long-standing history of manufacturing oncology drugs in a multi-product facility for early phase drug formulation through commercial scale-up, product launch and lifecycle management. Biologics, ADCs, small molecules and nanoparticle-based formulations such as emulsions, liposomes and suspensions are a few of the types of products manufactured. The Halle facility is focused on handling both cytotoxic and non-cytotoxic APIs. To help ensure the high quality and safety of all products at the facility, Baxter has established a comprehensive risk matrix that considers both the pharmacological and toxicological data, as well as the cleanability of any product that might be manufactured at the site.

Furthermore, all oncology products are manufactured in dedicated areas of the facility. State-of-the-art isolators and restricted barrier access systems (RABS) are equipped with separate HVAC and air exhaust systems. The highest filter classes are applied in the cleanrooms, and additional HEPA filters are used for the air exhaust. Clinical and commercial filling lines are equipped with automated loading/unloading, capping and inspection infrastructure. Baxter BioPharma Solutions has elected to use product-dedicated filling equipment within its Halle multi-product plant. Isolators are installed at every point where there is a risk of exposure or breakage – weighing, compounding, filling and freeze-drier unloading areas – to prevent contamination between rooms and through operator interaction. Once vials are filled and closed, they are also subjected to a final decontamination rinse to minimize the risk of contamination on the outside of the product packaging. These built-in operations are just some of the many ways Baxter BioPharma Solutions is committed to advancing quality manufacturing in a multi-product facility. P

> Manufacturing in a multi-product facility offers one approach to reaching greater efficiencies and quicker time to market.

Vladas Algirdas Bumelis, Ph.D.
CEO and Chairman of the Board
Biotechpharma

State-of-the-Art Biologics Manufacturing in an Unexpected Location

Lithuania is a small country in the Baltic region of northeastern Europe bordering the southeastern shore of the Baltic Sea. While largely a service economy, Lithuania, which is a member of the European Union, has a substantial industrial sector that produces chemical products, plastics, machinery and appliances. Biotechpharma UAB, a rapidly growing contract development and manufacturing organization located in Vilnius, is adding biologic drug substances and drug products to the list of goods exported throughout Europe, North America, Asia and the Middle East.

Rapidly Expanding

Biotechpharma was founded in 2004 as a contract development and manufacturing organization (CDMO) providing support for branded biologics and biosimilars. Initially, the company rented space for its product development and small-scale GMP manufacturing activities. As customer projects advanced from early to late phase, we received a growing number of requests to expand our capabilities.

In response, we inaugurated our own R&D facilities with reactors up to 10L in capacity in 2011. By the end of 2012, we were operating in a new state-of-the art GMP manufacturing plant. The investments required for these two new sites were approximately €12 million and €30 million, respectively. In 2014, a top-ten pharmaceutical company became a key customer, bringing a number of different development projects to Biotechpharma; since then we have attracted customers from around the world.

The growing demand for manufacturing of monoclonal antibodies and mammalian-cell derived products led to the need for additional capacity. In 2017, a 2000L mammalian single-use line including a seed train consisting of 10L, 50L and 500L bioreactors became operational. A cGMP pilot plant was also completed in 2017 for the production of both microbial and mammalian products to meet growing demand for small-scale GMP production of material for initial preclinical and clinical studies, and the installation of a new 3000L microbial fermentation line is currently underway.

Integrated, Full-Service Biologics CDMO

Biotechpharma is a fully integrated CDMO with the ability to satisfy all customer needs, from gene sequencing to final product manufacturing. We can perform cloning/cell-line development for both bacterial and mammalian processes, execute efficient upstream and downstream process development and optimization and provide GMP manufacturing of clinical and commercial drug substances and formulated products packaged in vials and syringes.

Flexible and Responsive

As a midsized CDMO, Biotechpharma is able to provide flexibility and responsiveness backed by a strong foundation in science and technology. We focus on understanding our customers and meeting their specific needs without binding them to one single approach. We are able to react rapidly to unexpected project changes, adjusting timelines, capacities and other activities to meet their evolving needs. We have on average 25–30 development projects underway each year, covering gene cloning to final drug product manufacturing.

Biotechpharma is a fully integrated CDMO with the ability to satisfy all customer needs, from gene sequencing to final product manufacturing.

Lithuania for Biotechnology

Lithuania is a small country that is generally not well known to many in the biopharmaceutical industry. It has proven for Biotechpharma, though, to be a good location. Initially, it took some effort to prove that Biotechpharma is great at biologic drug development and manufacturing. One visit to our site, however, was typically all that was needed to allay any concerns. Today, the track record of performance and high level of trust we have since established with our customers results in frequent recommendations. Our commitment to our customers is also reflected in our ongoing willingness to reinvest in the company.

While we serve customers located around the world, we do anticipate ultimately expanding Biotechpharma's physical footprint outside of Lithuania. Northway is a separate holding company located in California that may serve as a basis for the acquisition of process development companies in the region. U.S. customers would then be able to access our process development capabilities more easily, with internal technology transfer to the manufacturing plant in Lithuania as their projects progress. P

OVERCOMING RAW MATERIAL AND SUPPLY CHAIN CHALLENGES IN VIRAL VECTOR MANUFACTURING

→ BY **RICHARD O. SNYDER, Ph.D., SUSAN D'COSTA, Ph.D., CHRISTOPHER MURPHY** AND **CAMERON JONES,** BRAMMER BIO

Viral vector manufacturing presents numerous challenges. In addition to developing practical commercial-scale processes, raw material sourcing and management of the supply chain are crucial. Access to high-quality raw and starting materials, from cell lines and serum to excipients and single-use components, is key. Risk assessment and management with appropriate testing, vendor qualification and supply chain transparency are essential to establishing security of supply.

IDENTIFYING RAW MATERIALS FOR THE PRODUCTION OF VIRAL VECTORS

Identity verification of raw and starting materials used in the production of biologic drug substances and drug products must take place before manufacturing can proceed. The identity, purity and quality of raw materials must be confirmed to be suitable for use, to ensure patient safety, product efficacy and process consistency and to avoid costly production problems.

According to the European Biopharmaceutical Enterprises, raw materials for biopharmaceutical manufacturing must be safe, of consistent quality, well characterized and understood with respect to their role in drug production processes, compliant with regulations and compendial requirements, and backed by supplier agreements with qualified vendors and purchased through transparent supply chains.[1] In addition, "only raw materials that perform a specific role in a manufacturing process should be used, and in all cases, they should be of the highest quality available."[1]

Table 1 presents a list of the main raw and starting materials used in viral vector manufacturing. Some of these materials present more challenges than others. All biologic (animal- or plant-derived) raw materials require testing for contamination by adventitious agents (e.g., viruses, bacteria, fungi, mycoplasma, endotoxins, etc.).

Animal-derived materials such as serum have inherent variability and greater potential for contamination by pathogens than other biologic raw materials. The supply and production of serum are also complex and require acquisition from certain select regions of the world and from herds that are well characterized to be pathogen free; they also must be accompanied by certificates of analysis and certificates of origin. In addition, regulatory authorities are increasingly requiring more extensive testing of animal-derived raw and starting materials. Serum, therefore, requires a higher level of management than, for example, chemicals used as buffer components.

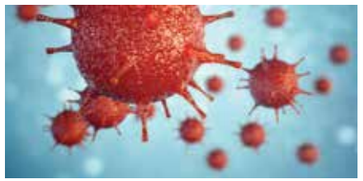
For cell lines, in addition to testing for adventitious agents, it is necessary to confirm identity and purity (e.g., that no cross-contamination has occurred with other cell lines during generation, maintenance and banking). Viral vector manufacturing may also require large amounts of high-quality plasmid DNA for transient transfection, dependent on the scale of the viral vector lot needed to be manufactured. There are limited vendors capable of suitable plasmid DNA affecting the supply of this critical custom raw material.

CHALLENGES WITH CONSUMABLES

Viral vector manufacturers involved in all stages of clinical-trial-material and commercial product production rely on single-use (SU) technologies to meet the needs for manufacturing flexibility and to prevent product-to-product cross-contamination. While there are many advantages to SU equipment, its use does introduce new risks over conventional stainless steel/glass equipment and puts a high reliance on vendors to ensure adequate supply and control of secondary suppliers (e.g., film manufacturers), where extractables and leachables may be a concern.

SU materials that come in direct or indirect contact with cell culture and viral vector products can impact their performance, quality, safety, stability and/or efficacy. As such, their sourcing must be achieved in a manner similar to the sourcing of other critical raw materials used in GMP manufacturing.[2] For instance, with the adoption of SU equipment, the verification of process container integrity must also be performed for each SU bag used in critical operations.[3]

TABLE 1



Common Raw and Starting Materials Used in **Viral Vector Manufacturing**

- Media
- Serum
- Plasmids
- Cell Lines (Animal-, Insect- or Human-derived)
- Viral Vectors Used in Production
- Buffer Components
- Chromatography Resins
- Consumables for Single-Use Equipment (Bags,Tubing, Connectors, Sensors, Etc.)
- Packaging Components (Vials, Stoppers, Seals)

TABLE 2

Considerations for **Testing Raw Materials**

	Compendial	Non-compendial	Inspection
Critical	X	X	X
Noncritical	X		X
Consumables			X

IMPORTANCE OF RISK ASSESSMENTS

To ensure that raw materials are fit for purpose and of the appropriate quality, viral vector manufacturers employ risk management strategies. Risk assessments of the manufacturing process are conducted to determine the criticality of each raw material at each step of the process, which in turn determines the level of testing and vendor management necessary to ensure the consistent supply of high-quality materials.[4]

Those raw materials (i.e., chemicals) that inherently present a lower level of risk may require less testing and vendor audits. Biologic or animal-derived raw and starting materials have greater inherent variability, and the potential for adventitious agent contamination carries a higher risk and thus requires a higher level of risk mitigation to ensure security of supply. Similarly, SU equipment that comes in direct contact with the biologic drug substance or drug product will carry a higher risk than noncontact components and may involve leachables and extractables testing.

When conducting risk assessments, factors to be considered include risks presented by the vendor, the amount of material used throughout the process, the grade of material (i.e., pharmaceutical vs. research), the process context (i.e., where the material is used in the process, such as cell culture or final formulation) and the maturity of the program (i.e., preclinical development vs. commercial).[5]

Based on their criticality as determined via risk assessments, raw and starting materials are placed into different risk categories that in turn determine the level of risk management required.[6] For instance, in USP <1043> Ancillary Materials for Cell, Gene and Tissue-Engineered Products, raw materials are placed into four different tiers according to the level of risk they present.[5]

The maturity of the process will impact the types of raw materials used and the level of testing and supplier auditing that are required. At the preclinical development stage, research-grade material may be appropriate, whereas pharmaceutical grade material may be essential for clinical stage and commercial production.[6] The number of audits of vendors for critical raw materials also increases as the project moves through the development stages. Similarly, the depth within the supply chain for which on-site audits are conducted increases as projects progress to commercialization.

For SU components, factors to be considered include whether or not they have direct, indirect or no contact with the biologic drug substance or drug product, manufacturing controls and vendor risks.[4]

TESTING NEEDS

Testing is required to enable the identification and purity of raw and starting materials used in viral vector manufacturing. The level of risk associated with a given raw material dictates the appropriate testing that should be conducted for that material. Table 2 lists potential categories for raw materials used in viral vector manufacturing and the types of testing they may require.

Specific testing requirements for certain classes of raw materials may be established by regulation, regional pharmacopeias (Europe, U.S., Japan) and other industry standards and guidelines. For critical raw materials, manufacturers also often develop proprietary in-house test methods (noncompendial) in order to be confident in the quality/consistency of these key process components.[7]

Regardless of the test methods that are performed, however, testing strategies must be developed within the context of the entire production process and be an

integral component of the quality system. In addition to the criticality of raw materials, the level of testing and control needed increases as a project matures. For raw materials used in early-phase projects, it may be sufficient to check the certificate of analysis. As the project moves closer to commercial production, more in-depth testing may be appropriate, including identity verification and performance of compendial testing. Critical raw materials require additional testing beyond identification, such as performance confirmation, because these materials are being qualified for eventual commercial manufacturing processes.

It is worth noting that the current trend is towards more extensive testing to provide a higher level of quality assurance for incoming raw materials. FDA's quality initiatives emphasize the need to design quality into the manufacturing process from the start. To achieve this goal, an understanding of the role that each raw material plays and the information that analytical testing methods must provide is needed.[6] This knowledge combined with effective vendor qualification enables proactive change management, which is essential to maintaining consistent processes and steady supply of lifesaving medicines.

ONGOING CHALLENGES

Ensuring security of supply for raw materials used in viral vector manufacturing presents ongoing challenges. As this new sector of the pharmaceutical industry matures and more therapies that require viral vectors graduate from the clinic to the market, viral vector producers need to be prepared to overcome availability and quality challenges for basic and critical raw materials. Going forward, hurdles are anticipated ranging from greater unreliability in serum supply to increasing use of SU technologies with a concomitant rise in quality and testing requirements to further raising of the bar with respect to GMP guidelines. P

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→ **OSD FACILITY DESIGN**

MODERN OSD FACILITY DESIGN CONSIDERATIONS FOR OPERATIONAL EFFICIENCY AND REGULATORY COMPLIANCE

→ **DAVE DIPROSPERO,** CRB USA

Oral solid dosage (OSD) remains the preferred dosage delivery form for the formulation of many of today's drug products. Tablets and capsules tend to be lower in cost to manufacture and provide ease of administration for patients and their caregivers. When engineering and designing today's OSD manufacturing facilities, the primary goal is to develop a modern and efficient operation that provides for the highest levels of product quality and operational efficiency. Protecting the product from contamination and minimizing the chance of mix-ups are two key elements that must be adequately addressed. This brief will highlight just a few elements of consideration for the architects and engineers engaged in an OSD facility design.

REGULATORY ASPECTS OF OSD FACILITY DESIGN

Every pharmaceutical manufacturing facility design must meet the regulatory requirements for the regions of the world where the products will be sold. All international regulatory bodies focus on product quality via Good Manufacturing Practice (GMP) regulations. In the U.S., regulations on current good manufacturing practices (cGMPs) for drug products are outlined in CFR Title 21 Parts 210 and 211.[1] In Europe, good manufacturing practices for medicinal products for human and veterinary use are covered in volume 4 of *EudraLex*.[2] Most other regulatory bodies around the world have requirements that are similar to those established by the U.S. FDA and European Medicines Agency. PIC/S (Pharmaceutical Inspection Co-operation Scheme) is a nonbinding, informal cooperative arrangement between regulatory authorities in the field of GMP. It is presently comprised of 52 participating authorities from all over the world (Europe, Africa, America, Asia and Australasia), with the aim to harmonize inspection procedures worldwide by developing common standards in the field of GMP.

The primary focus of the regulatory requirements is protecting the drug product and ensuring the highest levels of product quality. They are intended to ensure that any opportunities for cross contamination and product mix-ups are minimized. Best practice is to consider the specific needs for each OSD facility and the processes that will be performed therein. Appropriate product protection measures can then be designed into the facility, equipment and processes early in the facility design phase.

ESTABLISHING THE FRAMEWORK

Before you can actually embark on the design of an OSD facility, it is important to determine the processing requirements and the desired output capacity (or scale) of the desired facility. A general rule of thumb for scale is that small is <1 billion units, medium is 1–4 billion units, and large is >4–5 billion units per year. The product mix must also be understood. Whether a facility will be producing a single product or multiple products will have a significant impact on the design of the plant and the choice of equipment. The opportunities for cross contamination and product mix-ups increase dramatically when multiple products are produced concurrently. The design elements of the facility can offer the added protection and control that are necessary here.

