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A WORLD OF PARTNERSHIP

BY CYNTHIA CHALLENGER, Ph.D., NICE INSIGHT

ike individuals, companies require strong relationships to thrive. This includes relationships with family, jompeys, stakeholders, friends (similar companies in adjacent markets) and colleagues (supply chain partners). In the past, those relationships were typically local or regional. However, due to ongoing globalization, they now must be international and cross-cultural in scope.

Indeed, effective collaboration is essential to developing the ability and technical expertise necessary to be competitive in the biopharmaceutical industry. Companies must have a global reach, yet still provide local service and support, ensuring not only compliance with all applicable regulations but the same high-quality performance wherever they operate. The increasing preference for more strategic, long-term relationships between biopharma companies and their service providers is therefore not surprising.

Consolidation within the pharmaceutical sector has an impact on relationships as well. There are fewer sponsors, and those that remain are looking to build strategic partnerships with contract service organizations that can support them throughout the increasingly complex and accelerated drug development and commercialization process across all geographies.

Innovation and creativity are thus essential components of sponsor-supplier relationships. Companies that offer creative partnering opportunities to help de-risk outsourcing — combined with a broad range of innovative solutions — are well positioned to help their customers differentiate themselves in the marketplace. All of this is part of the exciting dialogue happening constantly across markets worldwide.

That being said, we would like to thank our extended worldwide community who engage in our insights by taking part in proprietary surveys, serving as subject matter experts, responding to roundtable questions, providing insightful thought leadership articles and, most of all, actively following our content.

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A NOTE FROM THE EDITOR

GLITTERMINS INSIGHT FROM INSIDE THE INDUSTRY...

WE’VE GOT TO DOCUMENT THE CAPABILITY TO LEARN SO MUCH FROM A SIMPLE DROP. IT’S SUCH A VALUABLE GLIMPSE INTO THE FUTURE THAT WILL BENEFIT MANY.

BY GUY TIENNE, NICE INSIGHT

Nice Insight is the market research division of That’s Nice LLC, a Science Agency, leading marketing to the life sciences.
Pharma’s Almanac is printed quarterly and distributed as a supplement to American Pharmaceutical Review (APR) 14, 200 BPA-verified readers and/or Pharmaceutical Outsourcing (PO) 20,000 BPA-audited readers, depending on the print dates, throughout North America to senior executives, scientists and others seeking outsourced services. Additional content is promoted via the APR and PO newsletters to 22,000 and 12,000 readers, respectively. All content is also promoted via mail to service and outsourced suppliers. With print copies and digital promotions, each issue reaches a total of 83,024 to 107,000 industry professionals. All content can be found on www.PharmasAlmanac.com.

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Many Drivers for Consolidation
Deals involving contract service provid-
ers — acquisitions of one by the other or by private equity, mergers, the purchase of manufacturing sites from sponsor firms, etc. — continue to take place on a fre-
quent basis. A look at the dynamics of the pharma and biotech industry reveals the underlying forces driving this high level of M&A activity.

• Consolidation of pharma manufacturers is leading to fewer sponsors; contract service providers need to differentiate themselves with a breadth of capabilities, including unique technologies, efficiency, excellent customer service and the ability to rapidly acquire new knowledge in response to customer needs.6

• The contract services market is highly fragmented, with even the biggest players holding < 5% market share.7

• Pharma customers are looking to eliminate costs from their supply chain through the establishment of fewer, more strategic partnerships with efficient, full-service providers;

• Emphasis on acceleration of the drug development and commercialization processes — exhibited by the growing number of candidates receiving accelerated approval designations (FastTrack, Priority Review, etc.) — is also leading to the need for more efficient, full-service providers;

• The increasing focus on orphan/niche therapies is creating a need for more flexible, responsive manufacturing capabilities;

• Next generation therapies that require small and large molecule production capabilities — and often the ability to handle highly potent compounds — are advancing rapidly and requiring contract service providers with specialized expertise;

• Many compounds in the pharma industry pipeline are poorly soluble with low bioavailability and require advanced formulation technologies that are not practical for sponsor firms to invest in; and

• A significant portion of innovation in the industry is taking place in emerging pharma companies, who require extensive support from service providers through the discovery, development and commercialization of new drug candidates.

To meet these needs, many contract manufacturers have been busy convert-
ing themselves into contract development and manufacturing organizations (CDMOs). Others have extended their ability to sup-
port the full commercialization process with the addition of final drug product man-
factoring capabilities (or drug substance manufacturing in the opposite case).

Contract research organizations (CROs) have been equally busy building out their capabilities to support the full range of ac-
tivities associated with clinical trials and/or analytical testing and build value.8 Like contract manufacturers, they are looking to add technical expertise and to support the full range of clinical needs for many different therapeutic categories in phase I through post-marketing studies.9

In addition to efforts to build integrated service portfolios, contract service provid-
ers are also actively extending their geographic reach in recognition of the global nature of the pharma industry. Larger con-
tact service providers are in a good posi-
tion to continue making purchases. Private equity firms are also looking to benefit from the healthy growth rate of the contract services market.10 They are, in fact, facili-
tating a portion of the deals taking place.11 Medium-sized contract service providers are also very active as they seek to broaden their offerings.

Big and Mega Deals Keep Coming
Despite the large number of big deals that have taken place in recent years, several more have been announced within the last 12 months. Notable past CDMO deals have included:

• Merck KGaA’s acquisition of Sigma-Aldrich;

• Pfizer’s acquisition of Hospira, including its contract parenteral drug manufacturing operations;

• The merger of Patheon and DSM; and

• The merger of Cambridge Major Laboratories with AAIPharma to form Alcami.

The more recent announcements that may have a significant impact on the CMO and pharma industry in general include:

• The purchase of AMRI by the private equity firms The Carlyle Group and GTCR LLC;

• The acquisition of Patheon by Thermo Fisher Scientific; and

• The acquisition of Capsugel by Lonza.

While the AMRI acquisition does not re-
sult directly in further consolidation of the CMO/CDMO space, the financial resourc-
es of these two PE firms, according to AMRI’s President and CEO William Marth, “offer a compelling opportunity to accel-
erate our growth and enhance delivery of world-class solutions to our customers.”12
In addition to efforts to build integrated service portfolios, contract service providers are also actively extending their geographic reach in recognition of the global nature of the pharma industry.

Similarly, the acquisition of Patheon by Thermo Fisher Scientific is a complementary one. As Patheon CEO James C. Mul- les has stated, he is “confident that one-combined offerings and Thermo Fisher’s proven track record of disciplined M&A operations will take our business to the next level.” The acquisition of Capsugel provides Lonza access to advanced capsule technology for addressing Capsugel provides Lonza access to advanced capsule technology for addressing of KBI and very recently Selaxis.

Packaging Coordinators Inc. (PCI) acquired Penn Pharma.

Fujifilm’s acquisitions of Merck & Co. biopharmaceutical operations in the US and UK and Rigel Biotherapeutics, forming Fujimion Dioxys Biosciences.

PolyTherics’ acquisition of Wavewell Effect Polymers and Antifoam to form Abzana, which then acquired PacificGMP and The Chemistry Research Solution.

Brammer Biopharmaceuticals acquired of Nova BioPharmaceuticals which then acquired a cell and gene therapy manufacturing plant from Biogen; and

The acquisition by CDMO Frontida BioPharm, which was formed by CRO Frontange Laboratories, of solid dosage manufacturing facilities and related pharma products from a wholly owned US subsidiary of Sun Pharma.

The latter is an interesting example of a CRO looking to leverage its existing pharma-aceutical customer base with expansion into the CDMO market. There have been, of course, numerous small and medium-sized CRO-CDMO acquisitions as well. A few examples include:

- Far Pharmaceuticals’ acquisition of JHP Pharmaceuticals.
- Siegfried Group’s acquisition of Hameln Pharma and BASF’s API business.
- Cortmont Medical’s acquisition of Axelle BioPharmaceuticals Limited.
- Piramal Enterprises’ purchase of Coldstream Laboratories and related niche products. In some cases, these firms prefer these smaller firms over bigger providers because they can be more responsive, as they often work with and their production equipment is on a scale more suited to small-volume products.

Examples of this type of consolidation in the CMO/CDMO space over the past several years include:

- AstraZeneca’s genetic testing business and Selexis; Gram BioSciences, Orchid Cellmark, Genzyme’s clinical lab business.
- IRIX Pharmaceuticals, Agere Pharmaceuticals, LabCorp’s Aesica, Coldstream Laboratories, Ash Stevens; and
- WuXi AppTec’s acquisition of Florida Biologix to form WuXi AppTec’s site in 2010. Another strategic alliance between MedIm-mune and WuXi AppTec to support biologics manufacturing in the U.S. and China.
- PolyTherics’ acquisition of Warwick Effect’s manufacturing facilities without ownership changing hands; and CDMOs acting as general contractors for management of the supply chains for pharma products.

One example of a large strategic part-nership in the CMO space is that between Covance and Sanofi, which was established when Covance acquired the drug company’s European sites in 2010. Another is the strategic alliance between MedIm-mune and WuXi AppTec to support biologics manufacturing in Sanofi’s European sites in 2010. Another is the strategic alliance between MedIm-mune and WuXi AppTec to support biologics manufacturing for Sanofi’s European sites in 2010.

Astrazeneca has also taken an option to acquire the WuXi AppTec facility. In a third case, Siena Biotech took a minority stake to acquire the WuXi AppTec facility. In a third case, Siena Biotech took a minority stake in Apta’s Italian operations and made

Aptuit, a provider of choice for its drug development efforts.

Close collaborations between strate-gic partners can, in fact, lead to acquisi-tions. Catapult, for instance, acquired Redwood Bioscience after working with the company for several years. Close working relationships provide great insight into the technology, culture and potential of a company to be successful in the future. As a result, these acquisitions tend to be smoother and provide more value-added. Close collaborations are also becoming more important as the complexity of the pharma pipeline continues to increase while expectations for accelerated development times and lower costs are growing.

What Does It All Mean for the Pharma Industry?

The consolidation that has occurred to date certainly changed the contract services market. Service providers that offer an integrated set of capabilities to support pharmaceutical clients regard-less of stage of development, provide the development needs, formulation and production requirements and intended markets can better manage and anticipate their clients’ supply chains, but also benefit from economies of scale and gain access to dif-ferentiating technologies.

Indeed, drug development service providers are employing advanced, state-of-the-art technologies that in the past would likely have been kept in-house at pharmaceuti-cal companies (and left unused) is increas-ing the level of innovation across the entire pharmaceutical industry. One consequence of consolidation, then, has been the greater spread of technologies and innovation, according to Tim Scott, President of Pharmatek, which is now part of Catapult.

The rise of creative partner-ships and collaborations has been another result, if indirectly, of consolidation that ultimately facilitates innovation and accelerated drug development and com-mercialization.

Consolidation is expected to continue as the drivers outlined above remain in play. Some provid-ers will continue to grow and transform, while others will remain in the same mar-ket. Private equity investors will continue to play a role as they seek to leverage their investments. The market will look quite different even just a few years from now. One constant, however, will be the increasing importance of innovation and the development of novel, advanced technologies to solve the production and formulation challenges presented by increasingly complex small molecule and biologic drug substances.

ABOUT THE AUTHOR

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Mr. Walker is the founder and managing director of That’s Nice LLC. That’s Nice LLC is a research and development agency with 20 years dedicated to life sciences. Nigel harnesses the strategic capabilities of his research, the insight arm of That’s Nice, to help companies communicate a science-based vision to grow their businesses. Mr. Walker earned a bachelor’s degree in graphic design with honors from Kent State University.

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REFERENCES


NEW MANUFACTURING PARADIGMS

Life sciences companies continue to focus on breakthrough therapies with accelerated approval timelines. These drugs are high-value and typically serve smaller patient populations than the blockbuster products of the past. New drug therapies require flexible manufacturing capabilities in multiple locations worldwide. At the same time, cost pressures continue to mount, not only due to greater competition, but as governments, payers and patients demand less expensive medicines that are clearly proven to be more effective than existing drugs.

In this age of value- and evidence-based medicine, accelerated development and commercialization is essential. The design and construction of facilities that incorporate state-of-the-art construction technologies and take into account both present and potential future needs — all achieved quickly and cost effectively — is a key factor in successful market launches and maintaining production of safe, high-quality drug products.

All aspects of manufacturing, not just the individual unit operations, must be considered as a whole when designing a modern-day production facility. In addition to the actual process design and production equipment used to make the drug substance, material, personnel and equipment flows, along with the distribution of utilities, etc., are essential factors when integrating a process design with a facility design in accordance with current regulatory requirements. Today’s best solutions allow for reduced construction times and costs, provide for enhanced energy efficiency and minimize risk throughout the project delivery cycle. These goals must be achieved regardless of the pharmaceutical technology being commercialized, whether it is an oral solid dosage drug with a new delivery system, a highly potent antibody-drug conjugate or a personalized gene or cell therapy.

SYSTEMS INTEGRATORS AND TECHNOLOGISTS

Evolving Role of the Process Architect

BY PETER CRAMER, M+W GROUP

volution in the life sciences industry is driving the need for new manufacturing paradigms based on advanced technologies. Traditional approaches to facility design and engineering, such as stainless steel facilities, have a place, but the trend is towards single use. As a result of this, process architects must transform themselves into system integrators to better serve their customers’ needs for fast-track production facilities.