DETERMINING PRIMARY PROCESSING PLATFORMS

For typical OSD manufacturing operations, three primary process platforms are used: direct compression, dry granulation and wet granulation. Each involves a series of unit operations, equipment configurations and subprocesses that increase in complexity.

For example, in direct compression, the API and other dry powder formulation ingredients are basically blended into a homogenous mixture and then compressed into tablets. The main unit operations include weigh/dispense, blend and compress; these are the simplest platforms.

Granulation (dry or wet) is used when the formulation is not conducive to direct compression. Perhaps the particle characteristics, such as bulk density, particle size, flowability, etc., of the ingredients are too varied to allow for effective mixing and compressibility without some form of additional processing. Dry granulation is achieved, for instance, via roller compaction, which incorporates a shearing mechanism to alter the characteristics of the particles – aimed at creating a compressible mixture. Wet granulation involves adding a liquid to the powders. Wet granulation can be subcategorized further into low shear or high shear based on the type of granulator and process operation needed to develop the appropriate particle characteristics. The added liquid must then be removed using some type of drying process. As a result, wet granulation is the most complex process, requiring the most pieces of equipment and the greatest number of unit operations. The main unit operations include weigh/dispense, sizing/sifting, granulation, drying, blend and compress.

ALL CRB WAREHOUSES ARE DESIGNED WITH OVERALL EFFICIENCY IN MIND. THE ORGANIZATION OF THE WAREHOUSE TAKES INTO CONSIDERATION MATERIAL FLOWS, WHICH START IN SHIPPING AND RECEIVING.

The size and design of the facility is heavily dependent on the processes needed and the processing platforms incorporated – in many cases, it may be one, two or all three in the requirement mix.

BUILDINGS AND FACILITIES

Subpart C of 21 CFR, Part 211 is the key FDA guidance for pharmaceutical buildings and facilities. Part 211.42 relates to design and construction features. This section states that buildings for pharmaceutical manufacturing must have adequate space to allow for proper flow of materials and operations, such that contamination and mix-ups are prevented.[3] When designing new OSD facilities, "right-sizing" and "process flow" are two essential elements to address.

The GMP spaces within a facility, where products are in-process of manufacture and/or open to the environment, are the most expensive spaces in a facility both to build and to operate. Cleanable surface finishes, temperature and humidity control, air filtration, monitoring, lighting and containment aspects are among the key considerations for the design engineer. Oversizing a room leads to greater energy consumption, the need for more cleaning and additional costs.

In today's modern facilities there is a trend to minimize square footage and maximize efficiency. As examples, blending rooms used to be as big as 20'x20'. Today they are typically 10'x10' with the control room for the bin blender outside of the room. Similarly, modern compression rooms have separate control rooms that can be used to operate multiple compression suites with much greater efficiency.

Personnel, product, material and waste flows are also a key element of OSD facility design, with the goal of a unidirectional flow path without backtracking. Materials should move from the warehouse to the various unit ops in a process-sequential fashion (e.g., weigh/dispense to blending, granulation, compression, coating, packaging and, ultimately, back to the warehouse as finished product). This approach not only is more efficient but also by preventing backtracking, minimizes the risk of cross contamination and product mix-up.

All CRB warehouses are designed with overall efficiency in mind. The organization of the warehouse takes into consideration material flows, which start in shipping and receiving. Materials used in manufacturing processes are placed in a holding area until they can be sampled. Once it is assured that they meet quality specifications, they are moved to an area for materials that are ready for use.

FACILITY LEVELS OF PROTECTION

In an attempt to allow manufacturers a bit more freedom in their design and operational approaches, modern guides – such as the *International Society for Pharmaceutical Engineering's OSD Baseline Guide*, third edition, released in November 2016 – use a level of protection scheme based on risk assessment and mitigation of risks. It defines a matrix used for cGMP spaces that identifies three levels of protection centering on in-process materials: being open (white, Level 3), partially open (gray, Level 2) or closed (black, Level 1) to the environment and the operation.

When the process is always closed and the operation is not open to the environment, fewer controls (temperature, humidity control and uniforms) are needed to reduce the risk of contamination. In partially open systems, there is some risk of exposure, but it is typically minimal. A few additional control measures are needed, such as air filtration and overgowning. In open systems, the material is exposed to the environment and operators, and therefore a higher level of control measures is needed to minimize the likelihood of contamination. Examples include more extensive air filtration, unidirectional air flows, engineering controls and containment equipment. These areas may also be segregated with separate HVAC and air systems, as well as gowning/degowning stations.

EQUIPMENT

Equipment for OSD manufacturing must be designed, sized and constructed in a fashion that is cleanable. No aspects of the equipment should provide opportunities for contamination. While much of the equipment used for OSD manufacturing has not changed extensively during the last 30 years (except with regard to equipment designed for continuous manufacturing), there have been a number of noteworthy advances.

First, OSD production equipment is now designed to be ergonomic and user-friendly. Operators today rarely climb ladders to manually feed ingredients into a process system. Instead, column lifts, manipulators and automated feed systems are employed. These automated systems minimize operator interactions with processes, reducing the potential for errors and improving the containment of OSD processes. Downflow booths, glove box isolators and split butterfly valves are additional examples of containment technologies being employed.

Second, present-day equipment is generally provided with some configuration for clean-in-place or wash-in-place capabilities via semi- to fully automated operations. Several pieces of OSD equipment no longer need to be taken apart and manually cleaned. Equipment suppliers are also working to reduce the number of components that need to be cleaned to offer further improvement.

WORKING WITH CRB

At CRB, we specialize in providing integrated solutions. This has been our guiding force for the last 30+ years, as we have become one of the leading design and construction firms worldwide. We employ quality, honesty and technical excellence in all that we do, from the design of oral solid dose facilities and beyond, to provide best-in-class engineering from start to finish. P

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Dave DiProspero has 25+ years of pharmaceutical engineering experience in internationally regulated oral solid dose form manufacturing operations. He has worked as an owner's representative and as a direct employee for well-known equipment/technology suppliers and engineering firms. As an Associate/Director of Pharmaceutical Process Technology for CRB-Philadelphia, Dave is involved in front-end/back-end project consultation and planning, strategizing, design and engineering implementation/execution and is an experienced team communicator. He has a strong facility/process, design/engineering, containment, equipment, material handling and facility systems integration background.

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STRENGTHENING THE OUTSOURCE SERVICE OFFERING THROUGH INTEGRATION

> BY **LUIGI TRUSSARDO**, OLON RICERCA BIOSCIENCE LLC

Controlling costs and increasing efficiencies are two fundamental drivers for outsourcing of pharmaceutical manufacturing. Use of integrated contract development and manufacturing organizations (CDMOs) that can support projects from early-development phases through commercial production reduces timelines and costs by facilitating scale-up and technology transfer. With the addition of Olon Ricerca Bioscience, Olon S.p.A. now offers end-to-end support for the development and manufacture of chemical APIs and intermediates.

BUILDING A BROADER SERVICE OFFERING

Olon S.p.A. is a world-leading advanced intermediates and small-molecule active pharmaceutical ingredient (API) contract development and manufacturing organization (CDMO) and generics supplier, with headquarters and seven manufacturing facilities located in Italy and one in Spain. Our company also has subsidiaries in the U.S. (Olon USA Inc.), Germany (Infa GmbH) and China (P&R Shanghai–International Trading Co. Ltd).

In June 2017, we significantly broadened our service offering with the acquisition of the Chemical Division of U.S. CDMO/contract research organization (CRO) Ricerca Biosciences. The business was renamed Olon Ricerca Bioscience LLC and continues to operate from its Concord, Ohio location.

With the acquisition of this research and manufacturing base in the U.S., Olon has added new early-phase CDMO capabilities and expertise, while also gaining additional access to the American market. Olon Ricerca Bioscience, in turn, has gained access to large-scale manufacturing capabilities in Europe. As a result, we have broadened our overall contract research, development and manufacturing services for all of our global customers.

Today we can support the full development and production of chemical intermediates and APIs, including new chemical entities, from preclinical to phase I-II at Olon Ricerca Bioscience and phase III and commercial production at our facilities in Europe. With internal technology transfer there is no need to work with an external organization; there are no confidentiality issues and the process can be implemented seamlessly using the same technologies within the same quality and management systems.

A STRONG U.S. PRESENCE

Olon Ricerca Bioscience is recognized as a very reliable U.S.-based CRO/CDMO supporting the development and manufacture of APIs and performance materials for clinical studies, market development and commercial distribution. Our highly experienced scientific team has a proven history of achievement with complex chemistry challenges, providing a complete solution for any small-molecule chemical development need and creating synergies that accelerate first-time scale-ups and the subsequent development of safe, reliable, robust and cost-effective manufacturing processes.

Our scientists also offer synthetic and process chemistry services such as process research and route selection, stable labeling synthesis, metabolite/degradant identification and synthesis, synthesis of analytical reference standards and much more. In addition to these capabilities, Olon Ricerca Bioscience provides a comprehensive range of on-site analytical chemistry services (both stand-alone and in support of projects) to fully support the drug development process – from preclinical to post-marketing phases for both drug product and drug substance.

As part of Olon Group, we can also guarantee our clients long-term partnerships that include large-scale manufacturing capabilities in Europe at eight FDA-inspected manufacturing plants. In addition, access to Olon's skilled regulatory team, who manage more than 350 DMFs in over 70 countries and have established experience in global regulatory and quality procedures, allows Ricerca Bioscience to support both large pharmaceutical companies seeking specialized services and/or complementary capacities and small and midsized pharmaceutical firms that have limited manufacturing infrastructure and rely on CDMOs for a range of services, including regulatory filings, quality assurance, procurement and supply management support.

BIDIRECTIONAL BENEFITS

The combination of the CRO/early-phase CDMO services of Olon Ricerca Bioscience in the U.S. and the late-stage and commercial CDMO offerings of Olon in Europe benefits both organizations and our customers.

Olon Ricerca Bioscience is building on its excellent reputation. The strong finan-

OLON GROUP, AS A WHOLE, HAS THE ABILITY TO SUPPORT CUSTOMERS FROM **EARLY-PHASE DEVELOPMENT TO COMMERCIAL PRODUCTION AND TO PRODUCE MILLIGRAMS TO TONS OF MATERIAL.**

cial stability of the Olon Group and the commitment of our owners to continued growth make use even more appealing to customers. They can be assured that any projects started by the company will be completed and that the same procedures and quality systems are in place from the earliest development stages through commercial manufacturing.

Olon Ricerca Bioscience can now also rely on the deep regulatory expertise and experience that Olon has in preparing DMFs, which it has completed for more than 150 APIs in the U.S. market. The close relationships that Olon has established with the global regulatory agencies will facilitate future filings for the U.S. organization. The portfolio of technologies that Olon Ricerca Bioscience can offer to its customers has also been expanded. Examples include fermentation, recombinant peptides, the performance of hazardous chemistry and new technologies such as fluorination and carbonylation reactions and the production of highly potent APIs.

The European CDMO business, meanwhile, benefits from not only the added ability to offer early-phase development and manufacturing capabilities to its customers, but also the addition of the strong, stand-alone analytical services (i.e., impurity and polymorph identification, etc.) offered in the U.S.

OVERCOMING INTEGRATION CHALLENGES

Acquisitions require integration, of course, and integration is always a delicate/challenging process. With the integration of Olon Ricerca Bioscience into the Olon CDMO operations, we melded different company organizations with different cultural environments and business approaches. The companies not only were of different sizes, but also had different business architectures and were focused on different commercial targets within the drug development cycle – small, early-phase projects for Olon Ricerca Bioscience and large-volume and commercial projects for Olon.

To overcome these challenges, starting on day one, we established a plan to pursue ongoing interactions between the two organizations with the intent to understand these differences and identify the best approaches to adopt that would benefit the entire group. We first had to understand the two types of targets and determine how best to implement the Olon approach to customer service.

We also needed to migrate all of the Olon Ricerca Bioscience financial, information technology and purchasing systems to those used by the Olon Group. Olon's Corporate Quality System (procedures, inspection protocols, internal auditing, etc.) was also implemented across Olon Ricerca Bioscience operations to ensure that all projects are managed under the same conditions. A plan for an FDA pre-approval inspection at the Ohio facility was also initiated in preparation for the approval of an API that will be produced at the site and sold in the U.S. API market.

Just as important, we instituted daily information exchanges between the R&D groups in Ohio and Europe. This ongoing discussion ensures that regardless of where our customers are located or which services they are seeking, all of the technical groups are familiar with the full range of technologies and capabilities of the entire organization, from analytical services at Olon Ricerca Bioscience to commercial contract manufacturing in Italy. In addition, the project teams in Italy and the U.S. are both involved in the evaluation of requests for proposal and preparation of a combined offer for potential customers. Exchanging information is crucial for this process to be implemented efficiently and effectively.

ONE COMMERCIAL TEAM

Another aspect of our approach to the integration of Olon and Olon Ricerca Bioscience is the formation of our One Olon Commercial Team and the centralized management of global accounts and key customers. The goal is to enable the identification of potential benefits for our customers that would not be realized through a compartmentalized commercial strategy.

Customers, wherever they are located and whatever projects they are focused on, will be served by one commercial team with knowledge of the offerings (technologies, capabilities and capacities) of Olon Ricerca Bioscience, the Olon CDMO group in Europe and the Olon USA and European generics businesses.

Customers are presented with information about our full range of services, from our generic API offerings to our stand-alone analytical services, because in many cases technologies and capabilities in one area may be applicable in another. For instance, one of our generic APIs with minor modifications may be suitable as a raw material for a new chemical entity being developed by a potential customer, which could lead to significant cost and time-saving. Similarly, it may be easier to modify an existing analytical method rather than start from scratch.

Training of our commercial team is underway to ensure that all members have a detailed understanding of all of the capabilities of the company as a whole.

In a similar vein, key account managers will be responsible for global accounts, with the different commercial teams reporting to these centralized managers so that an organized and comprehensive offer can be made for all worldwide services.

TRAINING OF OUR COMMERCIAL TEAM IS UNDERWAY TO ENSURE THAT ALL MEMBERS HAVE A DETAILED UNDERSTANDING OF ALL OF THE CAPABILITIES OF THE COMPANY AS A WHOLE.

UNITED BY A FIVE STRONG PILLARS APPROACH

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. Olon Ricerca Bioscience is in the process of adopting this approach.

The Five Strong Pillars include:

1. Quality On Time In Full (QOTIF)
2. Supporting customers from R&D to commercial quantities
3. A strong team-based project management culture
4. Security of project information
5. Cost management

Excellent customer service requires an in-depth understanding of the customer's needs. Across the Olon Group, flexibility is also essential because projects may be initiated at any of our sites but require support from different or multiple locations. Cooperation is, therefore, also fundamental to achieving QOTIF. Having the same quality system across the entire group provides assurance to our customers that their products will be produced to the same exacting standards throughout the lifetime of each project. On-time delivery, in essence, involves providing our customers with the services they have asked for.

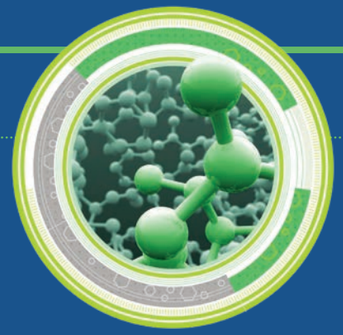
Olon Group, as a whole, has the ability to support customers from early-phase development to commercial production and to produce milligrams to tons of material. These capabilities are backed by the strong financial stability of the company. We are also interested in being strategic partners with our customers and are committed to forming long-term, risk-sharing, win-win relationships.

Our management approach involves the use of dedicated project teams that support each project from start to finish. This approach allows for excellent communication and the building of strong relationships between Olon scientists and our clients. We have, in fact, had many customers that bring us repeat business, where clients specifically request the same project teams.