IT IS IMPORTANT TO REMEMBER, HOWEVER, THAT SYSTEM INTEGRATION ISN’T PERFORMED FOR THE SAKE OF PRODUCING A MODULAR SOLUTION. IT IS INTENDED TO PROVIDE AN OPTIMUM SOLUTION FOR DELIVERING A FAST-TRACK PHARMACEUTICAL MANUFACTURING FACILITY WITH A MINIMUM OF RISK BY TAKING ADVANTAGE OF MODULAR AND PRE-ENGINEERED SOLUTIONS THAT PROVIDE THE OPPORTUNITY FOR PARALLEL CONSTRUCTION ACTIVITIES.
Modular systems are being developed to meet the needs of all aspects of a life sciences manufacturing facility. Specialty companies are finding unique and innovative ways to address pharmaceutical manufacturing activities with pre-engineered solutions that are cost effective and significantly reduce the time it takes to build a facility. One notable example is the adoption of modular cleanroom systems with integrated mechanical, electrical, and plumbing systems. These modular cleanroom systems offer an obvious method for reducing the time to deliver a project by allowing the parallel construction of the building and the cleanrooms at the same time. Modular cleanroom systems deliver guaranteed quality for the cleanroom environment and allow a single vendor to be responsible for delivering a facility that meets the clients overall system requirements. Advances in single-use component technologies are also moving at a fast pace and should be understood by the process architect when preparing equipment arrangement. Systems that require fewer operators, reduce floor space and should be designed for ease of installation and use should be integrated into the process layout whenever possible.

Many suppliers are now integrating advanced modular technologies into their solutions in order to stay competitive with the ever-increasing demand for a kit-of-parts and modular solution that reduces the need for a customized solution. Important process architects as Integrators take on the role of determining how different systems can be brought together to provide the most flexible and adaptable cost-effective solutions for a process intensive facility. Technologists and system integrators with up-to-date knowledge of the ever-growing number of options provided by modular suppliers of solutions for pharmaceutical manufacturing have the opportunity to design tomorrow’s production facility with a built-in delivery model that reduces risk and delivers real cost savings to his/her clients.

Life sciences companies are asking for platform designs that can be repeated globally, which not only reduces engineering labor costs, but also allows modular and pre-engineered systems to be delivered easily and reliably around the world. Today’s advanced single-use technology processes reduce the need for customization and allow the standardization of facility design based on the space and utility needs of readily available components. Standardizing on single-use equipment has been a game changer because it now allows a design to be built the exact same way, anywhere in the world.

The benefits of employing modular solution providers continues to evolve, but the building did not have sufficient room for all of the necessary central utility functions on the roof of the building. The systems were delivered in compact modules and installed within a couple of weeks, rather than the 4-5 months required for building a traditional penthouse. The project schedule was also significantly reduced, allowing the company to begin critical research and development operations earlier than originally planned.

The constant introduction of new, innovative modular manufacturing solutions is creating significant opportunities for process architects to contribute their skills in ways that will have major impacts on the duration and cost of future manufacturing facilities. In fact, the term “process architect” no longer adequately describes the roles played by these highly trained and knowledgeable experts.

Traditionally, process architects have been involved in preparing equipment arrangements and the space required to fit a specific process inside a production facility. Today, process architects are expanding their role as technologists and systems integrators focused on finding the best way to deliver a project using modular and pre-engineering systems through the facility design with the clear goal of improving quality, while reducing the cost and time required to deliver a project. The demand for this enhanced role is evident with numerous life sciences companies asking for modular platform designs that leverage modular and pre-engineered components. System integrators and technologists must be aware of new ways to deliver the utility and mechanical systems to a project.

**Benefits of Modular Projects**

**Earlier Completion Date**
- Shorter time to market
- Earlier return on investment

**Traditional Construction Project**

**Conventional Project**
- Defer investment decision
- Efficient use of finance

**Later Start Date**

**Modular Penthouse Solution**

The client wanted to construct a new drug development facility in an existing structure, but the building did not have sufficient room for all of the necessary central utility functions on the roof of the building. The systems were delivered in compact modules and installed within a couple of weeks, rather than the 4-5 months required for building a traditional penthouse. The project schedule was also significantly reduced, allowing the company to begin critical research and development operations earlier than originally planned.

**System Integrators and Technologists for the Future**

The modern pharmaceutical manufacturing facility must be flexible and adaptable, not only to the ability to scale up to meet increased market demands but also the flexibility to house changing production equipment requirements. This can be complicated by the increasing demand for multiproduct facilities that must operate in a manner that prevents cross-contamination. Facility designs must integrate individual unit operations in a way as to allow for the optimized flow of personnel, materials and equipment while providing easy access by operators and maintenance personnel. HVAC and other utility requirements must be carefully considered, in addition to compliance with current Good Manufacturing Practices.

These issues must be addressed whether a new facility is being designed or an existing facility is being expanded or upgraded. Often facility designs must be created while manufacturing processes are still under development. Establishing the optimum solution under these conditions can be highly challenging. Successful systems integrators and technologists have knowledge not only about process equipment but also about utility and mechanical systems and building technologies. Examples include modular penthouse solutions and co-generation plants. System integrators should also have an understanding of the company culture and both the short- and long-term goals for the facility and the site it occupies.

With this knowledge, it is possible for process architects to act as true technology integrators across the entire spectrum of pharmaceutical manufacturing activities and project deliverables. Because pre-engineered systems have guaranteed performance with detailed operating specifications, technology integrators can greatly reduce the time required to provide comprehensive facility solutions. They no longer focus on the building envelope, but on interconnected systems comprising pre-engineered modular solutions that can be rapidly installed, validated and operational.

**Conventional Project**

- Defer investment decision
- Efficient use of finance

**Modular Penthouse Solution**

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**Expanding Horizons**

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The TIG has been established to define how the innovative use of modular and pre-engineered components delivers a fully functional facility design that is easily scaled to meet a specific project’s needs and deliver plants at the lowest cost in the shortest time while providing the most optimal solutions.

To most effectively implement this approach, we work with partners and suppliers across all aspects of pharmaceutical manufacturing. We select whichever organization — internal M+W groups or external suppliers — that can offer the most cost- and performance-effective results. Our efforts are focused, therefore, on integrating what is best, rather than spending time and money to determine how to engineer them from scratch. Our global network is also key to the success of this approach. M+W has relationships with equipment and modular solution suppliers from around the world, allowing us to identify the optimal solutions for clients no matter where they are located.

The TECHNOLOGY INTEGRATION GROUP AT M+W

Highlighting the importance of integrating process, technology and facility design, M+W created the Technology Integration Group (TIG). The TIG focuses on business sectors where it can provide superior value through technical innovation while utilizing design tools that leverage our existing portfolio of capabilities. The TIG’s “Road Map for Success” focuses on defining resource needs, strategies, activities and short-, medium- and long-term measurable project results.

The TIG includes three centers of excellence to enable the delivery of the best solutions the market has to offer: small molecule/oral solid dose (OSD) manufacturing, biologics manufacturing, and fill/finish. Each team consists of people with expertise in manufacturing technology, technology integration and construction management, with the system integrator strongly supported by the center of excellence appropriate for a given project. By linking the integrator with people that have expansive experience in process design and project delivery, M+W ensures that the big picture approach can be effectively implemented using the latest technologies and considering the latest trends in the industry. The members of the team not only have the expertise needed, but an understanding of how the market intends to deliver the potential solutions that can be applied to a given project — allowing them to identify the lowest cost solution with the highest output.

Specifically, the TIG’s role is to define how the innovative use of modular and pre-assembled components will deliver a fully functional facility design that is easily scaled to match a specific process. Perfecting a combined platform design and integrated project delivery approach allows M+W to achieve our goal of becoming the go-to company for advanced technology facilities.

The TIG expands M+W’s offerings by demonstrating how pre-engineered solutions (platform design) can take advantage of new technology and prefabricated components to better serve our clients. Additionally, the TIG demonstrates M+W’s unique ability to deliver new technologies for measurable advantages over conventional designs and delivery models. Advantages of this approach include reduced times for estimating and scheduling, lower project costs, reduced project risk and increased likelihood for project success. M+W’s portfolio of projects that demonstrate our expertise in leveraging technology include pre-engineered biotechnology factories and associated support buildings; single-use manufacturing suites for retrofit applications; continuous processing solutions for OSD manufacturing; robotic filling stations; factory optimization; prototype buildings using modular delivery methods; pre-engineered building solutions for 3-6 month shell delivery; and strategic planning, feasibility studies and high-level concept designs.

Peter Cramer
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Innovating technology and process solutions globally — driving successful outcomes for our clients. M+W Group delivers the services you count on to improve your manufacturing capacity.
MANAGING THE COMPLEXITY OF GLOBAL CLINICAL LOGISTICS FOR NEXT GENERATION PERSONALIZED MEDICINES

By Wes Wheeler and Ariette Van Strien

Clinical trials have grown both more numerous and more complex. Clinical trial materials, many of which are time and temperature sensitive, must be delivered to all parts of the world, including remote locations. To properly facilitate this, Supply Chain Logistics Providers must not only be experienced with all relevant customs regulations and the specialized requirements for shipping these sensitive materials, they must be adept at risk management and contingency planning to ensure that clinical trial materials are safeguarded throughout the delivery process.

INCREASING COMPLEXITY OF GLOBAL TRIALS

Clinical trials have not been immune to the dramatic changes occurring in the biopharmaceutical industry. The evolution towards evidence and value-based medicine, coming after a focus on blockbuster, orphan drugs and next-generation personalized treatments, such as cell and gene therapies, has had a direct impact on the number — and nature — of clinical trials conducted today.

Since 2006, the number of clinical trials has increased by a factor of 33, according to the National Institutes of Health.1 Trials today are also conducted around the world, many with multiple sites. These sites are often in remote locations with little medical infrastructure. The need to demonstrate improved efficacy over existing drugs and long-term safety for products intended to treat chronic diseases means that many trials last much longer than ever before.2 The increased use of adaptive trial designs, more complicated dosing schedules and the growing percentage of biologics in the pipeline, which frequently must be maintained at very low temperatures, are additional factors contributing to the greater intricacies of clinical trials.3

Cell and gene therapies, such as CAR-T autologous, or patient-specific cell therapies, are particularly challenging, though not all therapies are autologous. Allogeneic treatments are also crucial to the supply chain. All biologic samples and advanced therapies require special handling under very stringent temperature requirements. They are also typically time sensitive and must be delivered within clearly agreed time frames, despite traveling through many countries with different regulations. They also require the appropriate design of the clinical supply chain to establish an effective chain of identity.4 The clear layout of each transportation lane with clearly identified contingency solutions must be implemented to ensure that the advanced therapy medicinal product (ATMP) produced is returned to the patient.4 It should be noted that ATMP is not a part of direct-to-patient (DTP) delivery, as ATMPs are always administered in the hospital or at a physician’s office.

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THE SUPPLY CHAIN AND DTP SERVICES

With the increased use of cell and gene therapies, there is an increased demand for DTP delivery.5 DTP services allow patients to receive therapy at home, thus addressing the logistically demanding delivery of sensitive materials to patients.6 DTP services also enable patients to receive treatment in other locations, including those that are out of reach for traditional delivery services, and ensures that patients receive treatment in a timely manner.

De-Risking Clinical Trial Services with a Personal Touch

Supply Chain Logistics Providers must have extremely flexible global networks, highly trained personnel, complementary technology and extensive regulatory expertise to offer efficient, compliant and cost-effective services. Flexible worldwide networks and highly trained personnel ensure the seamless flow of shipments and information, as well as the reduction of waste and inefficiencies in the supply chain. State-of-the-art information, inventory, temperature control and other technological systems allow for patient-focused delivery of clinical trial materials to any location in the world, on time and within specifications.

As the clinical subsidiary of United Parcel Service (UPS), Marken offers truly personally-focused delivery services, including highly secure standards, specialty and hybrid services. Marken has been successful for more than 35 years by focusing on the evolving nature of the regulatory requirements. In June 2017, we launched our DTP White Book Industry Guide, a client resource that provides clear logistics standards for DTP trials.

At Marken, we manage the largest portfolio of active DTP trials in the industry, including global trials with more than 10,000 patients. Marken is continually seeking ways to better improve its services. In April 2017, we launched our Patient Communications Center, now called PCC, a 24/7 call center dedicated to meeting the logistics needs of patients participating in at-home-based clinical trials. The call center enhances Marken’s ability to provide home services while also ensuring strict compliance with each clinical protocol and all relevant
state-of-the-art GPS technology, integrated logistics with a just-in-time approach to optimize shipment numbers and supplies, temperature-controlled packaging solutions, the transportation of clinical drug product, customs and trade compliance, dangerous goods handling, risk assessment, and validation advice and consulting.

The Sentry Device, which is exclusive to Marken, allows real-time GPS tracking of a package’s location and monitoring of any exposure to temperature variations, vibration, light and shock.x

CONCLUSION

Marken continues to specialize in high-touch, personalized supply chain solutions for clinical trial materials and sensitive drug shipments worldwide, now with maximized efficiency and an enhanced service offering. A leading patient-centric supply chain logistics organization with a complete focus on the pharmaceutical and life sciences industries, Marken operates a global network of clinical supply chain solutions to meet the increasingly complex demands of its clients, with no geographic boundaries. With the backing of a leading global transportation provider, Marken is positioned to safeguard clinical trial materials throughout the entire delivery process, even when the unexpected occurs, offering end-to-end visibility, planning, packaging, time- and temp-sensitive material storage, distribution, tracking and additional value-added services when needed.

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ABOUT THE AUTHORS

Wes Wheeler
Chief Executive Officer, Marken

Wes Wheeler joined Marken in 2011 to transform the company, which has grown to more than 40 locations in 19 countries throughout the world. Wes joined the pharmaceutical industry in 1989 with GlaxoSmithKline and has served as CEO/President at four different companies. 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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Ariette van Strien
Chief Commercial Officer, Marken

Ariette van Strien is Marken’s voice of the customer, having spent 25 years in the clinical research industry, with the last six years developing new services for Marken, spanning sales, marketing, business development, and global operational and project management roles. Having worked on the central lab and clinical side, Ariette brings a unique perspective from this portion of the supply chain. Ariette has a diploma as a National Public Relation Consultant, a Superior French Language degree from the International College of Cannes, and a baccalauréat of modern languages and biological sciences.

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Marken is the market leader in patient-centric supply chain solutions for clinical trial materials and sensitive drug shipments worldwide. For more than 35 years, Marken has been committed to developing innovative solutions that anticipate the ever-evolving, increasingly complex needs of its clients and patient populations across the globe. In 2016, Marken became the clinical subsidiary of a leading transportation and logistics organization, resulting in an enhanced offering that delivers optimized efficiency for clients.

Marken has expanded its breadth of clinical trial solutions beyond its core specialty offering to also include standard and hybrid services, which leverage the resources of a global transportation network. When bringing these capabilities to market, it was important to convey that Marken maintains its position as the only patient-centric supply chain organization 100% dedicated to the cardiovascular system and Marken’s commitment to personalized clinical trial logistics is central to its offering, and was therefore also central to the new corporate campaign.

**PERSONALIZED CLINICAL TRIAL LOGISTICS**

As the need for patient-centric clinical trial logistics services is increasing, so are the regulatory guidelines around the privacy of patient data. Marken manages the largest portfolio of active Direct-to-Patient/Direct-from-Patient trials in the industry, and is fully committed to the privacy of patients worldwide. Driven by its global GMP depot network, highly trained personnel and state-of-the-art technologies, Marken’s commitment to personalized clinical trial logistics is central to its offering, and was therefore also central to the new corporate campaign.

**THE LIFEBLOOD OF YOUR CLINICAL SUPPLY CHAIN**

Now stronger than ever, Marken needed a bold visual direction to illustrate its expanding breadth of services, flexible worldwide network and ongoing commitment to personalized medicine, and an equally engaging messaging platform to tie it all together. The resulting creative concept was a combination of both human and geographic elements – an outline of an individual encompassing the classic topography and detail of a geographic map. The infrastructural elements of roads and other pathways make reference to the vascular and musculoskeletal structures of a human body, while the plot points draw attention to Marken’s unparalleled scale of clinical supply chain solutions.

In this instance, the creative came before the content, which in essence means the artwork inspired the messaging. Lifeblood, in its most literal sense, alludes to the cardiovascular system and Marken’s commitment to the patient, but also means “the thing that is most important to the continuing success and existence of something else,” which describes Marken’s value across the clinical supply chain. “The Lifeblood of Your Clinical Supply Chain” was chosen as the headline for the initial iteration of the campaign, a message that blends the concept of complex supply chain logistics with the bodily challenges and disease states that bring humans into clinical trials.

**THE REVEAL**

While the new aesthetic will make its boldest debut at CPhI 2017, the campaign is being rolled out in different iterations and through various channels leading up to the event, including web, literature, print and digital advertising, and editorial content. Following CPhI, the corporate brand evolution will continue, with a full website update and continuous optimization of the artwork and content across key platforms.
n December 2015, The Dow Chemical Company announced that it would acquire the remaining ownership of Dow Corning, which has shared ownership with Corning for more than seven decades. Dow became the 100% owner of Dow Corning. In addition to this, Gary notes, “our silicones and transdermal drug delivery solutions can now leverage Dow’s world-class core R&D capabilities to accelerate innovation.”

**DAGO CACERES**

**Marketing Director, Dow Pharma & Medical**

Gary’s career with Dow Corning spans more than 20 years, during which time he gained global experience in a variety of commercial and marketing roles. These have given him a deep insight into strategic business-to-business marketing, business development and commercial leadership.

Gary joined Dow Corning in 1995 after working for BASF in Strasbourg. He currently manages all healthcare marketing strategies for Dow Corning’s expanded portfolio. Gary holds a degree in Business Administration from the Adventist University, Benin City, Nigeria.

**GARY LORD**

**Global Strategic Marketing Director, Dow Corning**

Gary’s current role focuses on solutions serving the pharmaceutical, medical device and food manufacturing markets. In this role, Gary is in charge of developing comprehensive product offerings, access to new technologies, and expanded R&D to help quicken commercialization innovations.

**IN CONVERSATION**

**GUY TIENE, NICE INSIGHT**

**THE DRIVE TO BE INNOVATIVE**

“One of the key drivers for the merger of Dow and Dow Corning was to expand our capability to develop broader, innovative solutions that help our customers differentiate themselves in the marketplace,“ Gary says. As the two companies were previously so embedded, incorporation of Dow Corning’s portfolio has been relatively seamless. While Dow has traditionally been strong in Oral Solid Dosage Forms (OSDF), primarily tablets and capsules, Dow Corning has placed a higher emphasis on transdermal, topical and dermatological applications. “The combination of the two portfolios creates a synergistic, broader and complementary offering that expands the applicability for our current and future customers,” states Dago Caceres.

“Here we see multiple angles to improve our position. For instance, we can explore synergistic combinations or blends of known and approved chemistries coming from both heritage companies. We can also explore the same synergies in new market segments or applications,” Gary Lord explains further. In addition to this, Gary notes, “our silicones portfolio can now leverage Dow’s world-class core R&D capabilities to accelerate innovation.”

**BROADER SOLUTIONS**

So what can Dow’s pharma customers expect now that Dow Corning has been fully integrated into Dow Chemical? According to Dago Caceres, an increased emphasis and broader solutions. “We remain fully committed to the pharmaceutical industry and will leverage best practices from both companies to improve our service to customers. At the same time we will continue to focus on quality, reliability, regulatory compliance and innovation.” Dago asserts.

The goal is to elevate the integrated company across the board. Gary Lord confirms the strategy has been to “leverage Dow’s manufacturing excellence processes and tools across the silicone product line,” and thus create advanced opportunities for the company’s customers.

**THE FUTURE OF THE MERGER**

With a much broader portfolio of solutions, Dow will be able to have deeper and broader conversations with customers who view the company as a strategic partner. To this effect, Dow has married technology and application expertise. Dago Caceres observes, “We are now combining the deep polymer understanding that the heritage Dow Corning team has on silicones and transdermal drug delivery with the knowledge that Dow Pharma has on cellulose and oral solid dosage forms. The result is our ability to now innovate and design new solutions for well-known unmet needs in this particular area. We call this synergy the ‘Power of Two’.”

**IN CERTAIN REGIONS, DOW HAS A STRONG PRESENCE THAT CAN BE LEVERAGED TO INTRODUCE OUR EXPANDED PORTFOLIO.**

**PRIORITIZING GROWTH OPPORTUNITIES**

As of yet, the biggest challenge moving forward has been prioritizing the multiple growth opportunities created by the merger. “The combination of these versatile technologies creates a vast and wide array of opportunities to serve our customers and the pharmaceutical industry. We systematically review them,” notes Lord, reviewing those that “have a sustainable impact for our customers, us and, of course, patients and consumers.”

With the added growth has come the potential for geographic expansion. “In certain regions, we have a strong presence that can be leveraged to introduce our expanded portfolio. Equally important is the depth of relationships forged by Dow Corning with customers, which will allow us to broaden, deepen, solidify and accelerate our business relationships with them,” Gary Lord says.
The globalization of healthcare and the demand for drugs worldwide are continuously rising. Currently, the global pharmaceutical market is expanding at a robust compound annual growth rate (CAGR) of 6.3%, according to Evaluate Pharma, with global pharmaceutical R&D spending increasing annually at approximately 2.5%. This spending will drive further growth and is expected to increase added revenues derived from new products currently in the R&D pipeline by 50% in 2022.

A STRATEGIC EXPANSION
A strategy that provides increasing and lasting value to the global pharmaceutical industry involves outsourcing, increasingly with contract partners positioned both operationally and geographically to serve potential markets most effectively. Mordor Intelligence predicts the contract manufacturing sector is likely to expand at a 6.4% annual rate to reach $84 billion in 2021. Grand View Research estimates agree, projecting the global healthcare contract research industry to grow at greater than 6.0% annual and be valued at $45.2 billion by 2022. The Japanese portion of this market will grow faster.

In the context of global pharmaceutical trends and changing Japanese law, which in the early 2000s allowed companies for the first time to fully outsource the manufacture of pharmaceuticals, Japan has seen the emergence of its own contract research, development and manufacturing services industry, including Bushu Pharmaceuticals Group, which operates Bushu Pharmaceuticals Ltd. Bushu has provided supply chain management hub functions to multinational companies, and is the country’s largest and most comprehensive contract development and manufacturing organization (CDMO), with the capacity to service clients internationally. Bushu is also the first to create a full-service development unit to suit the needs of Japan’s drug developers, as well as those companies looking to enter Japan’s home market or venture into nearby markets with a strong partner.

BUSHU PHARMACEUTICALS LTD.
Bushu Pharmaceuticals Ltd. has deep roots in Japan, with its operations and quality culture growing from legacy affiliations with Sandoz, Novartis and Japan’s Shionogi & Co. The company operates as a world-class, single-source, end-to-end contract services provider, accommodating various oral solid dose formulations and full-service packaging operations.

SPERA PHARMA, INC.
In July 2017, the company’s CMC capabilities were extended further when Takeda spun-out part of its pharmaceutical sciences/CMC business – known now as Spera Pharma, Inc. – to Bushu, and in the process, Bushu will become Takeda’s strategic contract services partner. The acquisition creates a complementary relationship between Takeda and Bushu that aims to improve operating efficiencies and create a more agile organization to serve the needs of both companies. The Spera subsidiary integrates Takeda’s Pharmaceutical Sciences business, in-cluding approximately 200 employees from three main divisions: Chemical Research & Development, Pharmaceutical Technology Research & Development and Analytical Research & Development.

The Spera acquisition was particularly strategic for Bushu because it creates a uniquely comprehensive top-tier CDMO in Japan, offering a complete and integrated range of research/development services and networked manufacturing facilities to support client outsourcing strategies in Japan and the region. With Spera, Bushu can offer services from preclinical CMC to through regulatory filing and technical transfer stages, and on to clinical trial materials (CTM) and commercial manufacturing. The acquisition also creates excellent economies for Bushu customers by providing a quick and low-risk transition from development to commercialization.

A PACIFIC BASE FOR GLOBAL PLANS
To meet global markets head-on with its customers, Bushu and Spera have built a capable proactive organization fielding a network of development and manufacturing facilities that are well positioned in Japan to serve the region. Bushu has made it a priority to expand its intellectual capacity through world-class talent acquisition and operational leadership to help set it apart. Bringing experience supplying finished goods to more than 40 countries, Bushu helps its customers overcome cultural and other barriers to entry. Bushu will continue to energize the global strategies of the world’s largest pharmaceutical companies seeking to enter markets in Japan, the Asia-Pacific region and beyond.

Currently, the Bushu Group operates three advanced cGMP manufacturing and development facilities, including Kawanishi, which specializes in drug product manufacturing and packaging, and Misa- goe, which specializes in drug product development facilities, including Kawamura and Osaka. The third facility is Spera’s operation in Juso (Yodogawa-ku, Osaka city), which encompasses CMC and clinical trial materials. The combination of these facilities now propels the Bushu Group to its “Number One” CDMO status.
QUALITY AS A CULTURAL IMPERATIVE

Culturally, Japanese companies take extreme pride in promoting and maintaining the quality of their products. While this is true for most of the pharmaceutical industry in Japan, Bushu’s attention and focus is especially acute, sustaining quality that extends into every aspect of its operations and provides all partners with a “Japanese standard” customer experience.

With operations approved by major regulatory bodies including EMA, FDA and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), among others, Bushu’s facilities are cGMP compliant and able to meet the most stringent international regulatory requirements. Certainly, compliant, internationally sanctioned facilities are important and a business imperative, but effective global product strategies require flexibility. This translates to versatile operations geared to manufacture products destined for diverse global markets. The Bushu Group, which now owns the development assets of Takeda, can develop products destined for diverse global markets.

INVESTING FOR SUCCESS

Over the past decade, Bushu has invested heavily to upgrade the capabilities of their packaging lines in order to accommodate serialization and other complexities associated with distribution to Japanese and global markets. Bushu’s warehousing and distribution operations, for example, have evolved with state-of-the-art IT-assisted material tracing system and automated material transfer vehicles to manage millions of global product SKUs.

Bushu’s investment into its capabilities and processes is ongoing, and lately a great deal of attention has been paid to implementing advanced automation and controls to better manage manufacturing and process operations more effectively. Much of Bushu Group’s growth and acquisition strategy has been financed by Baring Private Equity Asia.

Ultimately, Bushu Pharmaceuticals’ strategy reflects the interests of its clients. Going forward, Bushu plans to continue its path to growth and extend its pure CDMO play in oral solid dose manufacturing and parenteral drug development and manufacture for pharmaceutical companies both internal and external to Japan. But true to its earliest beginnings, the company is dedicated to helping companies realize their outsourcing strategies in this very important region.

REFERENCES


ABOUT THE AUTHORS

Jun Yokohama
President & CEO, Bushu Pharmaceuticals Ltd.

After graduating from the Faculty of Economics at the University of Tokyo, Jun Yokohama entered the Hokusaid Takushoku Bank. He later studied at the University of Chicago Business School and obtained an MBA. Yokohama joined Boston Consulting Group Japan in 1998 and worked on a wide range of projects. In 2015, he was an advisor to Bushu Pharmaceuticals Ltd. and in April 2016 he took office as President and Representative Director and CEO of the company.

Toshio Yoshioka
President, Spera Pharma, Inc.