The security of customer information is absolutely essential. At Olon, we take this issue seriously and have procedures in place to ensure that security is maintained at all times. In addition to our dedicated project teams, we have separate teams for our generics and contract manufacturing businesses. Our information technology and informatics systems are also designed to protect customer information. Further, we cooperate with our customers to ensure that appropriate measures are implemented to protect their information.

Cost management is always an issue for any business and it is of particular concern today for the pharmaceutical industry. Because Olon is involved in the generics market, where competition is largely based on pricing, we have gained experience in achieving cost-effective production methods. This experience is then applied to projects implemented by our CRO/CDMO businesses to the benefit of our customers. P

Integrating Purchasing Operations



Olon's purchasing activities are located in Italy and China. The latter group is responsible for sourcing raw materials for the entire Olon group and consists of local people who speak the native language and are capable of auditing suppliers to ensure quality. This group was, however, previously familiar only with sourcing raw materials for larger-volume projects.

Olon Ricerca Bioscience requires much smaller volumes of raw materials. In some cases, material may need to be purchased just one time for a specific project — and even customer-ordered. Today, whenever possible, Olon-approved suppliers are now used for raw materials purchased by Olon Ricerca Bioscience. There are ongoing conversations among the Ohio, Italy and China purchasing groups to identify appropriate suppliers. For raw materials that cannot be obtained from pre-approved suppliers, the Chinese team is involved in auditing potential vendors.

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CORPORATE SOCIAL RESPONSIBILITY AS A DRIVER FOR IMPROVED SUSTAINABILITY

> BY **ALLAIN DE WILDE, LOÏC ALLANOS,** SERVIER GROUP

The pharmaceutical industry must respond to growing expectations for product safety, the conduct of clinical trials, access to therapeutic care and the environmental impact of medicinal products and manufacturing. Servier Group formalized its Corporate Social Responsibility (CSR) strategy to integrate and communicate the actions it is taking in collaboration with internal and external stakeholders.

WHAT IS CSR?

Corporate social responsibility (CSR) encompasses activities taken by companies, typically those that go beyond legal requirements, to reduce their environmental impact and enhance the social well-being of their employees and members of their communities – and the world. CSR is important as large companies have significant influence over sizable groups of people, from their customer base to politicians, and measurable impact on the environment. With CSR, that influence is used to achieve positive change.

In 2018, many companies are ramping up their activism and investment in issues that impact their employees, customers and communities.[1] Some of the areas they are focusing on, according to Susan McPherson, CEO of McPherson Strategies and contributor to *Forbes*, are workplace harassment and inequality, diversity, privacy and data protection, brand activism, climate resilience and supplier standards.[1] She notes: "As 2018 unfolds, it's likely that companies will continue taking unprecedented action to accelerate social and environmental progress."[1]

ISO 26000:2010

The International Standards Organization first published ISO 26000 – Social responsibility in 2010.[2] This standard consists of a set of voluntary guidelines for implementing a CSR strategy and operating in a socially responsible manner. The goal of the guidance is to help companies understand the principles of CSR and to translate them into programs using best practices. It was developed with input from approximately 500 representatives of various governments, NGOs, companies, consumer groups and labor organizations from around the world.

WHY CSR IN THE PHARMA INDUSTRY?

It is the manufacturer's responsibility to ensure all medications are produced at the highest levels of quality and safety, using processes with minimal environmental impact. Workers and communities must be protected and supported, and the medications must be accessible to patients. Although most pharmaceutical companies take these responsibilities very seriously – and despite tremendous advances in the treatment of diseases and the exciting promise of next-generation biologic drugs – public perception of the industry has declined in recent years. CSR strategies provide a clear mechanism by which pharmaceutical companies can demonstrate and communicate their commitment to social and environmental issues.[3]

WHY CSR AT SERVIER?

At Servier, we recognize the power of CSR as a linking mechanism for social and environmental programs. A formal CSR strategy enables communication of company goals for creating positive social and environmental impacts in collaboration with all internal and external stakeholders – from employees to customers/partners. Our objective is to enable sustainable development. To do so, we are taking steps that go beyond legal obligations; it is a business strategy of Servier to be socially responsible as a means for creating value for all stakeholders and growth opportunities for the company.

Servier has implemented a formal, structured CSR strategy using an inclusive and participatory approach that aims to further spread social responsibility in each of the Group's business areas. Our CSR department conducted a materiality analysis for key stakes following ISO 26000 guidelines in 2016. Key CSR priorities were enumerated. Through more than 50 interviews with internal and external stakeholders, 17 priority stakes were identified to address main goals for the Group over the next 5–10 years.

COMMITMENT AREAS

The 17 stakes were classified into four "commitment areas" that are in keeping with the Group's values and strategic orientations. Our CSR strategy is based on these four commitment areas: a company committed to healthcare, caring about people, focused on our business practices and aiming for a positive footprint.

Servier's CSR is designed to meet stakeholders' expectations and is an integral part of all our operations, business areas and subsidiaries.

A company committed to healthcare

Servier is dedicated to developing and manufacturing therapies that benefit patients and meet their expectations for safe, high-quality products. We are committed to ensuring product safety and quality, anti-counterfeiting, ecodesign and a global approach to healthcare. We are highly experienced in achieving the utmost quality at all of our sites, internationally and especially at our industrial sites.

Over the coming years, Servier aims to develop an ecodesign approach in order to reinforce our capacity for innovation, to create value for the Group and to leverage this value for our partners and clients. We want to progressively develop life cycle analysis for our products and plan to test a pilot by the end of 2018 or into 2019. We believe this will optimize the various stages of our product, and we hope to identify some "quick wins" to improve our positive impacts while decreasing any negative impact (by, for instance, using green and white chemistry, packaging, the use of natural resources, design and services). Innovation is key for Servier, and this connection is present throughout all areas of the Group.

Caring about people

Servier has a robust social culture. We put people first, and this has been our priority since the beginning – people are at the heart of our strategy. In addition, we demand a very high level of safety on all of our sites. We have an operating Environmental Health and Safety (EHS) Team,

Corporate Social Responsibility

KEY DATES

2016
- Creation of CSR department and key stakes assessment of CSR

2017
- Development of an action plan

2018
- Policy launch and rollout
- Creation of a correspondent network

2019
- Contribution of policy to UN Sustainable Development Goals
- Publication of the first CSR report for 2017–2018

AT SERVIER, WE RECOGNIZE THE POWER OF CSR **AS A LINKING MECHANISM FOR SOCIAL AND ENVIRONMENTAL PROGRAMS.**

and many sites have already implemented a Safety Management System (OHSAS 18001 or equivalent). Again, this is because we consider health and safety to be top priorities. In addition, we strive to develop a "zero accident" culture. This not only has a positive effect on our people, but also indirectly benefits all our partners. When a partner or client works with Servier, they can be sure that the team on-site operates within a high level of EHS, meaning there is less risk of an accident ever taking place – this means our partners do not need to worry about their reputation being impacted in a negative way or business being interrupted.

Focused on our business practices

Stakeholders have high expectations for business ethics and transparency. To fulfill these expectations, we promote open and direct communication with patients, employees, partners, public authorities and civil society, in an effort to bolster business ethics, responsible purchasing, ethics and transparency of clinical trials and stakeholder engagement. Servier is currently working on a new Ethics Charter and a new code of conduct, which is addressed to all of our stakeholders. Stakeholder engagement is highly important for the Group. It is imperative to our long-term vision, with a high level of consideration and respect for our stakeholders (patients, partners and clients). We promote respect, transparency and ethics in all of our discussions and interactions with our stakeholders; our strategy is to create long-term partnership. Examples of initiatives that fall into our business ethics commitment are the creation of a Responsible Purchasing Committee and the training of a buyer network in responsible purchasing. Servier was also ranked No. 2 in the international CenterWatch 2017 for clinical trial quality.

Aiming for a positive footprint

As of now, eight Servier manufacturing sites hold ISO 140001 and/or ISO 50001 certifications for environmental and energy management systems, respectively. Our Arklow site in Ireland and Warsaw plant in Poland both are zero-waste-to-landfill facilities. One example of a community program involved training of young doctors in Abidjan in January 2016, in conjunction with the Africa Diabetes Academy. We have high ambitions regarding the environment, with climate change and waste and effluents management considered in all that we do. Servier wants to become a carbon neutral company (scope 1 and 2) in 10 years. The Group also has plans to be "zero waste to landfill" for all our industrial sites within a few years (we already have sites compliant with this internal objective). We treat the ecosystem with the high level of care it deserves and strive to forge strong relationships with the stakeholders of this system, from those in our neighborhood to our city, administration, local partners and industrial, as well as researchers. Our long-term vision is an asset; our people believe in this commitment, which has led to donations and volunteer work.

A HUMAN COMPANY

Our formalized CSR strategy is part of Servier's transformation plan and contributes to its dynamic of openness. Communication with stakeholders strengthens our ability to anticipate emerging topics in order to create the right conditions for a more sustainable model. The 17 stakes and four areas of commitment support our position as a human company focused on improving all aspects of humanity. Our new CSR strategy is being launched and rolled out in 2018 in combination with the creation of a correspondent network. Servier is also making policy contributions that will enable us to work toward achieving UN Sustainable Development Goals. We are looking forward to the publication of our first CSR report for 2017–2018, which will take place in 2019. P

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Loïc Allanos joined Servier in 2002. In 2006, he began working in the Legal Dept. in Risk Management and Insurance, serving as Servier's Risk Prevention Manager for more than 10 years. Loïc worked principally with the Servier Industrial Sites and Research Centers, internationally. During this time, he managed industrial risks, EHS, and business continuity plans, and participated in Strategic Risk Mapping for Servier Group. Loïc Allanos then joined the new Corporate Social Responsibility Department.

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Challenges for Next-Generation Biological Therapeutics Discovery and Development

By **Cynthia Challener, Ph.D., Guy Tiene, Emilie Branch**, Nice Insight

In the last three and half decades, the focus of drug discovery and development has gradually shifted away from small, well-defined chemical molecules to large, complex molecular entities – therapeutic biologics. Biotherapeutics are now playing an increasingly prominent role in combating cancer, diabetes and autoimmune diseases. The recent debut of cellular and gene therapy products has opened the door for biologics to tap into areas of genetic disorder, regenerative therapy, and personalized medicine. In the coming years, novel biological therapeutics will continue to enrich our medicinal arsenal for serious diseases and address unmet medical needs.

The biopharmaceutical industry is booming from the success of biologics. Currently, biologics represent the fastest growing sector in the global pharmaceutical market, generating revenues of $231.2 billion in 2017. This market is projected to reach $479.7 billion by 2024 at a compound annual growth rate (CAGR) of 10.9%. Over the next six years, monoclonal antibodies (mAbs) are predicted to rise, taking a leading position among a diverse array of biological products. Monoclonal antibodies are anticipated to capture 46% of the total biologics market share at a CAGR of 11.9%.[1]

Treatment potential and the associated financial rewards have fueled the search for next-generation biological therapeutics. However, drug discovery and development is a long, difficult and expensive process. Biologics, given their inherent complexity, impose unique challenges to this endeavor. The fundamental challenge facing biopharmaceutical drug innovators is how to optimize their research and development (R&D) efficiency and productivity from early-stage discovery to commercial manufacturing. There is a growing trend towards earlier decision-making so that drug candidates fail earlier, especially during early-phase discovery and development. This, in turn, reduces overall development costs.

In general, drug discovery begins with target identification and validation, followed by assay development, which is used to determine binding and/or modulations of the target. The assay is then performed over a pool of potential candidates to generate lead compounds that interact with the target. There are often repeated cycles of refinement assays, which narrow the pool of leads by improving their biophysical and biochemical characteristics, making them suitable for human trials.[2] Typically, there is a 5.5-year time interval between the start of a research project to a phase IA clinical trial, including 4.5 years of discovery research and 1 year of preclinical testing.[3] It is usually more costly to develop biologics than small molecule therapeutics.

Select Better Targets

One approach to improving drug discovery efficiency is to select better biological targets for the disease. This strategy requires a deep understanding of the pathogenesis of the underlying disease, as well as the biology of the target. It is commonly believed that better disease targets are essential to develop more effective therapies, improve R&D efficiency, boost success rate, and reduce costs.

Two key questions should be asked at the onset of seeking a biological targeted therapeutic. First, is there sufficient evidence to link the target to the disease? Second, is the target viable for biological therapeutics, antibody-based or other formats? A thorough data mining of available biomedical data is usually a good starting point. A wealth of information can be gained from a variety of data sources such as publications, patent information, gene expression data, proteomics data, transgenic phenotyping and compound profiling data. Further, phenotypic screening methods are gaining traction in antibody discovery as a means to identify either disease-relevant targets or antibodies that are eliciting desired physiological responses.[4, 5] To ensure the accuracy of the target, a multi-validation approach is necessary by collecting enough evidence to support target rationale and performing experiments using knock-out cell lines and/or animal models to validate the target.[4]

In the search for better disease targets, the National Institutes of Health (NIH) launched a public-private venture program, the Accelerating Medicines Partnership (AMP) in 2014, to identify and validate promising biological targets for new diagnostics and therapies at reduced time and cost. As of 2018, 12 biopharmaceutical and life science companies and 13 non-profit organizations along with NIH and the U.S. Food and Drug Administration (FDA) have joined the AMP. Current AMP research projects are focused on four areas: Alzheimer's disease; type 2 diabetes; autoimmune disorders of rheumatoid arthritis and lupus; and Parkinson's disease.[6] The AMP represents a trend of increasing collaborations between governments, industry, academia and non-profit organizations to promote scientific communication, information exchange and data sharing, and thus accelerating drug discovery and development.

Improve Screening Technology

Another approach to speeding drug discovery relies on the development of more robust, sensitive and accurate assay technology that simplifies and expedites the process. In a traditional antibody discovery stage, potential antibodies go through a series of sequential assays: primary screens for binding and specificity in biochemical assays (e.g. ELISA); secondary cell-based binding assays; functional assays; and optimization screens composed of three steps — optimization binding assay, specificity assay and cell-based binding assay. There are several limitations embedded in this workflow. First, it is resource-intensive in terms of time, instrument requirements, and reagents. Second, denatured proteins are used in biochemical assays, which can lead to missed hits. Lastly, data inconsistency and errors are likely to be introduced between each step.[7] Technology advancement is needed to streamline the antibody screening process with improved simplicity and efficiency.

In addition, a more sensitive primary high-throughput screen (HTS) that can tolerate crude preparations is quite desirable. In the initial screen, protein libraries are often present in bacterial lysates or extracts, or hybridoma supernatants, rather than purified forms. Components in bacterial preparations (i.e. bacterial by-products) and hybridoma supernatants (i.e. serum and growth factors) can interfere with HTS performance resulting in decreased sensitivity and accuracy.[5]

Moreover, the requirement for using purified antibodies or IgG reformatting (the technique for reformatting phage-displayed antibody fragments to full-length IgG) for functional cell-based assays has often been a bottleneck in antibody lead generation and selection. Several strategies have been proposed to address this issue including reformatting antibody libraries, IgG display on mammalian cells, and screening in IgG product format.[5]

Improve Intracellular Delivery

Targeting intracellular molecules has been a long-standing challenge for biologics. Their large molecular weight and high structure complexity impede them to effectively cross the cell membrane and interact with intracellular target consequently. On the other hand, intracellular protein-protein interactions (PPIs) offer a rich pool of potential therapeutic targets, awaiting next generation biologics to make a footprint.