Toshio Yoshioka, a graduate from the Faculty of Pharmaceutical Sciences of the University of Kyoto (B.S. and master degree), joined Takeda Pharmaceutical Company, Ltd in 1980, becoming Head of the Lab. In 2009, he moved to Pharmaceutical Production Division, becoming the Head of the Osaka plant, then the Head of Pharmaceutical Technology R&D Laboratories in the CMC Center. In April 2017, he joined Bushu Pharmaceuticals Ltd. and became President of Spera Pharma, Inc. in July 2017

The combined Bushu Group and Spera Pharma is Japan’s number one CDMO. We exemplify world-renowned quality and breadth of scientific expertise, offering pharma and biotech worldwide an efficient single source for early development to NDA or JNDA, globally competitive manufacturing and distribution.
**TRANSIENT TRANSFECTION AT A LARGE SCALE FOR FLEXIBILITY IN CLINICAL AND COMMERCIAL VECTOR MANUFACTURING**

By Richard Snyder, Ph.D., Scott Jeffers, Ph.D., and Ying Cai, Ph.D., Brammer Bio

The rapid progress of cell and gene therapies through clinical development is driving demand for late-stage clinical and commercial manufacturing capabilities. Transient transfection for vector production offers significant flexibility for cell and gene therapy development. Contract development and manufacturing organizations (CDMOs) with the ability to achieve high-yielding clinical and commercial manufacturing of high-quality viral vectors using transient transfection offer their clients this flexibility combined with scalability and speed to market.

**WHY TRANSIENT TRANSFECTION**

Transient transfection involves the introduction of genetic material into a cell without requiring integration of the material into the host cell genome. As a result, it is present in the cell for a limited period of time and is passed on during cell division. It is effectively achieved using plasmid DNA, but high-purity and high-quality siRNAs, miRNAs, and RNAs can also be used. The products of transiently transfected cells are thus typically harvested within one to three days post-transfection.

Transient transfection is an effective method because it allows for the rapid production of viral vectors such as recombinant adeno-associated viral (rAAV), recombinant retroviral (rRv) and recombinant lentiviral (rLV) gene transfer vectors in the quantities needed for clinical development and commercial manufacturing. In addition, the speed and flexibility of transient transfection is ideal for rapid and cost-effective evaluation of processes and therapeutic vector candidates during early-stage development, and transition to late-stage production, allowing for smooth scale-up and transfer of processes and technology.

**CHALLENGES WITH TRANSIENT TRANSFECTION AT LARGER SCALE**

There are few companies with the capability to commercially manufacture viral vectors; most of the 24 firms identified by Roots Analysis in a 2016 report are CDMOs. While in some ways similar to the production of conventional biological drug substances (use of bioreactors and the need for harvesting and downstream processing), in viral vector manufacturing care must be taken to ensure maintenance of viral vector potency, quality, and scalability. As mentioned above, transient transfection methods that utilize calcium phosphate (CaPO4), cationic lipids or polyethyleneimine (PEI) to deliver the DNA can be utilized in adherent or suspension culture. Identification of the equipment and manufacturing platforms that allow effective scale-up is essential.

Processes that occur in stirred-tank reactors (suspension culture) allow scale-up, as those that require plasticware vessels such as Cell Factories® (Nunc/Thermo) or CellStacks® and HyperStacks® (Corning) involve scale-out (adherent culture) to obtain a larger batch size, and can benefit from automation. Advances in bioreactor technology are helping to alleviate some of these difficulties. For instance, the iCELLis 500, a bioreactor from Pall Life Sciences (Figure 1), with up to 500 m² of cell growth surface area, allows for efficient scale-up using adherent cell lines to a much larger scale than previously possible, in some cases providing sufficient capacity for late-stage clinical and commercial production.

It is important, but challenging, to maintain comparable process performance for each unit operation when they are scaled-up. Cells and product intermediates (process materials before Drug Substance) typically are unstable, and the final vector product potency/infectivity may decrease significantly with increased process time. Ideally, a similar time frame is achieved for a unit operation, regardless of scale, to ensure comparability of process performance such as yield and product quality. During transient transfection, DNA must be mixed with a transfection reagent and then added to the bioreactor. Fluid dynamics in different bioreactor volumes are a concern, as there is a narrow window of time in which mixing and subsequent addition to the cells should be achieved to maintain consistent transfection efficiency and production yield. For downstream processing, similar processing times can be achieved by scaling-up volumetric flow rates for chromatography or filtration steps.

**CHOOSING ADHERENT OR SUSPENSION CULTURE**

As mentioned above, transient transfection can be achieved via either suspension or adherent cell culture. Suspension culture is typically performed in stirred tank or wave bioreactors, with which the biopharma industry has extensive experience. Approaches for scaling-up of these processes present unique challenges.

Conversely, adherent cell culture using microcarriers allows for the use of plasticware. Small-scale runs are typically performed using vessels comprised of plastic layers to which the cells adhere. There is a limit to the size at which these culture processes can be scaled, as vessels with 40 or 50 liters become cumbersome to manipulate, and often scale-out, and running a large number of vessels in parallel is required rather than scaling-up to a greater bioreactor volume.

In addition to direct scalability, suspension culture, and adherent culture using microcarriers, avoids the need for scale-out plasticware processes. Suspension culture also reduces operator variability from manual manipulation of a large number of plastic vessels, as automation and on-line monitoring tools can be easily integrated with a bioreactor. It is also easier to monitor and keep process records for a single larger bioreactor, allowing faster development of process knowledge and often improved process performance. In general, suspension culture is more robust, as well as less labor- and space-intensive.

**MOVING CLIENTS TO MODERN TECHNOLOGIES**

To fully support its clients, Brammer Bio invests regularly in modern, state-of-the-art technologies. In certain scenarios, clients are unable to switch to these advanced technologies because their products are ready to enter into late-stage clinical or even commercial production, and they are locked into the use of plasticware. Small-scale runs are typically performed using vessels comprised of plastic layers to which the cells adhere. There is a limit to the size at which these culture processes can be scaled, as vessels with 40 or 50 liters become cumbersome to manipulate, and often scale-out, and running a large number of vessels in parallel is required rather than scaling-up to a greater bioreactor volume.
using their legacy platforms due to financial or time constraints. However, Brammer is committed to migrating clients from legacy technologies to new platforms, including single-use stirred-tank or wave bioreactors, newer technologies such as the Pall iCELLis®500 system (shown in Figure 1) and appropriate disposable systems. Switching away from transient transfection and onto highly scalable manufacturing platforms such as insect cell lines/baculoviruses or stable mammalian producer cell lines for vector production is also an area of expertise for Brammer Bio, and these platforms rely on new analytical methodologies as well.

As an example, analysis of rAAV vector particles has conventionally required the use of two common assays: one based on PCR to determine the number of vector genome-containing particles and one based on ELISA to determine the number of total capsid particles. These results are used to calculate the empty-to-full particle ratio, which is an important product attribute. Brammer Bio has replaced these two separate assays with one assay — analytical ultracentrifugation — and as a result, evaluation of vector particles can be achieved more rapidly and accurately, accelerating product and process development.

Brammer has supported clients in transitioning from transient transfection processes using adherent cell lines to scalable suspension processes, many of which are also serum-free (to avoid the potential for exposure to prions). Conversion first requires weaning of the cell from serum and adapting the cells to suspension media. Lead cell clones that are capable of supporting the desired vector production yields and generational stability are identified, expanded and characterized. A master cell bank is generated for the clone that provides the optimum performance, which is subsequently used for manufacturing. It is a labor-intensive, multi-month effort, but once completed, clients have a process and reagents that can be scaled as needed to meet demand for clinical materials and commercial quantities.

In January 2017, Brammer Bio acquired a 65,000-sq.-ft. manufacturing facility and nearby 46,000-sq.-ft. warehouse in Cambridge, MA, from Biogen, retaining over 100 employees with experience in phase III and commercial biologics production. The Cambridge facility will support large- and small-scale vector manufacturing in Q4 of 2017. One notable feature of the Massachusetts operations is the company’s large warehouse and distribution capability, which allows for raw material sourcing and warehousing to meet a range of production needs. Brammer has recently doubled its clinical manufacturing capacity in Florida, with additional cleanrooms and support space, and added staff, bringing the total team to over 270 at all locations. Furthermore, Brammer Bio also has a 50,000-sq.-ft. facility in Lexington, MA, that is being designed for modified cell therapy manufacturing.

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The Russian market presents new growth opportunities for pharmaceutical companies with manufacturing capabilities within the country. Servier Group is well-positioned to serve the market directly with a wide range of solid oral dose products, while Servier CDMO can support other pharmaceutical companies looking to leverage the growth potential but who lack in-country production facilities.

**STRONG GROWTH POTENTIAL**

Following a period of recession, the Russian economy has strengthened and in some sectors, such as pharmaceuticals, is experiencing healthy growth. According to market research firm GlobalData, the Russian pharmaceutical market was valued at $20.01 billion in 2016 and expanding at a compound annual growth rate of 13% to reach $38.96 billion by 2021.

**IMPLEMENTATION OF PHARMA 2020**

One issue regarding the Russian pharmaceutical market that has attracted the attention of the Russian government is the fact that the majority of medicines sold in Russia are imported. In 2014, DSM Group estimated that domestically produced drugs accounted for just 23% of the Russian pharmaceutical market in terms of value.

In response to this situation, the Russian government introduced the “Development of the Pharmaceutical and Medical Industry for 2013-2020,” or the “Pharma 2020” strategy, in 2009. The goal of Pharma 2020 is to raise the market share of drugs produced within Russia to 50% by 2020. In addition, 90% of the drugs on the List of Vital and Essential Medicines (ZHKVLP) should be produced in the country. Perhaps most ambitiously, the strategy includes a goal of having Russia produce innovative drugs that currently have no Russian-manufactured equivalents.

A number of laws and regulations have also been implemented. For instance, domestic drug manufacturers can receive significant cash subsidies, and foreign manufacturers cannot participate in public tendering.

The first phase of the Pharma 2020 strategy (2009-2012) focused on the construction of new manufacturing facilities and investment in R&D, while the second phase (2012-2017) involves domestic production of generics and implementation of an import substitution policy. In the last phase (2018-2020), the emphasis will be on increasing exports.

This plan has already had an impact, according to Russian President Vladimir Putin, who indicated at the Quality and Affordable Medicine forum that in 2012 just 93 of the drugs on the ZHKVLP list were produced in Russia, with an additional 267 produced by joint ventures comprising Russian and foreign companies, while in December 2014, 413 of the 608 drugs on the list were manufactured in Russia.

**EURASIAN ECONOMIC UNION POTENTIAL**

In addition to developing its domestic pharmaceutical industry, Russia has also been participating in the new Eurasian Economic Union (EEU), which was established in 2014 with the goal of forming a larger economic trading group that would be more competitive with the European Union, the United States and other large nations.

The EEU includes Belarus, Kazakhstan, Armenia and Kyrgyzstan, along with Russia, and is a single market with over 180 million people. During its first two years, the Union has had some success at achieving mutual trade but continues to work to eliminate many internal barriers and establish free trade agreements abroad.

For Russian drug manufacturers, this common market represents a real opportunity. Most notably, the centralization of applications for marketing authorization (MA) in the form of mutual recognition is considered a part of the union’s framework. Thus, a marketing authorization should be granted for all member countries if it is — or has been — issued in one of these countries.

**Serving Russia**

Servier has been present in Russia for more than 30 years and is recognized as a leader in the Russian prescription drug market. The first research partnership agreement with Russian clinical research centers was signed in 1984. The first Servier Group subsidiary in Russia, ZAO Servier, was created in 1992, followed by the launch of the International Centre for Therapeutic Research (ICTR) in 1999, which allows the implementation and monitoring of clinical trials and thus registration of Servier drugs with Russian health authorities.

The company has been providing drug products to the Russian market since 2008, following the construction of its production site in Sophyno in Moscow in 2007. The company initially performed packaging activities, adding full final dosage manufacturing capabilities in 2010.

Servier currently employs over 1,200 people in Russia. The Sophyno plant has a very
While most big pharma companies are present in some form in the Russian market, many have not yet invested in local production facilities. They have taken a “wait-and-see” approach with respect to finalization of Russia’s Pharma 2020 strategy.

Low turnover of 3%, compared to an average turnover in the Russian labor market of 25%. Zao Servier is the private market leader for Russian prescriptions drugs, contributing to up to 30% of the Group’s yields. Importantly, 98% of Servier products sold in the Russian market are produced in this facility close to Moscow (only one syrup product is contracted to a local manufacturer).

Preparing for expanding markets
With implementation of the Pharma 2020 strategy progressing and the potential to serve a much wider Eurasian Economic Union, the need for a highly efficient and clearly defined, functional supply chain has become significant. Servier has responded by actively building a new organization with a sales subsidiary designed to manage the complexity of logistics and distribution in such an enormous country, as well as the additional supply chain issues posed by serving other EEU countries.

Planning is required to ensure that manufacturing and packaging schedules are sufficient to meet the expanding needs of the marketplace, manage the various warehouse partners and produce products that meet the requirements of different pharmacy chains and distributors.

In addition, given the sizable opportunity presented by the Russian market and its participation in the EEU, it is imperative for Servier and the Serdix facility to extend its technology offerings. Servier therefore continually invests in both new equipment and capabilities designed to improve production efficiencies and provide new products. Most recently, the company made a €3.5 million investment in a new encapsulation machine and tablet press, adding to its established granulation and tabletting capabilities. Both of these new pieces of equipment, as well as other systems at the facility, are intended for the production of Servier products but also have available capacity for customers of Servier CDMO.

Recognized quality
Servier’s plant has been operating for 40 years, and in that time has received only favorable reviews from Russian authorities (as latest in 2016) and new clients of Servier CDMO. In fact, Servier has a highly developed global quality systems management infrastructure that proactively assures the implementation of quality assurance/quality control best practices. As a result, the same quality and management systems and advanced technologies used in Servier’s European facilities are employed at the Serdix site, including Good Manufacturing Practices.