Many approaches have been raised to enhance intracellular delivery of biologics including protein engineering, nanoparticles, antibody engineering and novel drug delivery systems. One promising method involves coupling biologics with cell-penetrating peptides or protein transduction domains (PTDs), such as Tat, SynB, and penetratin. These cationic peptides are able to translocate across cell membranes and have been used to deliver peptides, oligonucleotides and proteins into the cells.[5]

In recent years, antibody fragments such as a single-domain antibody (sdAb) have gained much attention as the new generation of antibody drugs. In contrast to full-length Abs, antibody fragments are much smaller in molecular size with less structure complexity. They have showed better penetration into solid tumors and tissues. Engineering antibody fragments into functional intracellular antibodies, or "intrabodies," may provide an alternative to intracellular delivery. One disadvantage of antibody fragments lies in their shortened half-life. Several half-life extension techniques can be used to address this issue, including PEGylation and albumin conjugation. In addition, antibody fragments can also be used as building blocks to generate larger multivalent or multispecific molecules.[5]

Target Central Nervous System (CNS) and the Blood-Brain Barrier (BBB)

The brain is one of the least accessible organs in the human body and remains a challenging target for biologics due to their inability to cross the blood-brain barrier. One purpose of improving biologics delivery to the CNS is to target brain tumors; antibody-based therapy offers more specific treatment regimen and thus may achieve better treatment results and prognosis. A number of methods have been developed to achieve this goal, including invasive techniques (i.e. direct injection, mechanical or biochemical disruption of the BBB) that carry apparent risks and pharmacological modifications such as conjugation to a "molecular Trojan horse," cationization and encapsulation in liposome nanoparticles.[5]

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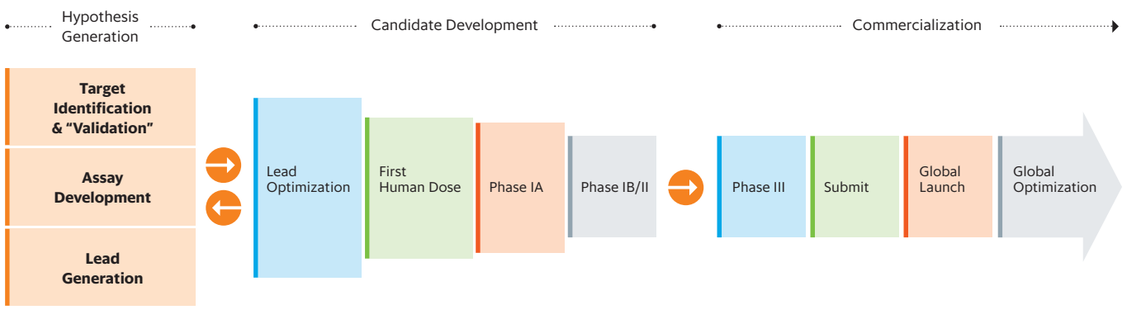
Overall Drug Discovery and Development Process

SOURCE Potter presentation, April 8, 2013



The Next-Generation Issue Feature

Thinking a Generation Ahead: Biologics-Based Therapy

By **Cynthia Challener, Ph.D., Guy Tiene, Emilie Branch**, Nice Insight

The next generation of drug development and manufacturing may take many forms: from a transformation in the way facilities are structured, to a reliance on continuous manufacturing, to embedding 3D printing systems into operations and incorporating flexibility into design. Changes made to operations will position companies ahead of the game, and as the industry races to meet an ever-increasing demand for drugs from a rising population, there is no time for a slow down. In addition to this, drug manufacturing must keep up with the drug discovery sector, for which possibilities seem truly endless. Whether dealing with stem cells, CRISPR Cas-9 technology or antibody-drug conjugates, there is no shortage of innovation. The challenge for drug manufacturers has become scaling these operations up and managing to commercialize such extremely resource-intensive processes.

In order for contract development and manufacturing organizations (CDMOs) to bring drugs to the market, a foundation of flexibility is crucial.[1] Multiple operations can be leveraged in support of drug discovery; as more complicated drugs are being formulated, drug manufacturing has also grown more complex. One-size-fits-all operations are a thing of the past, instead companies must diversify.[1] For a CDMO to remain truly competitive, multiple systems must be at play.

Segregate Operations

One way to ensure flexibility is building it into facilities. Manufacturing organizations that are looking to expand into cell and gene therapy and next-generation therapies benefit from diversifying their operations design. As Peter Walters, Lead Process Engineer from CRB USA, explained to *Pharma's Almanac*: "Constructing a process map for all of the intended processes in the facility from an operational perspective can be a key tool for communicating process requirements. Specific requirements for each process – equipment, material flows, personnel movements, etc. – must be considered."[2]

In order to confirm the safety of a multi-product facility, controls are needed to segregate and fully contain these processes from all other areas of the facility.[2] "For multi-product facilities, processing of multiple gene vectors should be performed either on a temporally segregated campaign basis (with sanitization between) or in parallel but in completely segregated viral production spaces for each product campaign produced," advised Walters.[2]

Turn Back to Single-Use

Single-use technology has been around for over 20 years, and primarily functioned as a means to achieve clinical batch and pilot-scale operations. However, as demand for bioprocessing has grown, this technology has likewise grown in demand. It is seen as an attractive option for a number of reasons.[3] Employing single-use eliminates cleaning, and cleaning validation steps, which reduces the risk of contamination.[3] Single-use technology also allows faster turnover from one product to another, reduces water consumption, allows small scale commercial production and gives a facility the ability to run multiple molecules in conjunction.[4] Single-use systems are also able to connect two unit operations.[4] Speaking to industry publication *Pharmaceutical Technology*, Miriam Monge, Director of Process Development and Bioprocess Platforms, Integrated Solutions at Sartorius Stedim Biotech, noted the versatility of molecules that can be manufactured using this process. "Antibodies, proteins, vaccines, cell therapy, and gene therapy all fall into categories of molecules that can benefit from being manufactured in fully single-use, end-to-end processes," said Monge of these next generation therapies.[4]

Of course, single-use is not without its own set of challenges. In the same interview, Steve Miller, Global Head of Next Generation System Development, Life Science, Upstream and Systems Business Field Millipore S.A.S., spoke on issues related to the technology. "Implementing single-use brings with it new challenges that traditional facilities do not face, such as ensuring skids from different vendors have compatible connectors and common spare components such as clamps. Other, lesser-known challenges are related to packaging, installation and disposal, as each manufacturer may have different approaches, making operator life more complex and introducing opportunities for more errors." Indeed, even single-use technology, though decades old at this point, has yet to be entirely perfected.[4]

Move From Batch to Continuous

Manufacturing for next-generation therapies is inherently challenging on multiple fronts and has challenged the way the industry produces drugs on all levels. Perhaps this is felt most acutely in the push for operations to transition from batch to continuous. Whereas batch manufacturing is burdened by the previously defined maximum asset utilization available, companies have been generally risk-averse in migrating from this model.[1] In continuous manufacturing, a product can be monitored continuously. If there is an issue, it is likely that it will be noticed in real time, leading to overall improvement.[3]

For a CDMO to remain truly competitive, multiple systems must be at play.

Perhaps the greatest ally of continuous manufacturing is the FDA. The process has been championed by the regulating body, and is considered a fast and efficient means of achieving production, especially when compared to batch processing.[5] The agency has identified continuous as a means to improve product quality, as there is hope that continuous processing will lead to the identification of the root causes of drug shortages or recalls.[5] Though the agency has recognized the challenging nature of transitioning to continuous, it is greatly encouraged.

Sau (Larry) Lee, Ph.D., Deputy Director of the Office of Testing and Research, and Chair of the Emerging Technology Team, Office of Pharmaceutical Quality, CDER, described the benefits of making the transition in an article which appears on the FDA website, titled: "Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing."[5] In contrast to batch, with continuous manufacturing, pharmaceuticals move nonstop through the manufacturing facility which speeds up processes by getting rid of hold times. "Material is fed through an assembly line of fully integrated components. This method saves time, reduces the likelihood for human error, and can respond more nimbly to market changes. To account for higher demand, continuous manufacturing can run for a longer period of time, which may reduce the likelihood of drug shortages," wrote Lee.[5]

The challenge of continuous is largely based on old processing systems. The cost associated with totally renovating a plant is prohibitive, especially as most manufacturing facilities are entirely outfitted for batch processing. In spite of this, the long-term cost-benefit will outweigh the challenge of a high start-up cost, and presents the opportunity for significant monetary savings.[5] Although continuous is practiced in the chemical and petrochemical industries, the technology for biopharmaceutical continuous processing is still in its infancy.[5]

The Bioprocessing Summit, taking place this year, will address this challenge and its potential for biopharmaceuticals specifically. Topics covered at the 4th Annual Continuous Processing in Biopharm Manufacturing will include integrated continuous processing, continuous processes for novel biotherapeutics, upstream perfusion processes, new technologies and approaches and economics in innovative manufacturing.[6] The FDA has partnered with the Biomedical Advanced Research and Development Authority, a program within the U.S. Department of Health and Human Services, in order to support both the research and funding of continuous manufacturing for biopharma. The agency has also taken steps to train staff and conduct internal research on any risk areas associated with the process, in order to evaluate like technology.[5]

A Three-Dimensional Future

To stay ahead of trends in the industry, manufacturing companies must not only plan for the next generation of pharmaceuticals but also for the next generation of manufacturing. All things considered, this will include a transition towards or fully incorporating 3D printing in operations. This new means of production could entirely revolutionize the industry. According to Leroy Cronin, a Chemist at the University of Glasgow in the United Kingdom, who was able to digitize chemistry in a standalone 3D printed device, creating 3D printed pharmaceuticals will democratize drug making.[7] For Cronin, one of the possibilities of 3D printed medicine includes "the on-demand production of chemicals and drugs that are in short supply, hard to make at big facilities, and allow[s] customization to tailor them to the application."[7] Cronin's device was "designed and constructed by using a chemical to computer-automated design (ChemCAD) approach that enables the translation of traditional bench-scale synthesis into a platform-independent digital code," read his abstract.[8] This code was able to guide the synthesis of four different chemical reactions, from filtering to evaporating solutions, in a total of 12 steps.[7]

3D printing applied to pharmaceuticals has tremendous potential. Research firm MarketsandMarkets estimates that by just 2020, the 3D printing of medicines could capture a total market value of approximately $2.13 billion.[9] This technology has the potential to impact the industry on all levels, from creating unique dosage forms and complex drug release profiles to the printing of living tissue. [9]

Into Industry 4.0

In order to successfully manufacture drugs into the next generation — whatever form that takes — CDMOs must embrace Industry 4.0. Industry 4.0 encompasses the methods for smarter production, including information technology-integrated facilities that are better able to capture data in real time, thereby improving processes. The next generation of manufacturing will be data-centric.[1] The goal of bettering facilities and operations is to reduce waste and increase the production of quality drugs, reliably. However it is implemented, Industry 4.0 will be a prime driver into the next ten years, and must be integrated into operations as a way to keep up with the next generation of drugs, and the manufacturing that is required to supply them.

From planning a facility so it that operations can be segregated, to bettering single-use technology and ultimately moving from batch to continuous manufacturing, to embracing the opportunity of 3D printing and what that means for the industry, drug manufacturing is at an crucial moment, and ultimately, the companies who encourage and build innovation into their operations are at an advantage when it comes to meeting the growing needs of the next generation. P

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Finishing Touches – The Future of Fill-Finish and Pharma Packaging

P A R T 3

By **Cynthia Challener, Ph.D., Guy Tiene, Emilie Branch**, Nice Insight

Fill-finish hasn't typically been associated with innovation. The decades-old process has remained relatively stable in spite of myriad developments in the industry over the last decade – especially in the case of vials.[1] Although there have been few changes, manufacturers rely on fill-finish operations heavily for current next-generation therapies. Fill-finish operations must evolve, however, in order to get more effective medicine to market in a timely manner, reliably and efficiently.

By the time a drug reaches the fill-finish stage, it has been through upstream processing, cell culture or fermentation and downstream purification.[1] Perhaps the hesitation in experimentation with fill-finish stems from the fact that the product is of extremely high value at this particular phase of operations. In this form, it is the result of all the manufacturing processes thus far. In addition to the labor that has gone into these vials, the fill-finish step is crucial from a compliance standpoint. Errors that occur during fill finish could lead to contamination, formulation issues or dosing problems, which could mean not only the loss of product but detrimental health risks and/or production failure.[1]

Fill-Finish Challenges

The many challenges associated with fill-finish operations have largely led to its outsourcing. According to the 12th Annual Report and Survey of Biopharmaceutical Manufacturing, an industry wide survey conducted by BioPlan Associates, seven out of ten respondents reported some outsourcing of fill-finish.[2] Fill-finish operations were outsourced most frequently, with respondents relying on external organizations for over one third (34.5%) of their fill-finish needs.[2]

Results from this survey also indicated the tremendous interest in developing these operations further, and the pressure that CDMOs are facing to evolve operations, and thus meet the demand for a more advanced process. According to the survey, out of ten respondents, eight said they were planning to add a minimum of one new technology to their fill-finish operations within the next two years. Of these respondents, the majority were employed by contract manufacturing organizations.[2]

Serialization Demand

The widespread demand to improve packaging is perhaps best exemplified through the race to meet the FDA's upcoming deadline for a fully traceable supply chain, following the passage of Drug Supply Chain & Security Act (DSCSA). The act mandates the use of an electronic track and trace system to identify prescription drugs throughout the United States.[3]

Going forward, serialization must be built into operations – and it can be argued, for good reason. According to the FDA, the DSCSA will "enhance the FDA's ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated or otherwise harmful. The system will also improve detection and removal of potentially dangerous drugs from the drug supply chain to protect U.S. consumers." At the 25th Annual Life Sciences and Technology Conference presented by the International Society for Pharmaceutical Engineering-Carolina-South Atlantic Chapter, keynote speaker Paul McKenzie, Ph.D. and Executive Vice President for Biogen addressed this pressing issue. "Eighty percent of product recalls from the market are due to packaging errors," he noted.[4]

Issues and Costs

Though serialization has the potential to drastically change the entire supply chain, with the patient ultimately benefiting the most, it is not without its challenges. There is a substantial cost burden for the industry to abide by the regulatory requirements of serialization. According to Medicines for Europe, the nonprofit association representing the industry, it will cost the average company €5 million to update packaging and production lines, plus an additional annual running and maintenance fee of €2 million.[5] It will cost the pharma industry €5 billion in general, with an implementation and running cost of €90 million annually.[5]

Aside from the obvious issues involved in financing a serialization production line, additional concerns include serialization overlap, as there is no standard code set up by regulatory agencies.[4,5] The lack of regulatory guidelines is another potential issue, as companies have been tasked to serialize operations with very little direction as to exactly how this is to be done. This has led to inconsistencies in what should be serialized. Although entire manufacturing operations should be integrated into serialization, organizations have treated the idea of serialization as limited to packaging. Transparency in the entire supply chain goes beyond packaging, however, and integration is key.

Going forward, serialization must be built into operations — and it can be argued, for good reason.

As Olsen pointed out at the annual event, corporate integration is crucial for an organization to successfully and holistically serialize. "Twenty to 25 percent of operational costs is simple product packaging," commented Olsen. "The OEE (overall equipment effectiveness) in the pharmaceutical industry runs between 40-60 percent. The addition of serialization can reduce efficiency by as much as 5%. This can be a financial game changer for the manufacturer, even big pharma," he continued.[4] There is a fear that this added cost will force smaller companies to abandon operations.