Servier also has a code of conduct and is committed to operational excellence. The company has developed both corporate social responsibility and health, security and environment policies, taking a holistic approach to ensuring the quality of its products and the protection of its employees and the environment. An anti-bribery program has also been launched at the Serdix plant, and all staff have been trained.

Ready to serve new customers
Russia is a difficult market to not only penetrate, but also participate. The Russian people are, however, eager for access to high-quality medicines, and their government is working to establish a better healthcare system.

While most Big Pharma companies are present in some form in the Russian market, many have not yet invested in local production facilities. They have taken a “wait-and-see” approach with respect to finalization of Russia’s Pharma 2020 strategy.

Servier, on the other hand, has taken a proactive approach and established one of the most advanced, state-of-the-art GMP manufacturing facilities for oral solid dosage drugs in Russia. Servier offers high-quality production grounded in 30 years of local operation, combined with the decades of experience and know-how of the internationally recognized Servier Group.

For the last three years, Servier CDMO has been offering contract development and manufacturing services to pharmaceutical clients. All of that experience and expertise enables Servier CDMO to provide high-quality contract manufacturing services at our Serdix facility to pharmaceutical companies looking to participate in the growing Russian market, but without the resources to invest in local, in-house capabilities.

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An engineer by background, Renaud has worked for more than 10 years in FMGC companies in Europe in managerial positions. He joined in February 2014 as Production Manager, before moving on as the Production Unit Manager for liquids and dry forms. Renaud has been responsible for the Servier production site for four years, and has developed the local CDMO’s offering. In his role, Renaud analyzes and proposes the best technical and commercial answer for the localization of products in Russia.

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With over 27 billion units of drug product manufactured annually, Servier CDMO is the CDMO to take your project from development through commercial-scale manufacture. Applying 60 years of experience and operating out of 11 worldwide facilities, Servier CDMO has the combined knowledge, capacity and empathy to deliver products in various dosage forms, with full development and regulatory support. As an embedded CDMO with large pharmaceutical tools, we understand the importance of protecting your molecule, and will treat yours as if it’s one of our own.

For more information, visit us at CPhI Worldwide, booth #41C50, www.servier-cdmo.com or contact cdmo@servier.com
A global supply chain becomes the new norm, local issues have increasingly entered the dialogue around production. It no longer makes sense to simply set up shop; one must consider international regulations, socio-political or economic conflict, and costs and benefits, and always be forward-looking – taking into account growth, as well as the potential for social discord, in consideration. As CDMOs become more than just tactical service providers, edging ever closer into strategic territory, it is the obligation of the organization to take all factors of a region into account when doing business. A Relationship Without Boundaries Contract development and manufacturing organizations (CDMOs) do not always benefit from the influence they have on sponsors at present. The relationship type sponsors have sought from CDMOs has shifted over the last several years, though the trend is clear – a preferred provider relationship has emerged ahead of a tactical service relationship. According to the 2017 Nice Insight Contract Development and Manufacturing Survey, 32% of over 700 respondents reported that they outsourced to a tactical service provider, 42% selecting a preferred provider or seeking a strategic partnership for their outsourcing needs. In 2015, only 28% of respondents to the survey indicated they were “very interested in a strategic partnership with a CDMO.”

Since CDMOs are held increasingly accountable and viewed as a trusted supplier entity that can lead both provider and sponsor to better business, it is interesting to note exactly what factors into CDMO selection. Of respondents to the 2017 CDMO survey, 72% confirmed that regulatory compliance was crucial when selecting a partner. Geographic convenience was also seen as a huge deciding factor, with 68% indicating the importance of location proximity. To further drive the point home that an international footprint can be make or break it for CDMOs, 63% of respondents stressed that they took the organization’s global presence into account when selecting an organization to work with. That CDMOs must be global, and that they must uphold strict quality standards regardless of where they are based, has become a theme. According to Tim Tyson, Chairman and CEO of Avara Pharmaceutical Services, regulatory concerns must be top of mind for both CDMOs and sponsors. As a result of this, CDMOs that have a proven track record dealing favorably with quality in emerging markets will often demonstrate an advantage over competitors. “With increasing globalization of the pharmaceutical industry and heightened restrictions on the import of pharmaceutical raw materials, intermediates, active ingredients and formulated products, sponsors can only be confident that their supply chain is secure when working with CDMOs that have a history of successful supply chain management on the international level under both normal and adverse conditions,” noted Tyson. The CEO also commented that operating region should not impact quality. “Excellent global supply chain management capabilities are also necessary to ensure the security of supply for customers and patients, regardless of location,” Tyson confirmed.

Where It Makes Sense to Partner So who do sponsors choose to work with? A sponsor’s perception of the country a CDMO is working in can affect how they treat a potential CDMO partner. It is interesting to note that in the Nice Insight CDMO Outsourcing Survey shows a positive correlation for CDMOs in emerging regions over the last few years. In 2014, 49% of respondents said they had worked with CDMOs in emerging markets. This number rose to 53% in 2015 and then shot up to 65% in 2016. Currently rates of 67%, which is still almost 20 points higher than it was three years ago. The number of trustworthy CDMOs in those markets is also increasing. In 2014, 20% of respondents said they were willing to outsource to emerging markets but were unable to, as they did not know “any reliable CDMOs yet.” This number has dwindled over the last few years, with only 9% indicating the inability to identify a qualifying partner in 2016. And where are buyers of CDMO services deciding to seek out providers? International interest varies across the board. The numbers have remained approximately the same since 2014. This year, of buyers who engage in outsourcing to emerging markets, only 23% outsource to projects in the US and Canada, 14% outsourcing to Western Europe, 12% India, 11% China, 10% to Argentina and Brazil, 10% to Eastern Europe and Turkey, 8% to Japan and Korea and 7% to the Middle East as well as to Singapore and Southeast Asia, with 0% indicating other regions. These numbers indicate that CDMOs have become more diverse across the supply chain, with an increasing amount of global partnership.

Regulatory Concerns in Emerging Markets Among those who did not wish to expand into foreign, emerging markets with partners, the top four indicated was the quality of the product being too risky, at 38%. This was directly followed by regulatory compliance concerns, with 37% accounting for this. While intellectual property concerns and safety have been an issue in the past, it is a top-of-mind concern for many. Now, appreciation over intellectual property issues has shot up over the last few years – only 10% indicated this was a fear in 2014. This number grew to 26% in 2015 and then shot up to 35% in 2017 – judging by this trend, IP issues will likely be an increasingly growing concern, enough so that sponsors may not enter into an agreement with a provider in a certain market, because for them, the risk is not worth the reward.

Think Global, Act Local For CDMOs looking to become more international across the supply chain, knowledge of all regulatory standards is not only to adhere to the regulatory standards, as well as participating in meetings with the FDA concerning quality metrics, is critical. Adding to this, del Boca noted that looking at the regulatory standards in place, “Continuous development of manufacturing sites and techniques to prepare them for future needs and requirements is necessary for manufacturers to deal with increasing regulatory requirements,” he commented in an interview with Pharmaceutical Manufacturing Magazine. “If systems are not according to regulations, these pharmaceutical companies may have difficulty entering markets that are regulated by these authorities,” he added.

It’s true, this is where the adage to “think global but act local” is applicable to CDMOs especially. A Compliance officer can manage the interface between two agencies is crucial. Trends in regional government no doubt dictate production, as is the case of Russia’s Pharma 2020 strategy. This long-term plan calls for pharmaceuticals to only be manufactured in the country in order to guard against volatility and sanc-

tions, and also as a way to bolster Russian exports and insert self-sufficiency from a global standpoint. However, this does not mean the doors are closed. Servier (Servier CDMO) has been a major player in Russia for more than 30 years; the French firm currently operates several locations either within or servicing Russia (including ZAO Servier, Sertix and EGB).5

A Golden Regulatory Standard We are far from having one set of regulatory standards dictate compliance on a worldwide scale; however, there are others willing to outsource to emerging markets, while others have been an issue in the past, it is a top-of-mind concern for many, now. Apprehension over intellectual property issues has shot up over the last few years – only 10% indicated this was a fear in 2014. This number grew to 26% in 2015 and then shot up to 35% in 2017 – judging by this trend, IP issues will likely be an increasingly growing concern, enough so that sponsors may not enter into an agreement with a provider in a certain market, because for them, the risk is not worth the reward.

Think Global, Act Local

For CDMOs looking to become more international across the supply chain, knowledge of all regulatory standards is paramount. The safest bet for CDMOs is not only to adhere to the regulatory standards of the country they are operating in, but implement an even higher set of standards. According to Joaichim del Boca, VP of Regulatory Affairs/Quality Compliance at Vetter Pharma-Fertigung GmbH & Co. KG, it is crucial to always stay abreast of regulatory demands in the country the organization is operating in, but more than one regulatory agency should be observed. “Cooperation with local authorities, as well as participating in meetings with the FDA concerning quality metrics, is critical.” Adding to this, del Boca noted that looking at the regulatory standards in place, “Continuous development of manufacturing sites and techniques to prepare them for future needs and requirements is necessary for manufacturers to deal with increasing regulatory requirements,” he commented in an interview with Pharmaceutical Manufacturing Magazine. “If systems are not according to regulations, these pharmaceutical companies may have difficulty entering markets that are regulated by these authorities,” he added.

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R E F E R E N C E S

Global CRO Market: Overview

Driven by the growing number of clinical trials and demand for advanced medicines across the globe, the CRO market is projected to reach $85.42 billion by 2020 at a compound annual growth rate (CAGR) of 9.8% from 2015 to 2020, according to Zion Market Research. Valued at $34 billion in 2014, clinical trial services accounted for over 70% of the market value; services for phases II to IV trials generated 50% revenue. By 2020, 72% of clinical trials are projected to be outsourced. In addition, the 2017 Nice Insight Preclinical and Clinical Contract Research Survey demonstrated that the most popular development phase for outsourcing services was phase II trials, followed by phase I (49%), phase III (47%), and phase IV/post-launch (22%) in 2017. Geographically, North America and Europe represent the two largest regional CRO markets, holding a 43% and 40% global share, respectively. In addition, the clientele for CROs have expanded from traditional pharma, biotech and medical institutions to emerging countries and several of these countries have a rapidly growing economy. China and India are the exemplars for a large population and growing economy—they present tremendous opportunities of high market growth and financial returns for both pharmaceutical and CRO industries. Rising personal income levels, increasing incidence rate of chronic and lifestyle diseases (i.e., cancer, diabetes) and demand for new drug products have been driving the vigorous growth of these markets in the 21st century.

Outsourcing services in emerging countries are expected to grow at a higher rate than in developed markets. By 2020, the emerging countries will harvest over a quarter of global CRO market share. To enter the emerging markets, some pharmaceutical companies have opened their own R&D and manufacturing facilities, while others have sought the assistance of global and local CROs.

The pharmaceutical industry has been cautious in terms of engaging emerging market CROs. According to the Nice Insight 2017 Preclinical and Clinical Research Survey, the willingness to consider emerging market CROs varies among different pharmaceutical sectors with big pharma/biotech showing the highest consideration rate of 62%, followed by small (44%), mid-sized (66%), and emerging (44%) pharma/biotech sectors. A total of 59% of the respondents who consider emerging market service providers have indeed worked with CROs in these regions. Quality is the greatest concern that hinders engagement with local CROs. Concerns with regulatory compliance, logistics, intellectual property and communication constitute other major barriers.

For clinical trials, emerging markets offer several appealing features, such as significant savings in clinical trial costs of 40–60% compared to the cost of clinical trials conducted in developed countries. Other features include the ease in patient enrollment, a skilled scientific research and healthcare working force, and government incentive programs (i.e., tax exemptions). Consequently, more large-scale multi-sites clinical trials have been conducted in these regions.

Globalization of Clinical Trials

One approach to improve clinical study efficiency has been to conduct trials in developing countries. As a result, clinical trials have moved from western countries to emerging markets. To date, the United States and Europe still host the largest proportion of clinical trials. However, Asian and Latin American/Caribbean has witnessed the fastest growth in terms of number of clinical trials: an average annual growth rate of 30% and 12%, respectively, between 2005 and 2012 in contrast to an average annual growth rate of 2% in the US in the same period.

Operating clinical trials at a global scale can be a daunting task. The pharmaceutical industry has relied heavily on outsourcing to reduce costs and shorten development timelines. To this end, selecting a CRO has become extremely critical to the success of an entire study. In recent years, the industry has witnessed a number of strategic partnerships formed between global pharmaceutical companies and global CROs to streamline clinical development processes. A prime example of this practice is Bristol-Myers Squibb and Parexel’s strategic partnership and Paragon as their strategic providers of clinical-trial implementation services in June 2010 and May 2011, respectively. A recent joint venture between Takata and PRA Health in 2016 has taken the sponsor-CRO strategic partnership to an unprecedented level of integration. Additionally, some of these businesses may serve as a platform for future pharma-CRO partnerships.

Selecting a CRO has become extremely critical to the success of an entire study. Current State of Sponsor-CRO Relationship

At present, sponsor-CRO relationships comprise a combination of tactical, preferred provider and strategic partner relationships. Again, according to the 2017 Nice Insight Preclinical and Clinical Contract Research Survey, being a preferred provider is the most common type of outsourcing relationship applied in 50% of emerging market projects; 25% are engaged with tactical service providers and strategic partners, respectively. For CROs, becoming a strategic partner is a gradual evolution from tactical contract research provider status. Overall, 62% of respondents agreed that a CRO that started off as a tactical service provider would become a preferred provider, and 68% felt it was highly likely that a preferred provider would become a strategic partner. Additionally, respondents showed a strong interest (84%) in establishing a strategic partnership with a CRO in the next 12-18 months.