The challenges of serialization extend throughout the supply chain. For companies to take on a new packaging process, new software will also need to be implemented and integrated into operations. Packaging lines must be tested and setup before running.[6] Considering the sheer numbers of products being serialized, an increase in the amount of SKUs (or Stock Keeping Units) generated is to be expected and planned for.[4] Additionally, these SKUs must be managed. Employee training is necessary to oversee these operations and in efforts to minimize any chance of error. With serialization implementation, compliance trickles all the way down from batch scale to an individual shipping unit.[4]

Coding for Success – Quantifying Standards

Another issue to consider is barcode appearance, which again, has not been strictly delineated by FDA. Without an effective verification process, the barcode does not serve its purpose. A QR code must convey data about the product's authenticity that translates through the product's code.[7] How this should look and is open for interpretation, though several features must be taken into account, including if the code is readable under a host of conditions and even how the barcode is read and what it means.[7] Barcode reading, known as scanning and barcode grading, is another way of saying the code is verified. Barcode grading includes either a number or letter score, which acts to quantify multiple barcodes against each other using known standards as a frame of reference.[7]

The 2D data matrix barcode is standardized by the GS1 DataMatrix, which is recognized by the International Organization for Standardization and the International Electrotechnical Commission (ISO/IEC). The GS1 standards body works in conjunction with regulators and the industry to develop a set of norms for codifying the serialization information necessary.[7] Various organizations including ISO/IEC and ANS have worked out grading standards. These organizations have developed standards of clarity that reflect different attributes of the system. For instance, GS1 DataMatrix barcode features are ranked numerically (4-0 - ISO) or using an alpha system, which is the (A, B, C, D, F) American National Standards Institute (ANSI) scale.[7]

Attributes considered include decodability, contrast, modulation, fixed pattern damage, grid non-uniformity, axial non-uniformity and unused error correction.[7] Decoding of the bar code signifies if it is readable. The bar code's contrast, or the difference between the colors that comprise the code, such as a white background with black squares or dots, is also taken into consideration. This extends to modulation, which includes the differences in color contrast throughout the bar code, with less being better. Fixed pattern damage is another attribute; the quality of squares or dots that make up the barcode's perimeter as well as the surrounding negative space of the barcode. Grid non-uniformity is how the bar code is able to fit in a specific boundary, and axial non-uniformity is the alignment of the bar code within its horizontal and vertical parameters. The unused error correction is the amount of error correction that is in a symbol. It corrects data that is lost due to an issue, such as damage or poor printing.[7] Under best circumstances, the barcode is graded in its ultimate form, for instance on a label that is in a bottle or case. How a bar code is printed will also obviously affect the way it looks, with three primary types of printing currently in use. These include thermal transfer, inkjet and laser ablation/marking.

As the industry moves towards the adoption of QR codes, which are essentially data matrixes in the supply chain, security of supply is ultimately more assured. There is little doubt that as the industry meets the demands of the FDA, standards of barcodes will become more sophisticated, with new methods for production and printing achieved, as well as more information conveyed, and easier. This will lead to, as the national regulating body has demanded, a decrease in the counterfeited prescription drugs distributed in the United States and eventually, around the world.

As the industry moves towards the adoption of QR codes, which are essentially data matrixes in the supply chain, security of supply is ultimately more assured.

The Future of Packaging in Next-Generation Pharma

Packaging is not without its challenges. The last step in getting a drug to market is also the riskiest, and the site where the most information is at risk of being lost in translation from the manufacturer to the patient. Innovations in packaging will continue to build, especially with the FDA mandate months away from testing the entire industry. However, the response will no doubt be positive sum, as transparency and safety are ensured throughout the supply chain. What's perhaps most interesting will be how the industry interprets this mandate – especially considering holograms and chips are all possible responses to the open call to end counterfeiting.[8] P

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MAXIMIZING ROI THROUGH EQUIPMENT LIQUIDATION

> BY **MATT HICKS,** FEDERAL EQUIPMENT COMPANY

Cost pressures are significant drivers for pharmaceutical manufacturers seeking to eliminate redundancies and increase productivity and efficiency. When selling equipment — whether to bring your facility up to current requirements, maximize the return from your existing footprint or liquidate assets when closing or selling a facility — the expertise and resources of a strategic, equipment management partner can optimize your resource recovery.[1]

ASSET MANAGEMENT OPTIONS

Larger pharmaceutical companies with multiple sites or those undertaking mergers and acquisitions typically have ongoing resource recovery initiatives. While these can be run in-house, they tend to require expertise that often isn't available or in place, which puts a burden on other resources. Specialized external equipment companies can facilitate the management of equipment assets to maximize investment recovery. The greatest return is achieved when internal redeployment is possible and capital expenditures are avoided. However, when liquidation is the best option, it's best to work with a strategic equipment partner to manage that process.

Facility liquidation projects are generally driven by two competing objectives – time available and expected monetary return. Granted, there is always a hard deadline to vacate or clean out a facility, and the expected monetary return becomes a factor when there is a loan to repay or a significant investment to recover within a short time span. For example, a facility that is just a few years old may have more pressure to recoup a higher return at sale versus a facility that is several years old and has earned the capital investment costs back multiple times.

There are some basic approaches to liquidating an entire facility:

Sell the Complete Facility with or without Products/Contracts

Facility liquidations are a great opportunity for other manufacturing sites to obtain much-needed equipment, capacity, workforce and maybe even products and manufacturing contracts.

Liquidation or Private Treaty Sales

Not every project requires the immediate sale and removal of all of the assets of an area or an entire facility. Equipment in storage or only certain pieces of equipment may be best handled with an item-by-item sale over a period of time often called "private treaty sales." In a private treaty sale, a reputable dealer will be in a good position to help identify the inventory, evaluate removal alternatives and costs, and suggest shipping and sales methods that can be helpful for the person who does not have resources available to help with investment recovery activities.[2]

Auction Contents of the Facility

Equipment commonly used among different industries is more likely to have a successful auction as opposed to machinery that is specialized or has a narrow use. There are three types of auctions: a lump-sum sale transfers all assets to the buyer and provides a target date for removal; a guaranteed minimum return ensures a minimum lump-sum sale price while allowing the dealer and seller to share in the upside of a positive sale after the dealer recovers the guaranteed minimum and expenses; and a commission sale puts the equipment seller in the best position for monetary return while the dealer recovers expenses and a commission from the sale. Since auction buyers generally pay for removal as part of the purchase price, the seller can enjoy significant cost savings, even if the auction-sale value itself is lower than expected.[2]

Sale and Removal by a Dealer

Strategic equipment partners will purchase individual machines, complete lines and even entire plants. They also have the expertise to dismantle, load and ship such machinery.

Consignment to a Dealer

The seller of the equipment retains title until sold by the dealer. Often, the dealer will coordinate removal and recover those expenses as part of the sale.

The approach taken reflects the needs

FACILITY LIQUIDATION PROJECTS ARE GENERALLY DRIVEN BY TWO COMPETING OBJECTIVES – **TIME AVAILABLE AND EXPECTED MONETARY RETURN.**

of the equipment seller, such as time available, monetary return, the equipment being sold and market conditions.

TIME AND INVESTMENT RETURN GO HAND IN HAND

No matter which disposal option is chosen, the goal is to recover as much return on investment as possible. Certified appraisers with knowledge of equipment values make accurate assessments, and sellers gain the benefit of fast cash offers based on these appraisals. Some asset classes can be liquidated quickly at values that are very close, if not equal, to retail or true market value. Other asset classes will not liquidate quickly and require time or a speculative buyer who purchases at wholesale prices with the intent to develop and sell to a buyer later at a retail price. Basically, the more commodity-like the asset class behaves, the higher the return will be on a quick sale. The more specific or customized equipment will take longer to achieve the best return. The ultimate goal for both the seller – and the dealer – is to get the best sale price in the time allowed.

Monetary return is heavily influenced by time, but "risk" is also a big consideration for many product manufacturers. Risk can be applied to managing the contract with the equipment buyer and removal team, as well regulatory risks, which include import-export compliance, asset classes and reporting sales of regulated equipment to the Department of Justice, Drug Enforcement Agency (when applicable*) or local government where the equipment is located.

THE BENEFITS OF AN EQUIPMENT DEALER

Recouping monetary investment is often not something with which manufacturing departments are familiar. Often, most manufacturing departments have not spent the time researching or gaining experience in selling equipment, nor understanding the market players, assessing values and how the market works. Even with a well-organized program, these entities *do not* have the resources to bring buyers and sellers together to initiate and close a manufacturing equipment purchase.

Thus, it is wise for a company to enlist a project manager who takes charge of an equipment disposal project. This person must have a clear understanding of the project's overall objective. Is it the speedy removal from the facility? Or is the objective to gain the highest monetary return possible? The project manager should also identify all assets to be sold and control the asset list. This list must be fixed at some point in advance of the sale to properly market the sale. If the sale list changes after marketing begins, the integrity of the sale may be compromised, which equates to a lower return from the sale.

A project manager can work with an outside equipment dealer who can help market the equipment. An equipment dealer understands the dynamics of the equipment marketplace, as they are solely dedicated to the market. Such equipment specialists have the facilities to store acquired inventory, allowing the liquidator to make cash offers and arrange to remove assets quickly.

An equipment dealer, such as Federal Equipment Company, acts as the equipment seller's guide throughout the liquidation process, presenting the best disposal option for the seller after considering all factors. In addition, an experienced equipment dealer can bring in the appropriate resources to manage the liquidation according to plan, including auctioneer selection, removal contractor, marketing plan, accommodating the seller's risk appetite and bringing a well-developed list of equipment buyers to the sale. P

Heavily in-demand equipment categories for specialty chemicals/APIs & pharmaceutical products:

- Tablet Presses
- Tanks & Kettles – solution prep tanks, storage tanks, mixing tanks, etc.
- Chemical Reactors
- Capsule Fillers / Encapsulators
- Fluid Bed Dryers
- Ribbon Blenders and Paddle Blenders
- Coating Pans
- Roller Compactors
- Spray Dryers
- Liquid Fillers

*DEA regulations governing the sale of tablet presses and capsule fillers, for example, were revised on March 31, 2017, updated from January 30, 2017.[3] These regulations mandate reporting for every transaction that involves either a tablet press or capsule filler including domestic (U.S.), import and export transactions. The regulation also requires mandatory, oral reporting of domestic transactions when the order is placed with the seller.[3]

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EXPERIENCE MEETS FLEXIBILITY

> BY **TERRY NOVAK,** TEDOR PHARMA INC.

Demand for solid oral dosage drugs continues to rise. In response, pharmaceutical companies are developing novel therapies to treat unmet medical needs. The highly complex active ingredients in these drugs are produced via complicated, multistep synthetic routes. Many are also poorly soluble with low bioavailability and require advanced delivery technologies. Controlled substances require extensive regulatory knowledge and specialized handling, storage and management capabilities. Contract development and manufacturing organizations (CDMOs) with experience and expertise in addressing these challenges are increasingly relied upon to get new products into the hands of patients as quickly and cost-effectively as possible.

GROWING MARKET FOR ORAL SOLID DOSAGE DRUGS

For many reasons, the preferred route of administration for new drugs is oral delivery, ideally using oral solid dosage (OSD) formulations. In addition to being the most cost-effective dosage form to produce, they have the advantage of extended storage stability, generally without need for refrigeration, and are easy to ship.[1] Brand recognition can also be built directly into tablets and capsules through the use of unique combinations of shape and color.[2] OSDs are also relatively easy for patients to take, with no need for dosage measurements or uncomfortable/painful injections.[1] They can also be formulated in a variety of modified/extended release formats to reduce the number of dosages – all properties that lead to increased medication adherence.[2] In addition, advanced delivery technologies provide enhancement of bioavailability and, in some cases, targeted delivery for improved efficacy and safety.[1]

With these factors as drivers for growth, it is not surprising that the global market for oral solid dosage pharmaceutical formulations is predicted to expand at a compound annual growth rate of 6.5%, rising from $493.2 billion in 2017 to $926.3 billion in 2027.[1] In 2017, North America was the dominant region, accounting for 37% of the consumption of OSD drugs.

The fastest-growing segments of the OSD market include small-scale, high-value dosage forms such as pediatric, geriatric, anti-abuse, controlled-release and taste-masked drugs.[3]

INCREASING COMPLEXITY DRIVING OUTSOURCING

Advances in rapid synthesis technologies are leading to the preparation of new classes of compounds with attractive therapeutic properties – but with challenging physicochemical and pharmacokinetic profiles, particularly with respect to solubility and bioavailability. Approximately 40% of currently marketed drugs and 80% of pipeline candidates meet the Biopharmaceutical Classification System (BCS) definition of poorly soluble (classes II and IV).[4] These issues are creating significant formulating challenges. There is also growing expectation in the pharmaceutical industry for new therapies to be designed with the patient in mind.

Often, advanced, specialized drug delivery technologies are required to overcome poor physicochemical and pharmacokinetic properties and enable the design of patient-centric medicines.[2] Application of many of these technologies requires access to advanced equipment and highly skilled and experienced scientific experts. For most pharmaceutical companies, maintaining these capabilities in-house is not practical or possible.

Many of the molecules under development today are also structurally complex and require advanced synthetic chemistry capabilities, as well as the ability to conduct multistep syntheses involving a broad array of chemical and engineering expertise. Drug substance and formulation complexity are, therefore, driving demand for support from contract service providers. The most successful CDMOs not only have the specialized technologies, expertise and experience needed for these complex projects, but also have achieved high efficiency and productivity levels, thus reducing development and commercialization costs and timelines.

They also offer integrated services from the preformulation stage through to commercial manufacturing, allowing for consideration of special formulation needs earlier in the development process, while eliminating the cost and time associated with tech transfer.[2] Close collaboration between CDMOs and their pharma customers is essential to the success of these complex projects. Flexibility in terms of development and manufacturing capabilities and partnering arrangements is also an asset.[3]

SPECIALIZING IN OSDs

At Tedor Pharma, we have provided the pharmaceutical industry with contract services for 16 years from our Cumberland, Rhode Island facility, which specializes in oral solid dose formulation development and manufacturing. We take projects from the earliest formulation stages through scale-up to commercial manufacturing. We have extensive experience working with the FDA in filing both new drug applications (NDAs), abbreviated new drug applications (ANDAs) and 505(b)(2)s – as demonstrated by the 16 approvals we have received.

Our FDA- and DEA-audited, 40,000-square-foot facility has 14 production-ready GMP suites, 2 formulation suites, and quality assurance and development labs for the production of high-quality OSD formulations with annual capacity to produce 620 million capsules to 2.5 billion tablets. On-site analytical labs provide support for in-process testing and product release. In addition to dry blends, we have a dedicated suite for fluid-bed coating, drying and granulation. We manufacture coated and uncoated single and multilayer tablets and capsules that contain powders, beads or granules. We also have the ability to produce immediate-, modified- and extended-release formulations, as well as controlled substances (Schedules CII–V).

MEETING THE NEEDS OF SMALL AND MIDSIZED PHARMA

Demand for CDMO support of oral solid dosage drug development and manufacturing is coming from all sectors of the pharmaceutical industry – from large pharma and start-ups to virtual companies and generic firms. While Tedor Pharma provides support to customers of all sizes, our focus is on small to midsized organizations.

Tedor Pharma is small enough to care about customers on an individualized basis and yet experienced enough to deliver for all companies, but particularly for

DRUG SUBSTANCE AND FORMULATION COMPLEXITY ARE, THEREFORE, **DRIVING DEMAND FOR SUPPORT FROM CONTRACT SERVICE PROVIDERS.**

smaller firms. These smaller firms might not get the attention they deserve from larger CDMOs serving larger customers.

We are very focused on the customer experience and pay the utmost attention to the needs of each and every customer we serve. With our milestone-based project management system, we provide one point of contact from the start of a project through to its completion. The project assessment phase includes consideration of ways to improve efficiency and productivity and reduce costs. With planning, implementation and launch considerations integrated into the project management system, we are able to focus on the process, quality, speed and cost – all of the factors that drive performance and ensure an outstanding customer experience.