Phases of development during which outsourcing partners are engaged

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The Rise of Emerging Markets

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New Manufacturing Paradigms in an Evolving Pharma Industry
Partnering in the Equipment Space Across Channels

The need for greater speed across all activities in the pharmaceutical industry not only impacts discovery and development of new drug candidates, but also the design, construction and validation of new facilities, and the upgrading of existing plants. Long-term strategic relationships between engineering/design firms and equipment suppliers are essential for accelerating this complex process.

New facilities must be flexible and incorporate state-of-the-art equipment that ensures increased efficiency with reduced downtime to achieve greater productivity. Increased use of automation to improve quality and enable continuous processing will lead to further manufacturing improvements. For instance, the concept of overall equipment effectiveness is rapidly gaining importance. Pharmaceutical companies and their engineering/design firm partners must be skilled at acquiring and integrating equipment. Next-generation manufacturing strategies are becoming imperative and are at least being considered by most pharmaceutical companies and implement by leading players.

From Old School to Right School

Like the pharmaceutical industry, relationships between pharmaceutical engineering/design firms and equipment suppliers have undergone significant change in recent years. The “old school” approach involved getting the most short-term “appeal” value for the customer from the supplier, with specifications so detailed that despite any changes in scope or other issues, the supplier would bear the cost, according to Robert L. Roy, P.E., Director, Aseptic Technology at Integrated Project Services, LLC. “This approach, however, ignored the need for pharma companies to maintain strong relationships with their suppliers for the life of the facility,” he says. The “millennial approach” features no relationship whatsoever with the supplier. Pharmaceutical equipment is treated like commodity items, with suppliers called to provide quotes. It also ignores the tremendous complexity associated with modern pharmaceutical production requirements, including the myriad equipment features required to produce product of adequate quality and those required to satisfy regulatory demands, according to Roy. “This approach only satisfies owners that don’t understand the industry, and only temporarily, because numerous issues typically arise during startup and transition to production that require administrative workarounds, loading to a less efficient and more expensive operation,” he explains.

The “right school” approach involves strong relationships between engineering/design firms and equipment suppliers, so that both can be engaged early on in the equipment design process. This approach is essential because, according to Roy, equipment suppliers work with many owners and in the process distill the best and most current pharmaceutical thinking in the world. “In order to purchase and install equipment with the ‘best available technology,’ a solid understanding of the various equipment features and approaches selected by owners is required. We need to know which features are truly ‘value added’ vs. those that are overly cumbersome or costly and thereby impede efficient, high-quality manufacturing. Only by having established relationships with equipment suppliers is it possible to gain this crucial information,” states Roy. There are some caveats, of course. Relationships between engineering firms and equipment suppliers must be cooperative and mutually respectful, states Carmine Stropoli, P.E., Director of Life Sciences Technologies with M+W Group. “Equipment suppliers need our investment and trust, and we need their equipment and trust. But beyond that, they need to nurture the cooperative relationship with the buyer, and we need available information and pricing for the development of our plans with customers. We also need to have insight on trends and their experience in the various installation applications of their equipment,” he observes.

Real Relationships Matter

Pharmaceutical facilities and processes tend to be highly integrated and customized, and therefore relationships between design firms and suppliers are quite important. In addition, “process equipment and technology are always evolving to align with the changing needs and requirements of pharma operations, methodologies and newer technologies. Having a cooperative relationship with suppliers expedites information sharing and an understanding of the supplier’s capability to meet the requirements of a project, including such items as containment, continuous processing, isolation technology, robotics, real-time quality control, serialization, disposables, etc.,” asserts Stropoli.

Indeed, strong, long-term relationships are now essential, according to Roy. “For example, based on an engineer’s familiarity with each suppliers’ strengths and weaknesses, when requested by an owner, the firm can recommend suppliers best suited for the job.” Furthermore, the pace of preparing proposals, pricing, facility layouts, utility requirements, etc., requires ready information on equipment offerings from suppliers, according to Stropoli. Having ongoing relationships with suppliers helps facilitate the flow of information.

There is a Right Time to Get Involved

Whatever the state of the facility, suppliers should only be contacted and involved when there is at least an idea of the performance requirements for the equipment, including any integration requirements, and how the equipment may be basically arranged. For example, according to Stropoli, “It is counterproductive to involve a supplier any sooner, but their eventual participation is valuable,” he adds. He also points out, “The earlier we are involved, the earlier, especially for newer applications, reinforces the cooperative relationship to help roadmap the path forward for the preparation of specifications and eventual purchase of equipment.

Keys to Successful Relationships

Early engagement when enough of the scope is defined to have productive discussions, and outlining the need and bidding process that will be undertaken to consider and evaluate the offerings of the supplier are essential for developing successful relationships. Design firms must also treat suppliers fairly and objectively. For instance, Roy notes that suppliers need reason-able turn-around times on quotations, and design firms must be mindful of supplier workloads and availability.

“The right supplier for the job is one you would ‘trust yourself,’” is his recommended approach. Suppliers should also not be used for check-price bids. They will quickly become aware of this tactic and the relationship will sour, according to Roy. From the design firm’s perspective, responsiveness is an essential supplier attribute. “We see responsiveness as part of these give-and-take relationships that when at their best can be mutually beneficial and a facility for both parties,” observes Roy. Stropoli adds that proposals should clearly address the items contained within the specifications relating to important services, testings, installation and scheduling.

Conclusion

Engineering/design firms and equipment suppliers alike are aware of the regulatory, pricing and competitive pressures facing their pharmaceutical industry customers. They are working closely with buyers, regulatory bodies and one another to develop solutions that will meet the needs for accelerated, efficient, safe and high-quality manufacture of the complex drug substance and drug products of the future.

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Increased use of automation to improve quality and enable continuous processing will lead to further manufacturing improvements. For instance, the concept of overall equipment effectiveness is rapidly gaining importance.
ACHIEVING A HIGH LEVEL OF CUSTOMER SERVICE THROUGH LEAN QUALITY MANAGEMENT

BY WARREN HORTON, AVARA PHARMACEUTICAL SERVICES

Providing customers with their order when they want it, at the right price and quantity, is only laying the foundation for excellent customer service. Mitigating risk through planning and rapidly responding to unexpected events are also essential. Teamwork and collaboration, both within a CDMO and with customers, combined with a lean quality management system, ensure the highest levels of customer service.

DEFINING A HIGH LEVEL OF CUSTOMER SERVICE

At the beginning of each new project, a CDMO works alongside its customer to set milestones that enable the customer to meet specific project timelines. To provide the highest level of customer service, the CDMO must be able to meet each of those milestones on time and to the expectations of the customer for quality, quantity and price. This requires the CDMO to have a thorough understanding of the project, its complexity and any inherent risks. The CDMO must also have the capability to develop a remediation plan to ideally eliminate, or otherwise reduce, those risks.

Projects do not often exactly follow the plan. To achieve a high level of customer service it is necessary to provide customers with what they expect, despite being faced with unexpected challenges. Whether the issue originates on the customer’s end or at the CDMO, having the ability to quickly resolve problems is paramount.

In this regard, flexibility is also essential. Market dynamics are fluid and situations often change. For instance, unexpected demand increases can occur. While a good problem to have, such increases require a contract manufacturing partner with flexible capacity to act as an extension of the customer and meet that need.

LEAN QUALITY MANAGEMENT IN THE PHARMA INDUSTRY

In recent years, cost pressures have continued to increase and evidenced-based and personalized medicine has begun to drive expectations for accelerated development of next-generation treatments, breakthrough therapies and orphan drugs. There has also been an increase in the number of 483s — citations for non-conformity/non-compliance with pharmaceutical regulations — issued by the US FDA.1

Consequently, drug manufacturers are seeking new approaches that facilitate drug development and manufacturing while maintaining high quality. Many have found that Six Sigma aligns well with the reduction of variability, a main goal of regulatory agencies.2 Lean manufacturing has also been introduced, with most efforts initially excluding quality programs for fear that quality performance would be reduced.3 Lean principles have since been applied to improve quality control and product quality, but these first initiatives kept quality programs separate from other company operations.

Manufacturers have realized, however, that incorporating quality into operational excellence programs leads to greater improvement. Such holistic, lean quality management platforms “strive for the ‘perfect’ end-to-end state, where value and responsiveness to the customer are maximized, and waste and delays are eradicated throughout the entire value chain.”4 Effective lean quality management systems enable pharmaceutical companies to balance operational efficiency with regulatory compliance, helping to ensure that quality programs and processes control and support, rather than constrain, drug development and manufacturing.

The results can be significant. Lean quality management systems that are validated to Good Manufacturing Practice guidelines and thus standardized, transparent (visual) and closely measured, when implemented by an experienced team, can lead to improved compliance, greater process and product quality and enhanced customer service.5

TRUST IS THE BASIS OF LEAN QUALITY MANAGEMENT

There are various elements to a lean quality management system, such as supplier, customer and regulatory audits, investigation of issues and thorough documentation, to name a few. Unlike these program components, however, the most important element — trust — is intangible. A customer must be able to trust that its CDMO partner will meet its expectations. To do so, the CDMO must have an effective team that can execute and manage its lean quality systems.

Such a team must be composed of highly experienced and qualified individuals. With multiple sites producing drug substances and drug products, Avara Pharmaceuticals has many people with different knowledge bases and areas of expertise creating a network of subject
matters. Rather than duplicate positions at each site, we capitalize on the passions and experiences of our people to support the various elements of our lean quality management system.

The team meets regularly and collaborates to develop a quality system that is consistent and effective across the entire Avara network. They also spend time in the quality control laboratories and on the production floor conducting visual management evaluations, not only as a management team but with company executives and customers, to look at all elements of the quality system. Such a dynamic approach and our striving for continuous improvement ensure that we not only meet our customers’ expectations and regulatory requirements, but that we continue to deliver the best results.

This consistent approach is also essential to facilitate trust building with our customers, who expect one quality system across our network. That includes one document system, one approach to investigating issues and one regulatory compliance approach at our API and finished-dosage manufacturing facilities.

MANAGING CULTURAL DIVERSITY AND RESISTANCE TO CHANGE

Bringing disparate sites together to form a new company can be challenging. Each facility has its own culture and legacy systems, including quality management initiatives. At Avara, we have taken great care to be sensitive to cultural differences while we collaborate to develop an effective global lean quality management system. Our experts across all of our different sites are not only willing to come together, but to listen and challenge each other to ensure real understanding of all possible approaches with the goal of identifying the most efficient and effective ways of working.

This network approach is also essential for overcoming resistance to change. Moving to new quality systems can be particularly difficult for people who have only worked at one facility and only have one experience with quality management. Creating an effective lean quality management system helps overcome this resistance to change. With sites that are new to the Avara network, existing procedures are employed initially and the site is gradually converted to our quality system. People with experience, skills and real passion are brought into the expert network to help with integration.

As an example, many sites have their own information technology systems – often locally modified versions of common software such as SAP, Empower and LabVantage – that must be migrated to Avara’s systems. In general, most pharmaceutical manufacturing sites are familiar with programs such as Empower, thus switching is a matter of upgrading from one version to another. It is more challenging to convert new sites that have mostly manual processes to Avara’s automated solution or to convert a documentation system to Avara’s customized module, because in these cases people must change the way they work. Helping make these changes is crucial to introducing leaner ways of thinking and working.

Again, honesty and openness are crucial. Communicating our expectations to people as quickly as possible helps them understand what is needed and also creates trust. People appreciate that we are genuinely interested in their opinions. We listen to all ideas and choose the best possible solutions. This approach also allows us to identify people that are passionate about quality and want to take an active role, so they can be incorporated into our expert community.

LOCAL TO GLOBAL APPROACH

Quality issues typically occur on the local level, but Avara takes a global approach to addressing them. When an issue or event occurs at one Avara facility, the problem is thoroughly investigated and resolved at the site, with the knowledge then applied across the Avara network.

This combined local and global approach guarantees that effective solutions are applied across the Avara network, even before issues can arise at other facilities.

THE GREATEST ASSET

Ultimately, we realize that what we do at Avara will impact the lives of people we will never know. We value employees with passion, drive and a desire to help implement a lean quality management system that allows us to revolutionize the industry by focusing on our people, our customers and the patients we ultimately serve.

As a result, we believe that our people are our greatest asset. We treat them fairly. We want them to be properly trained in all aspects of their job and informed and educated about the industry, as well as what Avara is doing. They, in turn, understand the importance of doing the right things right, every time, and the potential implications when they don’t. We have a high-quality standard, and our employees ensure that we maintain it. They recognize the importance of being partners with our clients and that by providing the highest possible approach to quality, we are in turn serving the patients that rely on the medicines we produce.

REFERENCES


ABOUT THE AUTHOR

Warren Horton
Executive Vice President Global Quality Assurance and Regulatory Affairs, Avara Pharmaceutical Services

Warren has 35 years of industry experience with a broad pharmaceutical background and extensive experience in manufacturing management, quality assurance, quality control and operational excellence. He joined Abbott Laboratories and the pharmaceutical industry in 1986 and has had successive levels of leadership and responsibility in manufacturing and quality assurance. Warren has experience in new plant start-ups, remediation of consent decrees and warning letters, quality system integration and data integrity remediation.

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EXPERIENCE A CDMO THAT DELIVERS ON ITS COMMITMENTS

Avara is a rapidly expanding CDMO led by some of the industry’s most experienced veterans. With five world-class facilities offering proven quality in APIs, liquid sterile and oral solid dose drug product, and packaging, we also bring flexibility and a seasoned understanding of how to optimize the customer experience. In fact, the Avara promise is a differentiating commitment to delivering on time, in full, and at a fair price.

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ORAL SOLID DOSE MANUFACTURING
EFFICIENCY IS DRIVING NEW ATTENTION TO PLANT DESIGN

WITOLD LEHMANN, CRB USA

Mapping out an effective, coherent, long-term manufacturing strategy is likely one of the more difficult tasks facing any drug owner or developer. For oral solid dose (OSD) drug manufacturers, the past 10-15 years have seen manufacturing strategies change drastically, with a focus on achieving more, with less. Advances in project management software usage, risk analysis, electronic data capture, containment, 3D, collaboration — and more — are driving strategic planning and efficient production.