Small and midsized customers also benefit from our extensive formulation development and regulatory expertise. Our formulators apply their extensive product development experience to identify the optimum formulation solution that is also robust and ready for scale-up and manufacturing. They are also experienced at lifecycle management and can, for instance, convert existing formulations to controlled- or modified-release versions to extend patent life. Similarly, our regulatory experience is very deep. We can assist customers with the turnkey filing of NDAs, ANDAs and 505(b)(92)s, ensuring that documentation is correct and complete.

SPECIALIZED IN CONTROLLED SUBSTANCE MANUFACTURING

Another differentiator for Tedor Pharma is our extensive experience with DEA scheduled products. Currently, 90% of our project portfolio comprises schedule II through V drugs as defined by the Controlled Substances Act (CSA) in the U.S. These products include a wide variety of controlled APIs that must be manufactured, stored and distributed following specific protocols to prevent their illegal use. The medical applicability and potential for creating dependency and being abused determine which schedule applies, with schedule II products more dangerous than schedule V drugs.

Manufacturers of these products must first install appropriate facilities, equipment and management systems to ensure control, traceability and accountability, and then obtain a State Board of Pharmacy license, after which they can register with DEA. The agency then conducts annual audits to ensure ongoing compliance.

Tedor Pharma understands the severe consequences that can result from noncompliance. We have an excellent relationship with DEA and are very familiar with the quota process and the steps needed to obtain appropriate quotas for the controlled substances we manufacture for our customers. As our long track record demonstrates, our employees have extensive experience working with scheduled products and efficiently meeting the extensive recordkeeping requirements and protocols that ensure prevention of the diversion of controlled substances.

PROACTIVE INVESTMENT

Part and parcel of our commitment to ensuring an outstanding customer experience is working hard to anticipate our customer's future needs. Rather than making facility investments only when specific customer projects require us to do so, we are proactive. Through our close collaboration with our customers and based on our understanding of the OSD market, we anticipate future customer needs and invest in the new technologies we believe they will require.

Recent examples from 2017 include an investment of $7 million for a dedicated fluid bed suite and the construction of several multipurpose manufacturing bays, all of which are qualified and ready for use. The new fluid bed suite was added because many manufacturing processes for the complex OSD formulations being developed require fluid-bed manufacturing processes. With this new capability, we are even better positioned to help our customers create optimum formulations.

Multipurpose manufacturing bays allow us to provide more flexibility for our customers. The complex projects brought to Tedor often require special handling and/or the use of multiple technologies to implement optimized processes that provide robust, high-quality differentiated formulations. With numerous multipurpose bays, we are able to meet the wide variety of needs of existing and future customers. To keep pace with these needs, we are currently exploring other opportunities for investment and will likely have additional capabilities later in 2018. P

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SCIENTIFIC EXPERTISE FACILITATES ORAL PEPTIDE PRODUCT DEVELOPMENT AND MANUFACTURING

> BY **ARIANA NAGEL** AND **MATTHEW FERRELL**, UPM PHARMACEUTICALS

Most often developed as injectable formulations, a few "oral peptide" drugs have been approved in recent years. Advances in delivery technologies have contributed to growing interest, and many more are in development. Access to a contract development and manufacturing organization with established success in the development and manufacturing of oral peptide drugs can reduce the time it takes for these complex therapeutics to enter the clinic and reach the market.

BENEFITS OF PEPTIDE THERAPIES

Comprising chains of 40–50 amino acids or fewer, peptides are neither small-molecule nor biologic drug substances, but fall in between. Examples of commercial peptide drugs include Byetta, Victoza and Trulicity – glucagon-like peptide-1 (GLP-1) receptor activators for the treatment of diabetes. Other indications being targeted by peptides include oncology, inflammation and infectious diseases. There are more than 100 peptides on the market and many more in development.[1]

Because peptides are widely present in the body and play specific functional roles, peptide drugs outperform small-molecule drugs with greater potency and specificity, leading to decreased side effects and greater efficacy.[1] They are well tolerated by the body and exhibit reduced systemic toxicity. Peptides also offer manufacturers the advantage of being less complex to produce than most other biologic drug substances.

The one less-attractive quality of peptide drugs is their delivery method, which for the vast majority of products on the market is by injection. Peptide drugs often require frequent injections. They can also suffer from inconsistent drug concentrations. There is consequently significant interest in developing other routes of administration for peptides, including oral, nasal, buccal, pulmonary, transdermal, rectal and ocular.[2]

WHY ORAL PEPTIDE DELIVERY IS CHALLENGING

Peptide drugs have been developed as injectable products because it is very challenging to achieve high bioavailability by oral administration. The upper gastrointestinal tract (GIT) is designed to digest peptides and proteins. Protective (enteric) coatings on tablets or capsules can enable passage of peptide drugs through the low pH conditions in the stomach, but resisting degradation by proteases (pancreatic and brush-border enzymes) and achieving permeability of these high-molecular-weight biomolecules through the intestinal epithelial layer are significant challenges.[3] Inter- and intrapatient variability is another important factor.[3]

A common approach to overcoming these challenges is to use excipients, including enzyme inhibitors and permeation enhancers to prevent degradation and enhance permeability, respectively. By co-releasing these excipients with the peptide near the gut wall, a high concentration gradient can be created at the site of absorption.[3]

Other technologies that are being explored include mucoadhesive polymeric systems and carrier systems such as emulsions, nanoparticles, microspheres and liposomes.[2] The derivatization of peptides using polyethylene glycol (PEG) to prevent degradation and improve solubility is another strategy.[2] More novel tactics include the following: the use of endogeneous cell carrier systems such as vitamin B12, modified toxins and viral hemagglutinin; the use of cell-penetrating peptides hybridized with target molecules; and the preparation of peptides as prodrugs.[2]

CURRENT STATE OF ORAL PEPTIDE DRUG MARKET

The global oral protein and peptide market is predicted by Allied Market Research to grow from $643 million in 2016 to $8.233 billion in 2028, expanding at a compound annual growth rate of 11.7% from 2022 to 2028.[4] As early as 2015, companies were investigating the oral delivery of insulin, calcitonin, cyclosporine, leucine encephalin, HIV protease and other peptides.[2]

In February 2017, Protagonist Therapeutics presented preclinical data on two oral peptide drug candidates for the treatment of moderate-to-severe active ulcerative colitis and for moderate-to-severe Crohn's disease.[5] In May that same year, Synergy Pharmaceuticals received FDA approval for its oral peptide Trulance™ (plecanatide), a uroguanylin derivative for the treatment of chronic idiopathic constipation (CIC). The drug is also being evaluated for the treatment of chronic irritable bowel syndrome.[6]

In December 2017, Entrega announced a research collaboration with Eli Lilly and Company to advance its peptide delivery technology, which uses a proprietary, customizable hydrogel dosage form to control local fluid microenvironments in the GIT for enhanced absorption and reduced drug exposure variability.[7] Enteris Biopharma is using its Peptelligence® oral drug-delivery platform in the development of orally delivered therapeutics that have been previously marketed as injectable-only formulations, with candidates in preclinical to phase II development stages.[8]

Advances in academia are also being achieved. Researchers at the University of Pennsylvania are manufacturing peptides in plant cells, where their structures are maintained and can be passed through the intestinal epithelium.[9] At Kumamoto University, scientists have identified cyclic peptides that facilitate the absorption of large biomolecules in human small intestine absorption models and mouse small intestines. These peptides could potentially enable the oral administration of other peptides and proteins.[10] Researchers at the Technical University of Munich have created a masked hexapeptide that exhibits the same biological effects when delivered orally as its unmasked version when injected.[11]

ROLE OF THE CDMO

Because the formulation development of oral peptide drugs is so challenging, most pharmaceutical companies rely on contract development and manufacturing organizations (CDMOs) with specialized expertise in this field.

A comprehensive understanding of the properties of each peptide is necessary to select the most effective drug-delivery system and develop an optimal drug formulation. As a result, extensive knowledge and experience are needed at the proof-of-concept stage. CDMOs that can take a project beyond this point through to commercialization offer further benefits, including elimination of the risk, time and cost associated with technology transfer and simplification of the supply chain. Effective CDMOs also offer comprehensive analytical and cGMP scale-up and commercial manufacturing services and are committed to meeting client objectives with the highest quality while maintaining the most efficient use of time and controlling costs.

DEMONSTRATED SUCCESS

UPM Pharmaceuticals was founded as a drug formulation services company focused on oral drug delivery. Today we support clients in formulation development through final product manufacture (tablets, capsules and beads in capsules) via various processes (see Table 1). Twenty scientists work in the product development area. Our technical services group supports our manufacturing teams for dosage form production and packaging. We also have methods development and quality control/quality assurance teams.

With respect to oral peptides, UPM was involved in the formulation development of two of the very few FDA-approved products. We invested in large-scale manufacturing capacity specifically for the commercial production of the second product we developed. Currently three additional oral peptide drugs are at the Investigational New Drug (IND) stage. Products include both immediate- and delayed-release formulations.

TABLE 1

UPM Process Capabilities Useful for **Oral Peptide Drug Production**

- Dry blend, low/high energy
- Fluid bed coating
- Encapsulation, hard shell
- Compression
- Pan coating
- Roller compaction
- Milling

Our knowledge of many different excipients has enabled the development of effective oral peptide formulations. Specialty excipients (see Table 2) can address stability and solubility issues and provide the desired controlled-release rate. For water- and moisture-sensitive peptides, they can be used to achieve both internal and external desiccation. Antioxidants prevent degradation due to exposure to oxygen.

Identifying the appropriate excipients for a given oral peptide formulation requires the performance of extensive compatibility studies to ensure that none impact the stability of the API. Because many peptides are high-potency compounds requiring low microgram dosages, issues of content uniformity must also be addressed. In addition, some peptides require solubilization to achieve drug distribution as a molecule rather than a particle, which can create additional challenges with respect to stability.

TABLE 2

Selected Specialty Excipients Used in **Oral Peptide Drug Formulation**

- Divalent ions
- Lipids
- Water-soluble polymers
- Proteins
- Enteric polymers
- Absorption enhancers
- Solubilizers
- Polymeric inert sugars
- Dessicants, internal and external
- Antioxidants

While for most processing steps conventional equipment can be used, because many peptides are water- and moisture-sensitive, it is necessary to provide a controlled environment during manufacturing. UPM has low-humidity suites designed for this purpose. In some cases, dehumidification is achieved locally; in others, a low-humidity environment is provided in the entire suite.

We also have low-humidity solutions in our packaging area and use heavy (thick)-wall bottles to protect final products from the external environment during storage. Nitrogen purging, external desiccants selected after extensive performance studies and antioxidants are also used for this purpose.

Analysis of peptides requires special expertise as well. UPM has knowledge of the latest chromatography column technology available for peptides and has worked closely with the ultra-performance liquid chromatography (UPLC) instrument manufacturer to ensure that our instruments and columns are appropriate. We have, for instance, replaced the stainless-steel tubing on instruments for peptide analysis with polyetheretherketone (PEEK) tubing to avoid potential interactions. We have developed proprietary methods using a quality-by-design (QbD) approach to ensure that the most appropriate, robust techniques and methods are developed for each specific peptide and that they are readily transferrable to commercial operations. UPM also has an established network of partners that can provide any analytical capabilities not available in-house.

TACKLING FORMULATION CHALLENGES

UPM's demonstrated success in oral peptide drug development and manufacturing provides security to our pharmaceutical partners in the peptide market. UPM currently manufactures 72 commercial SKUs with 47 R&D projects in development. With two commercially approved oral peptide products on the market that we developed and three additional oral peptide products currently in development at UPM, we have gained considerable experience and technical expertise. We now have a platform of technologies available for application to additional oral peptide drugs from development through commercialization.

We also recognize at UPM that the drug development process is unpredictable. Each peptide is unique and presents its own set of development challenges. We have therefore built in flexibility to overcome the hurdles presented by oral peptide drugs and to respond rapidly to the unexpected.

UPM's scientists are eager to apply their existing knowledge for the rapid development of highly effective, customized, innovative solutions for new oral peptide products. In fact, we enjoy the formulation and analytical development challenges presented by oral peptide drug delivery and are energized by the science behind these complex and promising therapies. P

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ACHIEVING CONTROLLED NUCLEATION DURING ASEPTIC LYOPHILIZATION

> BY **ROBERT DARRINGTON**, SP INDUSTRIES, INC.

SP INDUSTRIES HAS DEVELOPED A SOLUTION BASED ON THE OVER-PRESSURE METHOD THAT IS SUITABLE FOR LAB TO COMMERCIAL-SCALE PRODUCTION UNDER GMP CONDITIONS.

Controlled nucleation is essential for obtaining high-quality lyophilized products with intra- and inter-batch consistency. Two approaches to achieving controlled nucleation have been investigated recently: creating a pressure differential and using an ice fog to insert seed crystals into the vials within the lyophilization chamber. SP Industries has developed a solution based on the over-pressure method that is suitable for lab to commercial-scale production under GMP conditions.

IMPORTANCE OF CONTROLLED NUCLEATION

Freeze drying, or lyophilization, is often required to produce stable formulations for sensitive biologic drug formulations. The aseptic conditions required for lyophilization of parenteral products may create challenges for drug manufacturers because the high purity of the containers and the product solution leads to issues with ice nucleation, a critical step for the freezing to occur.

Where nucleation is uncontrolled, the longest theoretical freezing time must be used to ensure that the solution in every vial freezes. Longer freezing times equate to lower throughput of the expensive lyophilizer, and heterogeneity between the vials in a single batch also remains an issue. Supercooling of the vials during the freezing stage causes very small crystals to form and so can lead to vial breakage and "blow-out," because process water vapor cannot escape from the tightly packed small crystals. The result is the loss of expensive product and the need for additional cleaning. Controlled nucleation methods provide the operator with the ability to determine the point in time and the refrigeration temperature at which nucleation will occur for all of the vials in the lyophilization chamber.

METHODS FOR ACHIEVING CONTROLLED NUCLEATION

Two mechanisms have been investigated for controlled nucleation: creation of a pressure drop within the chamber and introduction of seed crystals to each vial. A pressure drop can involve over-pressurization, in which a sterile gas is pumped into the chamber to a specified pressure and then suddenly released, or by rapidly pulling a vacuum on the chamber. In both cases, the lyophilization system must be constructed to withstand these high/low pressures.

To induce an inflow of ice crystals within a lyophilization chamber at production scale, water-for-injection (WFI) is typically frozen in sterile liquid nitrogen in a separate tank to create a very fine "snow" powder. The freeze dryer is then evacuated to create a pressure differential sufficient to pull the ice fog into the chamber. At lab scale, the ice crystals may be formed on the condenser and then introduced to the chamber. In both methods, baffles must be inserted into the drying chamber to direct the flow of the ice fog.

ADVANTAGES AND DISADVANTAGES

The pressure-drop method has some advantages over the ice-fog technique. First, it provides consistent conditions within each vial. With the ice-fog method, an ice crystal must be inserted into each vial individually. In addition, latent heat in the steel structures within the drying chamber may induce early melting of the ice crystals before they can enter all of the vials.

Second, there is no need to install baffles into the lyophilization chamber with the pressure-drop method. This advantage is significant. The lyophilizer must be shut down while the work is being completed and then requalified and validated before use. Third, there is no insertion of material into the final drug product solution with the pressure-drop technique. In the ice-fog method, ice crystals are being added to the production solution after sterile filtration. There is a general presumption by the FDA that, after sterile filtration and filling of a product into a vial, nothing else will be inserted or added. The use of the ice-fog method may thus present additional regulatory hurdles.

With respect to the two pressure-drop methods, production-scale lyophilizers are designed to withstand sterilization with pressurized steam and, therefore, also the pressures needed for controlled nucleation. Investment would, however, be needed to obtain lab-scale lyophilizers with this capability. There are also differences between the two pressure-drop techniques. Over-pressurization followed by release leads to vials that are at atmospheric pressure. With evacuation from atmosphere, the vials end up at low pressure, and evaporation/sublimation in some vials may occur, leading to heterogeneity.

A PRACTICAL PRESSURE-DROP SOLUTION

SP Industries has developed ControLyo®, a controlled nucleation system based on the over-pressure method. A sterile inert gas is used to pressurize the chamber to 28-30 psi and then released. Once the pressure is back to the atmosphere, the freezing cycle is completed.

When ControLyo® is used for aseptic lyophilization, freezing times are shorter and cake uniformity and appearance are improved because uniform freezing occurs in each vial. The uniform formation of larger ice crystals allows for shorter drying times due to the larger pathways for release of water vapor. There is also reduced likelihood of vial blowout. Breakage rates are typically lower, even for formulations containing mannitol. In addition, dissolution times before administration are also reduced.

LINE OF SIGHT

In addition to ControLyo®, SP Industries offers a suite of scalable lyophilization technologies that provide line of sight from formulation development to cycle development and all the way through clinical trials and into production. This includes our software solutions; the same suite of tools can be used throughout all phases of drug development and manufacturing, making for truly seamless technology transfer.

SP INDUSTRIES HAS DEVELOPED CONTROLYO®, A CONTROLLED NUCLEATION SYSTEM BASED ON THE OVERPRESSURE METHOD.

LyoFlux® (a registred trademark of Physical Sciences Inc, Andover, MA) tunable diode laser assisted spectroscopy (TDLAS) enables real-time monitoring of lyophilization processes, including batch average temperature, cake resistance and the heat environment of the vials (Kv) to characterize the performance of the freeze dryer. The ability to obtain more homogeneous batches using ControLyo® makes it possible to use the data generated from this non-invasive technique. The information can be used to more easily scale processes up or down and identify sources of problems, should they occur.

Customers of SP Industries are using ControLyo® to take products into clinical trials that would not have been possible without access to this controlled nucleation technology. As biologics become increasingly complex and more challenging to lyophilize, controlled nucleation will become an essential technology. The capabilities of ControLyo® have already been clearly demonstrated, and we are excited to help even more customers overcome future challenges. P

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BIOPHARMA CDMO SUCCESS REQUIRES TECHNICAL LEADERSHIP AND PROBLEM-SOLVING CAPABILITIES

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

Biologics command a growing position in the biopharmaceutical market. As more antibody and other advanced therapies reach the commercialization stage, branded biologic and biosimilar development companies are increasingly turning to outsourcing partners that provide holistic solutions. CDMOs today must offer more than manufacturing support; they must be solution providers that can support clients from concept to market. Rentschler Biopharma has a long track record of innovation designed to support rapid development and commercialization.

EXPANDING MARKET

Since their introduction, biologic drugs have shown great potential to treat diseases not possible to remedy with traditional small-molecule drugs. As successes are achieved and our understanding of the physiology of diseases deepens, biologics are attracting even more attention. The advent of biosimilars and the expansion of the middle class in many emerging markets are further fueling the growth of the biopharmaceutical sector.

According to Transparency Market Research, the global biologics market will be valued at $479.7 billion by 2024 and is expanding at a compound annual growth rate (CAGR) of 10.9%.[1] Variant Market Research pegs the market as growing at a CAGR of 10.3% from 2016 to 2024, reaching a value of $394 billion by the end of the period.[2]

The Business Research Company estimates there are currently more than 1,000 biologic drugs in development and predicts that the U.S. FDA's focus on reducing time to market will lead to an increase in year-on-year growth of the biologic market from a recent 5.4% to 9.6%.[3]

PERIOD OF EVOLUTION

The first biologic drugs were hormones and simple proteins. Today, more complex monoclonal antibodies (mAbs) and recombinant proteins dominate. The market is dynamic, however. It is expanding in value and volume and broadening with respect to the types of disease mechanisms and disease classes being tackled.

Currently, treatments for autoimmune disorders, diabetes and cancer account for nine of the top ten marketed drugs; over 50% of generated revenue and 70% of market growth since 2010.[4] New therapies are, however, being developed to treat a host of other indications. More than 50% of biologics in development target diseases for which no or only a few biologics have previously been brought to market.[4]

According to QuintilesIMS, 25% of biologic pipeline candidates target diseases for which there are large patient populations that have mostly seen only small molecule therapies which can be improved upon and are now highly genericized.[4] The firm notes that "biologic agents entering these indications will be transformative not only because of their disease modifying efficacy in clinical trials, but also because of the rapid change in disease market size and growth that would follow a successful launch."

GREATER NEED FOR CDMOS

The evolution of the biologics market has resulted in increased complexity of development and manufacturing. Biologic drug substances are highly complex and more challenging to produce. Advances in automation and process analytics are leading to the generation of massive quantities of data that must be processed. Regulatory requirements are increasing while development timelines are decreasing, making project management more challenging.

Many branded biologic and biosimilar companies are, as a result, more frequently relying on contract development and manufacturing organizations (CDMOs) that have the capabilities, expertise and experience needed to rapidly move projects from concept to market.

From 2014 through 2017, the global biopharmaceutical contract manufacturing market grew at a much higher CAGR of 13% than was predicted (typically 8-10%) and included growth in both clinical and commercial manufacturing, according to HighTech Business Decisions.[5] Going forward, Future Market Insights estimates that the global biopharmaceutical contract manufacturing market will expand at a CAGR of 10.6% from a value of $5.625 billion at the end of 2017 to $15.468 billion by the end of 2027.[6]

BUILT BY TAKING BOLD STEPS

Founded in 1927 as a privately held pharmaceutical company, Rentschler Biopharma entered the biologics space in 1974 and is thus one of the pioneers in the development of biologics in the world. The company began working with recombinant cell lines in 1979 and was the first to receive market approval for a natural Interferon-β (Fiblaferon) in 1983. Approval of a recombinant Interferon-γ (Polyferon) followed in 1989.

Rentschler Biopharma became a 100% CDMO in 1997 and expanded its manufacturing capacity from 2008-2012, adding a 3000L stainless steel and two 1000L single-use (SU) bioreactors. Our proprietary TurboCell™ technology platform was first employed in 2014, and the first manufacturing runs in a 2000L SU bioreactor were

OUR **TURBOCELL™ CHO-K1 CELL-LINE** TECHNOLOGY ALLOWS IDENTIFICATION OF PREDICTABLE, ROBUST AND SCALABLE CHO CELL LINES.

completed in 2015. Another expansion in 2016 added two 3000L twin bioreactors and a second 2000L SU bioreactor. In 2017, the company established a strategic alliance with Leukocare AG in Munich, Germany in formulation development and a strategic partnership with Rentschler Fill Solutions GmbH in Rankweil, Austria.

When Rentschler Biopharma introduced its first 1000L SU bioreactors, we were the first CDMO to introduce disposable technology at this scale – and won a "Facility of the Year" award in 2012 for our modular and flexible single-use solution. We are a pioneer in single-use bioprocessing and have performed more than 120 batches in fed-batch or continuous mode. Rentschler Biopharma was also an early adopter of downstream disposable technologies, installing SU chromatography, tangential flow and viral filtration systems in 2010 and a second SU chromatography system in 2015.

ESTABLISHING STRATEGIC ALLIANCES AND PARTNERSHIPS

Rentschler Biopharma has responded to the growing needs of its clients with the establishment of strategic partnerships designed to expand its portfolio of services and capabilities.

Through our strategic alliance with Leukocare, we are able to offer advanced formulation development capabilities, with formulation issues considered at every step of the development and manufacturing process. Leukocare's proprietary SPS® formulation technology (SPS® = Stabilizing and Protecting Solutions) enables the development of cost-efficient dry and liquid protein formulations with significant improved stability at room temperature, even at high concentrations.

The strategic partnership with Rentschler Fill Solutions provides reliable full-service solutions and new state-of-the-art aseptic filling capabilities from a

TREATMENTS FOR AUTOIMMUNE DISORDERS, DIABETES AND CANCER ACCOUNT FOR **NINE OF THE TOP TEN MARKETED DRUGS; OVER 50% OF GENERATED REVENUE AND 70% OF MARKET GROWTH SINCE 2010.**

single source. The partnership unites two centers of excellence for the fast and efficient manufacturing of biopharmaceuticals with the Rentschler commitment to quality and enables optimally aligned processes to meet the client's time-to-market expectations.

MORE THAN MANUFACTURING

These investments in state-of-the art equipment, innovation and partnerships have made Rentschler Biopharma one of the global leaders focused on mammalian cell culture. We remain a medium-sized, family-owned company with a 100% focus on our clients' projects, which we support from gene to vial. Because we are fully dedicated to our customers and their projects, our clients have a clear advantage – their projects do not compete with any internal development efforts.

Our clients also benefit from our extensive experience in the manufacturing of a wide range of biomolecules, from monoclonal and bispecific antibodies to fusion proteins, enzymes, blood factors, cytokines and growth factors. Since 2000, Rentschler Biopharma has worked on more than 250 molecules and has produced more than 350 batches. Our TurboCell™ CHO-K1 cell line technology allows identification of predictable, robust and scalable CHO cell lines. With this platform – or a customized approach – we can provide cGMP-compliant manufacturing of master and working cell banks. With our platform technology we can produce material for screening studies within seven weeks and and up to 200g for tox studies within ten weeks, reducing development costs and timelines.

Overall, Rentschler Biopharma is a solution provider. We listen to our clients to understand their project objectives and specific challenges and find solutions where others don't even look. We can help customers solve problems with their biologic upstream and downstream processes, formulation and analytical development and optimization efforts. We help customers take their ideas from genetic engineering all the way through fill-finish, with cGMP production of both clinical and commercial quantities. Projects are supported by the elaboration of optimal global regulatory approval strategies from clinical studies to market approval, including compilation of all required documentation (IMPD/IND CMC-Parts, Module 3 of BLA/NDA/MAA).

RELIABLE GLOBAL PARTNER

With long-term expertise in development and manufacturing, Rentschler Biopharma has established itself as a reliable global partner and one of the world's leading biopharmaceutical CDMOs. We have worked with 130 clients worldwide since 1997, including 15 of the top 20 pharmaceutical companies, as well as emerging and medium-sized biotechnology firms. Half of those clients work with us on multiple projects, and 40% have relied on us for more than five years.

IDENTIFYING FUTURE SOLUTIONS

With the biopharmaceutical industry undergoing a significant transformation, it is essential that CDMOs serving the industry evolve to meet the changing needs of their customers. Rentschler Biopharma has always been a technology leader, and the implementation of our Strategy 2025 initiative will ensure that we continue to be a partner of choice for our customers.

Over the past two years, we have evaluated the key trends in the biopharmaceutical industry, talking with people across the sector and generating a vast data pool for in-depth analysis. The generated information gives Rentschler Biopharma a solid platform to determine the path the company should follow going forward.

We are considering important questions such as, "What will the treatment of rare and severe diseases look like in 10-20 years? Will mAbs continue to be the major therapies of choice? Or will the majority of treatments consist of cell and gene therapies?

The strategy will address all aspects of our development and manufacturing activities, from the platform technologies we need and determing how our people will work in the future to what our clients will expect from a company like Rentschler Biopharma. It is all about innovation and ensuring that Rentschler Biopharma remains a technology leader. P

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PROVIDING FLEXIBLE CAPABILITIES TO MEET MARKET DEMAND FOR STERILE FILL-FINISH SERVICES

> BY **ANDREA BAIOCCHI,** AVARA PHARMACEUTICAL SERVICES

Demand for aseptic fill-finish contract manufacturing services is increasing as APIs become more complex and more biologic drugs reach the market. Biopharmaceutical companies are relying on contract development and manufacturing organizations (CDMOs) with the highly specialized equipment and capabilities required to ensure the production of high-quality, safe sterile drug products. Avara Pharmaceutical Services, with the acquisition of Pfizer's Liscate, Italy facility, has added flexible, sterile fill-finish capabilities to its extensive portfolio of API and drug product development and manufacturing services.

GROWING DEMAND FOR STERILE FILL-FINISH

The fill-finish step in the manufacturing of drugs is a crucial one because it is the last step completed before a product is packaged and delivered to the patient. It requires specialized capacities and equipment and receives intense scrutiny from a regulatory perspective. Aseptic fill-finish processes are even more complicated.

There is a growing need for these capabilities as the increasing complexity of small-molecule APIs drives an increase in parenteral delivery and the percentage of biologic drugs (both branded and biosimilars), the vast majority of which are formulated as parenterals, continues to rise. Because with parenteral delivery the active agent enters the bloodstream directly, this method is advantageous for the delivery of medicines used to treat nausea and unconsciousness and during clinical emergency conditions. It is also beneficial for the delivery of small-molecule APIs with poor bioavailability and drugs with narrow therapeutic indications.[1]

The global fill-finish manufacturing market is predicted by Markets and Markets to expand at a CAGR of 8.6% from $2.96 billion in 2017 to $4.47 billion in 2022.[2] Europe is expected to account for the largest share of the market, with many major players enhancing their presence in the region, while Asia Pacific will experience the most rapid growth. Stricter regulatory oversight of aseptic fill-finish operations has also led some contract manufacturers to exit the market. Lyophilization (freeze-drying) capacity has also been tightening, in part due to quality and regulatory issues at various manufacturing sites around the world, with demand for aseptic fill-finish manufacturing exceeding available capacity in some cases.[3]

THE CHALLENGES OF ASEPTIC FILLING

Aseptic fill-finish operations carry more risk than non-sterile processes. Filling must be accomplished in a sterile environment (cleanroom, isolator, RABS), and greater levels of testing are required. All components used in the aseptic fill-finish process must be sterilized/sanitized before use. Sterilization with pressurized steam, irradiation or hydrogen peroxide must also be performed in a manner that does not impact the quality and stability of the drug product.[4] For those products that require lyophilization, steps must be taken to ensure that risk of contamination is minimized during the loading and unloading processes. Visual inspection of packaged products is also required.

CDMOs PROVIDE SPECIALIZED EXPERTISE

Due to the challenges associated with aseptic fill-finish operations today, many biopharmaceutical companies are relying on contract development and manufacturing organizations (CDMOs) to manage this important step in the manufacture of their drug products. In fact, the contract manufacturing segment of the fill-finish manufacturing market is growing faster than the pharma in-house segment.[1]

Many drugs today are being developed by small, virtual pharma companies that do not have any in-house production capabilities and thus rely completely on outsourcing partners. Larger companies that do have in-house fill-finish capabilities still outsource projects to CDMOs due to capacity constraints or for when specialized capabilities are required, such as for highly potent compounds. Some use CDMOs to establish a backup source, particularly for drug products that are medically necessary. Others may conduct fill-finish operations at early development stages then switch to an outsourcing partner for later stage development and commercial operations.[5] In fact, choosing the right aseptic-fill-finish partner can add value to a project.[3]

FLEXIBLE CAPABILITIES

One constant in the pharmaceutical industry is innovation, which leads to constant evolution of manufacturing needs. The shift away from blockbusters to specialized therapies targeting small patient populations is leading to demand for more flexible and efficient fill-finish operations.[6] For instance, the use of restricted access barrier system (RABS) rather than isolators can facilitate multi-product fill-finish operations.[3] In addition, because delivery systems are integral to patient-centric drug products, the choice of packaging systems used in fill-finish operations is often considered much earlier in the development process.[6]

Avara has eight sites: three in the United States, including corporate headquarters; one in Puerto Rico; one in the UK; one in Ireland, one in Italy; and one in France. The site in Liscate, Italy was acquired from Pfizer in early 2018 to expand our services through the addition of sterile processing capabilities, including liquid and lyophilized fill-finish of sterile injectable products. The facility has development labs and small-scale equipment, along with the capability to manufacture at commercial scale, including for products that require high-containment. The highly experienced staff at Liscate have a proven 15-year track record in contract manufacturing.