TIME TO LEAD — EFFICIENT, TRANSPARENT, PAPERLESS

In light of increasing spending on technology and operations,1 manufacturing for greater efficiency has become a top priority for innovative firms. Operational transparency is essential to product quality and primarily comes from collecting operating data in the most accurate, timely fashion possible.

In order to achieve higher accuracy, the elimination of paper-based methods is a foreseeable goal. Although existing paper-based systems are often validated, they rely on the transcription of manually collected data, which is an increasingly risky strategy. The integration of electronic data collection and documentation — electronic batch records, for instance — within drug manufacturing operations has become a priority. Paperless manufacturing and inventory management systems are in fact quite effective in operation; properly qualified, electronic data capture and management systems can help minimize errors and rework. Digital records are also being integrated with business decision-making applications like SAP® to facilitate plant scheduling and other activities.

BENDING THE COST CURVE WITH BETTER AUTOMATION AND CONTROL

In oral solid dose manufacturing, material handling, mixing, blending, compression/tableting and primary and secondary delivery, as well as packaging, are standard operations. Greater process understanding, however, can lead to both increased efficiencies and improved product quality, and ultimately reduced costs. Manufacturers are, therefore, applying process analytical technology to these unit operations, particularly blending, drying and tableting. In process testing and/or monitoring provides real- or near-real-time data and gives operators more in-depth process knowledge, allowing for enhanced process control. Transparency into these processes is one way to achieve the flexibility and cost control manufacturers need.

As OSD formulations have grown more sophisticated, technologies to match these advances have been developed for the manufacture of these novel delivery systems. For example, manufacturers interested in formulating APIs into sublingual thin strips — or using spray drying to create APIs in particle forms suitable for inhalation materials — need access to specialized processing equipment, knowledge and skills. From coating and granulation to spray drying, direct compression and roller compaction, and on to fluid bed and hot-melt extrusion techniques, advanced OSD drug forms require advanced process understanding and control, especially if continuous processes are considered. Interest in these innovative delivery technologies is driven in part by their ability to provide improved solubility and bioavailability, affording greater efficacy while simultaneously reducing the quantity of API required.

Similarly, there is a focus on reducing physical material handling needs and improving process flow and ergonomics. For example, using different types of containers, such as intermediate bulk containers (IBCs) and flexible intermediate bulk containers, rather than drums, helps with improved process feed/receipt, containment and inventory control, and can reduce waste. The delivery of material right from the warehouse to the processing plant and deploying automatic storage retrieval systems are also beneficial. This is one area where engineering and design firms like CRB can have a significant impact. CRB has experience with systems that not only store in-process material, but also retrieve and mix different materials as needed. As everything is computerized and barcoded, it is possible for operators to know where everything is in real time. Importantly, these systems can be rapidly installed because they are based on avail-
At the beginning of each project, CRB uses 3D software to show clients different design options.

CONTAINMENT CONSIDERATIONS

Containing OSD pharmaceutical processes not only assures product quality. It is essential for ensuring operator and environmental safety, especially when manufacturing involves highly potent API formulations. Modular and integrable, flexible isolators and contemporary restricted access barrier containment systems are now replacing open processing operations that were housed in expensive, inflexible clean-room environments.

Equipment manufacturers are developing solutions — from balances to mixers, and blenders to tablet presses — that are designed for use in flexible modular containment systems to meet the growing demand for these capabilities. Where possible, of course, closed equipment and blenders transfer from the fluid bed and closed transfer to IBCs.

The most effective containment solutions, however, are only developed after a thorough risk analysis is performed. While containment is essential to protect workers and the environment from exposure to hazardous substances and to ensure sterility of drug products, there are many unit operations in OSD manufacturing that do not require complete containment. Efficient and cost-effective solutions ensure that the right level of containment is provided for each unit operation.

SOFTWARE FOR THE FUTURE... TODAY

Advances in software are making it possible for engineering and design firms to be identified and addressed early on. Our clients have access to this information, which is integrated across the entire project.

CRB also uses smart process and instrumentation diagrams that can be integrated with instrument data. This information, including instrument data and calibration requirements, for instance, is then accessible to the plant owner, operators and maintenance people.

At the beginning of each project, CRB uses 3D software to show clients different design options. With this software, a client can take a virtual tour of the proposed plant to visualize the equipment layouts, piping and duct work. In essence, the client has an opportunity to see how the facility is going to work before actually being constructed. This tool is very beneficial to both CRB's engineers and architects and the client, because often it can be difficult to visualize how things will actually flow and function when looking at a flat piece of paper. At CRB we are fortunate to have an extensive library of equipment data provided by many different equipment suppliers that we can incorporate into the 3D software.

For renovation projects, CRB also has partners that can laser scan the space to be modified, including the piping and equipment, and convert this data to drawings. Access to this information facilitates the evaluation of the existing space and the design process, saving clients both time and money, as well as assuring true actual conditions.

FLEXIBILITY FOR THE LONG Haul

More than just space to house equipment, the industry is investing in facilities that are designed comprehensively to promote operator safety, material flow, sustainable quality and cost control for all operations. At CRB, we look at the process first and then build around it, always remaining forward-looking. Our first step is to understand how the process is intended to function. Then we look at whether any hazardous materials or solvents are involved in order to consider containment and utility issues. When this approach is implemented correctly, with process engineers driving many decisions — after considering input from all the relevant disciplines — projecting the potential for expansion is built in. At CRB, therefore, we design cost-effective, manufacturing capability built to sustain efficient flexible operations over the long term.

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Witold has over 30 years of experience working as a process engineer focusing on pharmaceutical facilities design, related process equipment and supporting infrastructure. Prior to his work at CRB, he had over 11 years of experience in process and project engineering with Novartis Pharmaceuticals (formerly SANDOZ).

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REFERENCES

OPIOID ADDICTION DRIVING THE OVERDOSE EPIDEMIC
In the US, drug overdose is the leading cause of accidental death, more so than even car accidents. In 2015 alone, 20,301 overdose deaths were related to prescription drugs and 12,990 to heroin. In addition, four out of five new heroin users switched from abusing prescription opioids. However, the number of fatal overdoses due to “natural,” “semi-synthetic,” and “synthetic” opioids (morphine, oxycodone, methadone) is falling while the number of overdoses due to heroin is increasing dramatically (three-fold from 2010 to 2015).  

ABUSE-DETERRENT FORMULATIONS HAVING AN IMPACT
The decline in fatal overdoses due to prescription drugs can be attributed to efforts by the U.S. Food and Drug Administration (FDA) and the pharmaceutical industry to better educate physicians about appropriate prescribing practices and the development of advanced abuse-deterrent formulations of prescription opioids. Many commonly abused prescription drugs are opioid painkillers, including oxycodones, hydrocodone and oxymorphone. These drugs are abused or misused in order to obtain a desirable physiological or physical effect typically by manipulating solid dosage forms and chewing or crushing them into a fine powder, so they can be snorted through the nose or dissolved in water for injection. While there are no legal requirements for the development of abuse-deterrent formulations of opioids, this approach is a key element of FDA’s strategy to combat the problem. The agency issued a final guidance in April 2015 on the evaluation and labeling of abuse-deterrent opioids. The document provides information on how drug manufacturers can prove that a formulation has abuse-deterrent properties; through laboratory-based in vitro manipulation and extraction studies, pharmaco kinetic studies and clinical abuse potential studies. In May 2016, the agency issued draft guidance with details on conducting in vitro manipulation and extraction studies to demonstrate abuse-deterrent properties for generic solid oral opioid drug products.  

ABUSE-DETERRENT FORMULATION STRATEGIES
Prevention of the misuse of prescription drugs has been achieved using a variety of methods. One of the most common strategies is to formulate tablets with some sort of physical or chemical barrier, which makes it difficult to convert them into powder form or to extract the active pharmaceutical ingredient (API) using solvents. Another approach is to reduce the feeling of euphoria that is often a driver for the misuse of opioids. Antagonists — agents that block the desired properties of the drug when abused — can be added to formulations. Delivery systems can be used that prevent immediate release of large quantities of the API. Or the formulation may be designed to have aversive properties, such as to create a bitter taste or be toxic, when the product is abused. Formulations can also be designed to require exposure to the metabolic and/or digestive systems to become active. Alternatively, the API itself can be modified generating a new molecular entity or product to provide limited bioavailability if abused; these compounds typically require some type of biochemical reaction in order to be released. Various combinations of all of these strategies are often used, and other solutions are continually being developed. The first step in creating an abuse-deterrent formulation is the selection of the most appropriate strategy for the given drug. To do so requires consideration of the drug substance and its route of administration, as well as the potential ways in which the product might be abused. Once these aspects are considered, an approach to engineering an alternative formulation that discourages and prevents abuse can be developed.

DEMONSTRATING ABUSE DETERRENCE
In order to receive FDA approval as an abuse-deterrent formulation, drug manufacturers must demonstrate that a drug product does indeed possess abuse-deterrent properties.

In vitro manipulation and extraction studies The first step is to conduct scientifically rigorous laboratory-based in vitro manipulation and extraction studies to determine whether the abuse-deterrent strategy is effective, i.e., whether it can be defeated or compromised. These studies should consider, for instance, how an abuser can modify the drug to change the release behavior of the API and whether the API can be dissolved or extracted to bypass the deterrent properties. The types of physical manipulation studies chosen will be dictated by the likely types of extractability and solubility studies chosen will be dictated by the likely types of extractability and solubility studies. 

ABUSE DETERRENT FORMULATIONS CAN ACCELERATE APPROVAL
As the number of opioid prescriptions in the US has climbed dramatically, so has the abuse and misuse of these drugs, leading to loss of life and significant social costs. The pharmaceutical industry, in conjunction with FDA, has focused on identifying approaches for the development of abuse-deterrent opioid formulations and methods for demonstrating their effectiveness. Choosing the right strategy for a given drug can be difficult. Partnering with a contract development and manufacturing organization (CDMO) that has experience with different abuse-deterrent opioid formulation methods and established expertise in the development of in vitro abuse-deterrent studies can accelerate approval.
made with care. There may be immediate and extended release formulations and other abuse-deterrent formulations on the market — using the right comparators will not only enable demonstration of abuse-deterrence but possibly indicate improved performance against existing products.

Analytical testing is a crucial component of in vitro manipulation and extraction studies but can also be challenging. Many of the solvents required (e.g., methylene chloride, hexane or ethyl acetate) for extraction studies are incompatible with standard analytical quantitation methods such as reverse phase HPLC. This requires the need for secondary sample processing (evaporation/reconstitution, liquid-liquid extraction, etc.) to ensure accurate analyses. Positive controls must also be used to clearly demonstrate that the low recoveries are due to the abuse-deterrent strategy and not an issue with the analytical method of quantitation. If antagonists are used in a formulation, analysis of both the API and added agent is necessary. Particle size analysis using laser light-scattering or sieve techniques should be performed to fully characterize drugs that can be crushed and add to core(API). Particle size analysis is also a requirement for in vivo administration.

Clinical Abuse Potential Studies

The step next is to determine the abuse liability or abuse potential of the abuse-deterrent formulations through the performance of clinical and abuse potential studies, which are also referred to as human abuse potential studies, human abuse liability studies and “drug-liking” studies. These studies are designed to provide a greater understanding of the abuse-deterrent properties of formulations through determination of the relative abuse potential of a drug compared to others in the same class.

Post-market Studies

Once an abuse-deterrent opioid product is on the market, the manufacturer should make sure that the drug does indeed result in meaningful reductions in abuse, misuse and related adverse clinical outcomes, including addiction, overdose and death. Appropriate post-market studies must, therefore, be conducted to gather relevant data.

THE RIGHT OUTSOURCING PARTNER MATTERS

Opioid abuse, including the abuse of prescription drugs, has been identified by the U.S. Centers for Disease Control and Prevention as an epidemic. Although the pharmaceutical industry has been actively involved in responding to this serious public health problem, it is likely that more will be expected of drug manufacturers to address the issue going forward. The development of abuse-deterrent formulations and formulations that lessen the risk of addiction and overdose is one way in which pharmaceutical companies can help alleviate this crisis.

As abuse-deterrent formulations must be truly effective at reducing the potential for misuse and abuse, it is essential that robust in vitro manipulation and extraction studies are performed to ensure the abuse-deterrent properties of any new formulation. Taking this into consideration, there is no “one size fits all” approach to in vitro abuse deterrent studies, however. Experience with those studies using a wide range of dosage forms and deterrent strategies is essential to success.

Alcami is an experienced partner for performing in vitro abuse-deterrent studies. The Alcami Development Laboratories have designed and executed several successful in vitro abuse-deterrent studies for a variety of dosage forms and abuse-deterrent strategies for several different clients over the last five years. Experiments involving physical manipulation and extraction studies are some examples of abuse deterrent testing performed with data presented to the FDA to support abuse-deterrent claims. Alcami is committed to playing a key role in facilitating the formulation of prescription opioid drugs with reduced risk of abuse.

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9. Alcami is committed to playing a key role in facilitating the formulation of prescription opioid drugs with reduced risk of abuse.
THE ROAD TO BIO

A ONCE-IN-A-LIFETIME JOURNEY FROM BOSTON TO SAN DIEGO INSPIRES HISTORICAL, CULTURAL AND SCIENTIFIC DISCOVERIES — AND GARNERS A DEEPER UNDERSTANDING OF THE PEOPLE WHO HAVE FUELED IT ALL.