AVARA HAS AN ESTABLISHED TRACK RECORD OF HIGH-QUALITY, RELIABLE, COST-EFFECTIVE PERFORMANCE **PROVIDED BY HIGHLY EXPERIENCED EMPLOYEES.**

Specific capabilities include aseptic filling of ampoules and liquid vials, lyophilization, terminal sterilization of ampoules and aseptic spray drying. Aseptic powder filling in RABS will be offered pending validation of recently installed equipment. Packaging services include single vials, vials in trays/cartons and kits, which can be completed manually or using automation, including high-volume automated packaging and labeling.

A FULLY INTEGRATED CDMO PORTFOLIO

Avara Pharmaceutical Services, founded in 2015, has been designed and constructed from the start to provide flexible development and manufacturing support for API formulation and manufacturing and the manufacturing and packaging of small molecule drugs, including highly potent compounds. We have secondary manufacturing technologies including granulation, coating, blending, encapsulation, compression and drying of tablets and capsules, as well as sterile processing of liquids and lyophilized fill-finish of sterile injectable products, including high-containment capabilities.

AVARA PHARMACEUTICAL SERVICES WAS CREATED TO HELP **REVOLUTIONIZE THE CDMO EXPERIENCE IN PREPARATION FOR THE CHANGES THAT MUST COME.**

Through the targeted acquisition of world-class manufacturing facilities from branded pharmaceutical companies, Avara is building a pharmaceutical services company with complementary offerings in key regions. Each site has significant professional experience, state-of-the-art capability and a long history of delivering high-quality pharmaceuticals that meet or exceed customer expectations and regulatory requirements in every major market around the world.

BACKED BY AN INTEGRATED NETWORK WITH RECOGNIZED PERFORMANCE

Avara has an established track record of high-quality, reliable, cost-effective performance provided by highly experienced employees. We are recognized as a full-service CDMO with integrated capabilities designed to meet customers' needs with respect to all aspects of drug development and manufacturing, including APIs and formulations. By offering end-to-end services and forming partnerships with our customers, we help them reduce risk and simplify their supplier bases while ensuring quality and regulatory compliance within their supply networks.

Although Avara was built through acquisition, we have established a tightly integrated CDMO by bringing the operations and people at each site into every aspect of the corporate culture under a single brand that is based on common values and standards. Operational Excellence; Safety, Health & Environment (SHE); and Manufacturing practices are established across the sites and deployed uniformly. Each site, however, retains the necessary autonomy to maintain total customer focus depending on the product and supply chain, with experienced managers empowered to align their site capabilities to meet the specific needs of their customers. The role of each and every Avara site is to reliably deliver product to the highest quality standards on-time and in-full while reducing costs and avoiding supply chain issues.

Our total commitment to our customers and the delivery on our promises for scope, schedule, quality/regulatory compliance and price were recognized recently with the announcement by Life Science Leader that Avara Pharmaceutical Services will receive awards in the six core categories (Capabilities, Compatibility, Expertise, Quality, Reliability and Service) of the 2018 Contract Manufacturing Organization (CMO) Leadership Awards. This industry recognition can be credited to the members of the Avara global team, who are key to our success.

REVOLUTIONIZING THE CDMO EXPERIENCE

The pharmaceutical industry is at a critical juncture. Change is essential or we will lose the ability to develop and manufacture new medicines.[7] Avara Pharmaceutical Services was created to help revolutionize the CDMO experience in preparation for the changes that must come. We are already simplifying the supply chain by offering end-to-end integrated services through a global network of state-of-the-art facilities. We are also focused on improving customers' cost structures by finding new ways to drive efficiencies, providing security of supply, enhancing regulatory compliance and building long-term confidence by delivering on our commitments.

We are, in fact, committed to creating value across the entire supply chain. We focus on and care about our people, who are our greatest asset. They all recognize the need for an operational approach that maximizes efficiency, productivity and quality. We are also committed to forming long-term strategic partnerships with our customers, providing security of supply and meeting regulatory compliance requirements – all at a fair price.

Overall, at Avara we want to help our customers succeed by accelerating the delivery of drugs to the marketplace while facilitating the changes that must happen in the industry. We will continue to expand our portfolio with a focus on key regions around the world, including emerging markets, and services that can add or be complementary to our existing offerings. Emphasis will continue to be placed on the maximization of productivity and the minimization of unexpected issues, with total focus on serving our customers. P

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DOPING

Famous Cases, Substances and Values in Sports

BY **MARC TECHNOW**, NICE INSIGHT

Doping remains a constant threat to the ethics and values in professional sports, as well as on the amateur level. Substances like anabolic steroids, erythropoietin (EPO) and human growth hormone (HGH) are only a few of the many substances used to tamper with the human body to illegally increase strength, stamina and overall performance.

WHAT IS DOPING? INFLUENCE ON AMATEUR AND PROFESSIONAL SPORTS

Per the United Nations Educational, Scientific and Cultural Organization (UNESCO), "Doping refers to an athlete's use of prohibited drugs or methods to improve training and sporting results."[1] Performance enhancement starts as early as high school, with students turning to performance enhancing drugs (PEDs) to increase their chances of earning scholarships to colleges and universities. A study conducted by the Partnership for Drug-Free Kids in 2013 showed that 11% of teens in grades 9–12 reported having used synthetic human growth hormone (2012: 5%), while 7% used steroids to enhance their performance.[2]

While illegal performance enhancements in sports can be dated back all the way to ancient Greece,[3] doping, as we know it today, has exponentially evolved over the last 30 years. With the development and advancement of medicine, it is more present in athletics than ever before. Ben Johnson, Lance Armstrong and Alex Rodriguez are only a few of the big-name professionals whose reputations have been tainted by the illegal use of PEDs in recent years.

DIFFERENT TYPES OF DOPING

« Anabolic Steroids While there are many different methods and drugs used in doping, anabolic steroids are the first that come to mind when talking about performance enhancement. Anabolic steroids are the synthetic version of the primary male hormone testosterone. The androgenic part of testosterone is responsible for typical male characteristics, such as the development of male genitals, growth of body and facial hair and the deepening of the voice.

The anabolic part, however, increases bone and muscle mass, helps athletes recover faster and reduces muscle damage by activating the androgen receptors mediated signaling, which stimulates both protein synthesis and erythropoietin production.[4] While all steroids have androgenic and anabolic effects, anabolic steroids used for performance enhancement have been altered significantly, thus minimizing the androgenic effects of the drug. They can be applied to the skin as a cream or patch, taken orally as a pill or injected directly into muscle.

One of the most prominent cases of anabolic steroid doping involved Canadian sprinter Ben Johnson at the Summer Olympics of 1988 in Seoul, South Korea. Johnson broke the world record, running a stunning 100 meters in 9.79 seconds.[5] Everyone was in awe as the Canadian seemed to fly away from the competition — only to find out 48 hours later that Johnson had tested positive for Stanozolol (also known as Winstrol), an orally active synthetic anabolic steroid.

Formed by the condensation of the 3-keto-aldehyde moiety of oxymetholone with hydrazine and androgenic activity, the drug stimulates fat loss, helping to maintain lean body mass.[6] The discovery of Johnson's steroid use sent shock waves through the sporting world. Even though the Canadian wasn't the first, or even the only, sprinter in the race to use PEDs, the excitement surrounding his win and world-record time made this one of the most infamous doping cases of all time.

« Blood Doping After denying the allegations for several years, seven-time Tour de France champion and Olympic bronze medal–winner Lance Armstrong admitted to using several PEDs over the course of his career in a 2013 interview with Oprah Winfrey.[7] One of the main methods used by the American cyclist was blood doping, defined by the World Anti-Doping Agency (WADA) as "the misuse of certain techniques and/or substances to increase one's red blood cell mass."[8]

A study conducted by the Partnership for Drug-Free Kids in 2013 **showed that 11% of teens in grades 9–12 reported having used synthetic human growth hormone** (2012: 5%), while 7% used steroids to enhance their performance.

The three widely known substances or methods used for blood doping are erythropoietin (EPO), synthetic oxygen carriers and blood transfusions.[8] Per the Mayo Clinic, EPO is a "large (193 amino acid residue) glycoprotein hormone secreted by the kidney which regulates the body's red blood cell production."[9]

Synthetic oxygen carriers are purified proteins or chemicals, separated into hemoglobin and perfluorocarbon-based carriers. Hemoglobin is a tetrameric protein responsible for the transport of oxygen from the lungs to other tissue, while perfluorocarbons are chemically synthesized compounds with fluorine atom backbones.[10]

While tests detecting EPO and synthetic oxygen carriers have been implemented successfully over the last decade, autologous blood doping (the transfusion of one's own blood which has been stored until needed) remains to this day undetectable. All three methods have the same effect: by increasing the number of red blood cells in the human body, the amount of oxygen which the blood can carry to the body's muscles increases, resulting in the improvement of stamina and overall performance.

« HGH Although performance enhancement in baseball has been an open secret for many years, serious testing did not start until the publication of the *Mitchell Report*, an independent investigation done on behalf of Major League Baseball by Chief Investigator George Mitchell in late 2007. This report stated that many players, including superstars Barry Bonds, Mark McGwire and Alex Rodriguez, have used PEDs such as anabolic steroids and/or human growth hormone (HGH).[11]

As stated by the World Anti-Doping Agency, HGH "is a hormone that is naturally produced by the body. It is synthesized and secreted by cells in the anterior pituitary gland located at the base of the brain."[12] The hormone exists as a complex combination of different molecular forms, including the major 22-kDa and minor isoforms such as the 20-kDa. It stimulates many metabolic processes in cells, affecting protein, fat carbohydrate and mineral metabolism. Hence the attraction for its use as a doping agent: it is said to reduce body fat, increase muscle strength and help speed recovery of the musculoskeletal system.[12]

DOPING REMAINS A THREAT TO VALUES AND ETHICS OF SPORTS

Even though successful tests have been implemented over the last decade, the illegal use of performance-enhancing substances remains a threat to the values and ethics which professional sport embodies. In a study conducted by the U.S. Anti-Doping Agency, 68% of all interviewees in the U.S. named the use of PEDs as the most serious issue facing sports today.[13] With the continuing advancements made in medicine and science, the use of PEDs will likely increase in the coming years. WADA's mission, "to lead a worldwide movement for doping-free sport,"[14] seems more crucial than ever before. P

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▶ Nice Insight and the Pharma's Almanac editorial team would like to thank all the companies participating in this quarter's edition. The following are the profiles of the industry-leading companies that have appeared in this issue.

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With over 15 years of leadership in contract process development and manufacturing, **AGC Biologics** offers a deep industry expertise and uniquely customized services for the scale-up and cGMP manufacture of protein-based therapeutics. The company's 850 dedicated employees are committed to providing solutions for more than 100 customers on five continents. Headquartered in Seattle, AGC's integrated service offerings include, among other things, cell line and bioprocess development, antibody drug development and conjugation and protein expression.

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Established in 2012, **Results Healthcare** is a leading global corporate advisory firm focused on public and private healthcare and life sciences companies. Based in London and New York, the company has completed over 75 healthcare transactions to date. The company was established in recognition of the clients' need for a specialist team with dedicated skills in healthcare, pharmaceutical and biotech sectors. As well as their headquarters in London and New York, Results Healthcare serves an international network from Dubai, Singapore, Tokyo, New Delhi and São Paulo. The company focuses on three highly complementary sectors, characterized by innovation, growth and disruption.

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Founded in 2002, **Tedor Pharma Inc.** is a Contract Development and Manufacturing Organization serving a wide range of pharma companies. The company's focus lies on solid dose products, which include immediate and modified release solid oral dose formulations in tablets and capsules. Headquartered in Cumberland, RI, the company has expanded its cGMP facility to accommodate a growing portfolio of solid dose products. Tedor offers an end-to-end holistic model of integrated processes, capabilities and expertise that engenders speed, thoroughness and versatility. The capabilities include formulation and analytical development, contract manufacturing and quality control.

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UPM Pharmaceuticals is a Bristol, TN–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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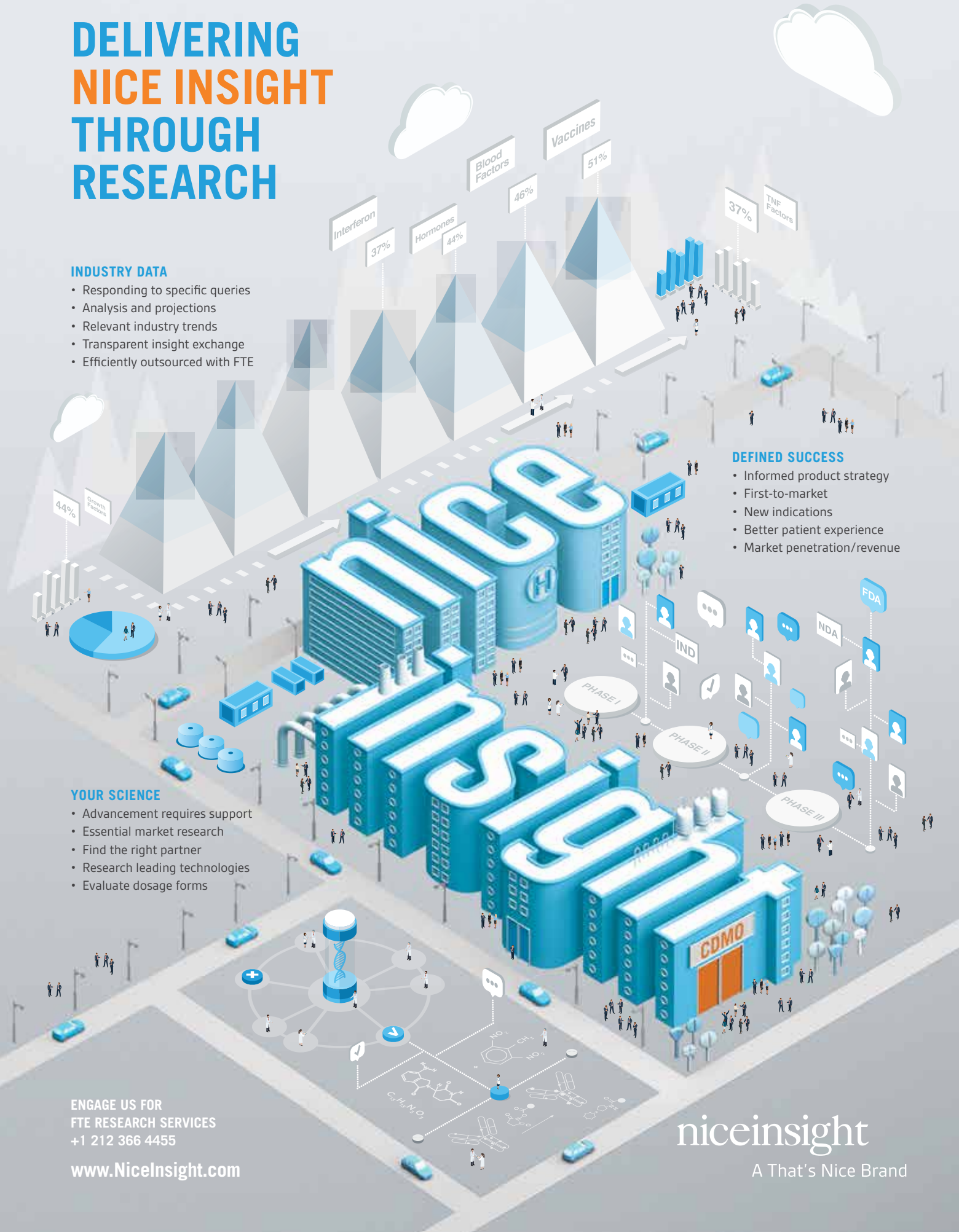

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