BY STEVE KUEHN, NICE INSIGHT

THE ROAD TO BIO 2017
The Road to BIO was a 12-day speed-to-market campaign culminating at the BIO International Convention in San Diego. A team of seven That’s Nice employees made the trek, with Nigel Walker, the agency’s Founder & Managing Director, at the helm of a 2017 Lamborghini Aventador Roadster SV. Along the way, the team stopped to speak with CDMOs, CROs, engineering firms and other innovators breaking ground in pharma and biopharma.

From the start, the Road to BIO was about breakthroughs — breaking through the cost, risk and regulatory pressures on the road to pharmaceutical and biopharmaceutical development. As an agency, That’s Nice has been there with clients through some of their biggest challenges and, equally, their greatest successes along the development pathway. In many ways, the Road to BIO was done in solidarity.

As the journey unfolded, it became evident that this was about more than drug development — it was about people. Whether it was a wide-eyed young cowboy at a Texas cookout or the CEO of BIO at the BIO International Convention, one thing we learned is this: everyone has a story.

EARLY DISCOVERIES IN THE NORTHEAST MEGALOPOLIS
Starting the journey at the epicenter of both American history and biotechnology, we hit the Road to BIO in Cambridge, Massachusetts, arriving in Boston Commons Park at sunrise. Too early for a ride in one of Boston’s famous swan boats, the park’s 19th century suspension bridge was the backdrop to our campaign’s inaugural meeting with Unither Pharmaceuticals’ David Kudla. A European leader in single-unit dose technologies, Unither established its North American presence in 2013, settling as many European pioneers did in Rochester, New York, a city whose rich manufacturing history dates back to the 18th century.

Across the Fort Point Channel in Boston’s Seaport “Innovation” District, a number of innovators were hard at work advancing future bio breakthroughs. Among them was M+W Group’s Peter Cramer, working to bring projects to the forefront of the “new pharma” reality with nanotech, bio-nano, cell therapy, and industrial biotechnologies.

A wrong turn and broken windshield wiper later, the Road to BIO was bound for Connecticut, arriving in Norwalk to a challenge we were grateful to have faced early on — our vehicle’s inability to scale the ramp to the parking lot of Avara Pharmaceuticals’ global headquarters. Speaking with Avara’s Bill Pasek, a 25-year industry veteran, we were reminded of the importance of navigating these types of pitfalls across the development pathway to deliver on our commitments.

From New York to Pennsylvania, our trip down the Northeast corridor was the most bio-heavy of the journey — save, perhaps, for the BIO International Convention itself. As the sun rose over New York’s Tappan Zee Bridges, currently under rapid reconstruction to meet the safety and demand of its over 10,000 daily commuters, BioVecra’s Oliver Technow shed some light on why building bridges for customers in their development efforts is so important — and the reasons were not dissimilar from those necessitating the rebuilding.
Safely over the bridge and through the verdant pasture land of New Jersey’s great Princeton area, we were greeted by En-vigo’s Joe Bedford with some sound advice on putting early development on the right road by meeting regulatory guidelines. Facing a minor run-in with ourselves with the local regulatory agency shortly thereafter, we were grateful for Bedford’s timely advice at this early stage of our journey.

Bristol, Pennsylvania, the site of Abzena’s award-winning CBO facility, was one of two cities on the Road to BIO where Abzena is expanding its global footprint, the second being its new biologics manufacturing facility in San Diego. After a discussion on ADCs with Sven Lee, it was on to Plymouth Meeting, where Matthew Kennedy and the CBG team are empowering customers to make smart manufacturing investment decisions with FutureFacility™ concepts.

FLAGGING CHEMICAL IMPURITIES — and consume plenty of barbeque in between — by the time we crossed the Texas border, we could not have been more excited to discover the breakthroughs underway in the Lone Star State.

SPÉEDWAY TO MARKET Fresh off our service in Virginia and well prepared from the circular traffic pattern of our nation’s capital, the Road to BIO quickly became the Race to BIO at the Bristol Motor Speedway in Bristol, Tennessee. Drawing the connection here was easy, we thought, as speed and precision are central to obtaining commercial success. But as UPM Pharmaceuticals’ James Gregory and Dr. Ed Scholtz reminded us, speed to market is not possible without a flexible, agile partner that can navigate the different directions a formulation development project can go while adhering to strict timelines.

CARRYING OUR “MOLECULE” THROUGH THE CAROLINAS Making our way from Tennessee to South Carolina on the scenic Blue Ridge Parkway, we realized that if there is one thing the Road to BIO has taught us, it’s that an endeavor of this scale would not be possible without a cohesive team powering our “molecule” toward the finish line. In this regard, drug development isn’t so different. As we learned from Alcam’s Natasha Howard in Charleston, part of the organization’s differentiating value lies in its ability to reduce timelines through the integration of teams and systems across the organization.

BIOETHIKAS While the city of Austin has emerged as Texas’ epicenter for biotech, we discovered plenty of innovation in progress outside of the state’s capital. Approximately 200 miles north in Irving, Dr. Donald Loveday described how Celanese is breaking barriers in bioavailability and compliance by combining innovative drug delivery technologies with EVA excipients. Down in College Station, G-CON Manufacturing’s Michael Katsis and Sidney Backstrom walked us through their manufacturing space, explaining how G-CON’s Cleanroom PODs® significantly reduce time and costs typically incurred during a construction project.

DUE WEST ON THE ROAD TO BIO The stretch from Alabama to Texas on Interstate 20 had us yearning for the days of the jam-packed meeting calendar on our journey through the northeast. Though we managed to take in plenty of sights amid the shifting landscape from east to west — and consume plenty of barbeque in between — by the time we crossed the Texas border, we could not have been more excited to discover the breakthroughs underway in the Lone Star State.

CALIFORNIA BY WAY OF TUCSON An organization usually involved in the earliest stages of the development journey was the penultimate stop on our tour. Broadcasting from Tucson’s Tucson site, Dr. Kenneth Wertman shared what it means to be a truly integrated partner in early discovery, employing interdiscipli- nary teams that have long-term, collabora- tive experience to execute successful discovery campaigns that set the stage for success further down the road. We may have met Dr. Wertman later in the game than is typical for the early discovery partner, but his words of wisdom could not have been more appropriate as we headed toward our final state line.

WELCOME TO BIO 2017 Recognizing that the road to drug discovery is a long one, Steven Ricks of Bio-Rad, our final visit on the Road to BIO, explained how Bio-Rad takes innovative technologies and creates workflows that enable developers to accelerate the process, while employing a system-wide approach that facilitates collaboration among teams. As we pulled into our booth at the BIO International Convention, we couldn’t help but think this was a most fitting end to a journey fueled by technology, executed by strategy and driven home by a team unified in its aspiration to reach a successful conclusion.

CAROLINA VISITORS — That’s Nice LLC PIT CREW | THAT’S NICE LLC

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Combining Content and Research

With over twenty years’ experience as a leading agency for life sciences, our aim has been to share insight across the industry, creating a community focused on quantitative research and the motivating, overarching trends behind them. To achieve this, we are merging Nice Insight’s proprietary research with our Pharma’s Almanac content forum. This new powerhouse site will serve as a unique content portal for the pharma-biotech industry with articles, news, blogs, videos and a wealth of statistics across the supply chain. The site will provide free access to industry-specific outsourcing research and will host an ongoing constructive dialogue around developments in R&D, formulation, process development, lead optimization, scale-up, processing and bioprocessing, finished dose and more.

With its extensive analysis of industry trends specific to significant and dynamic sectors of the industry, Pharma’s Almanac offers print and digital readers a fresh take on the very latest in the contract services industry, including how proven leaders are implementing new strategies. In order to elucidate the issues central to executive decision makers, we are primarily emphasizing the “leader” element of thought leadership. Our distinguished program delivers Subject Matter Expert advice to you directly.

The research enterprise of That’s Nice — Nice Insight — has grown significantly over the past seven years and now encompasses our core Nice Insight Research Services, as well as Pharma’s Almanac, which offers rich data-driven content.
The integration of the Pharma’s Almanac with Nice Insight was a clear next step, as both sites are powered by research. Nice Insight, the research arm of That’s Nice, was launched in 2010. Since then, there have been 23 proprietary annual surveys conducted, all of which target buyers of outsourced services, including research, drug substance, drug product, excipients and intermediates, equipment and logistics. The new Nice Insight portal offers free access to comparative buyer ratings of over 800 service providers across six service segments, as well as company profiles of 856 suppliers. This provides a unique online asset to both buyers and sellers of outsourcing services, including the leading market trends and buyer preferences across each of our six major market segments.

Getting Involved
Supplier company contributions to our ongoing dialogue have been compelling and insightful; we thank our community for sharing so many diverse aspects of the global supply chain. Among many things, we have learned that the pharma-biotech world continues to ask us all to come to the table with new ideas of every kind. From advances in targeted drug screening, chemical synthesis, continuous manufacturing, downstream processing, encapsulation technology, cold chain solutions or automated clinical trials and data management, to partnership-minded service, at-risk deal structuring, dedicated manufacturing capacity, accelerated analytical services and more, our diversified content is ever-expanding.

To make sure all are able to access this content, we have designed seven different custom access levels to promote high visibility among users of this unique platform.
Alcami is a world-class supplier of comprehensive pharmaceutical development and manufacturing services. With seven sites across the globe, Alcami’s combined capabilities include API development and manufacturing, solid-state chemistry, formulation development, analytical development and testing services. Alcami also provides packaging and stability services.

Avara Pharmaceutical Services was founded by a team of industry veterans who, through personal experience, understand both sides of the contract manufacturing market. A state-of-the-art contract development and manufacturing organization, Avara provides API and bulk drug formulation and manufacturing as well as primary and secondary packaging services for solid-dose drugs, including highly potent compounds. The company’s manufacturing technologies include granulation, coating, blending, encapsulation, compression and drying of tablets and capsules.

Marken maintains the leading position for direct-to-patient services and biological sample shipments, and offers a state-of-the-art GDP-compliant depot network and logistic hubs in 45 locations worldwide. Marken’s 683 staff members manage 50,000 drug and biological shipments every month at all temperature ranges in more than 150 countries. Additional services such as biological kit production, ancillary material sourcing, storage and distribution, and shipment lane qualifications — as well as GDP, regulatory and compliance consultancy — add to Marken’s unique position in the pharma and logistics industry.

Bushu Pharmaceuticals Ltd.

The Bushu Group currently operates three advanced GMP-manufacturing and development facilities specializing in drug product manufacturing and packaging, oral solid dosage and injectables, and the Spera Pharma facility, which encompasses R&D and clinical trial materials. Bushu Pharmaceuticals and Spera Pharma have built a capable proactive organization with a network of development and manufacturing facilities that are well positioned in Japan to serve the region and world markets.

For over 30 years, CRB has specialized in delivering high-quality biopharmaceutical facilities that are safe, reliable and sustainable. CRB provides services across the entire project life cycle, from conceptual design through preliminary and detailed design, construction, commissioning and validation. The company has more than 900 employees across 14 offices and hundreds of project locations around the world. CRB offers a range of services from packaging solutions, fit/finish design and aseptic processing to operations improvement solutions.

M+W Group is a leading global high-tech engineering and construction company with 6,000 employees in more than 30 countries, offering a full range of services from concept and design to turnkey solutions. Services offered by the company include consulting and planning, design and engineering, (pre-) construction and project management and service, maintenance and installation. Founded in 1992 and headquartered in Germany, M+W now has locations in over 30 countries worldwide.

Servier CDMO provides fully integrated manufacturing and supply chain services for small molecules and drug product, from development and clinical supply up to commercial launch. Servier CDMO includes a worldwide footprint with 11 state-of-the-art facilities, a proven track record in chemical synthesis, pharmaceutical formulation, development and manufacturing, and a complete range of services offering full flexibility. Services include process and analytical development, pilot production and industrial scale production, and regulatory dossier, in collaboration with the Servier network.

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Key to driving this success across multiple international locations are the partnerships we develop with internationally based clients and suppliers, where communication is critical to a successful project.

We also value international relationships inside our Intertek team encompassing globally located project teams and experts. In terms of our customer and supply base, we are increasingly supplying equipment or materials from international providers, engineering firms, equipment manufacturers, and other business partners making it possible to standardize concepts and simplify the set-up and implementation of global projects.

One key example for Recipharm is our global project in implementing the new regulatory requirements for product integrity and serialization. This is a large project, extending over 15 locations and including installations on close to 100 packing lines. Here we have chosen to run the project globally and work with single partners for machine equipment and software solutions. This has clearly helped to deliver project objectives and has made it possible to work both faster and in a more cost-efficient way. For example, when setting up a user requirement specification for machine equipment, only one standard document has been required, with just a few exceptions. The project is very clear for people working internally, but it has also shown benefits when presenting the project to customers. Serialization requires a lot of engagement with our customers and, by having a standardized approach, partnering with our suppliers, it makes the whole customer interface a lot more efficient.

For Polpharma Biologics, international partnerships are key to building up our own capacities in development and production, and to becoming visible within the contract development and production arena. In our industrial set-up, we are working with internationally recognized engineering companies, which not only have the knowledge to construct state-of-the-art and efficient production platforms, but are also aware of regulatory framework requirements. Our core target markets are EMA, FDA and PMDA regulated territories. With this knowledge, we are able to provide tailor-made solutions to fully satisfy the needs of the market and the regulators. Our presence is already a pan-European one, with subsidiaries in Poland, the Netherlands and Germany. We have established a global network for work on our global clinical trials programs that connects with potential codevelopment partners and with customers interested in our one-stop-shop offering: from cell line development through production of clinical trials material and large-scale production for drug substance, as well as formulation drug product.

We work in the service of the world's leading pharmaceutical companies, helping them to bring new and effective medicines to patients, and to develop innovative and safe products.

In order to constantly serve its clients better and meet their ever-evolving needs, SGS Clinical Research has set up R&D partnerships agreements with hospitals across Europe to enable access to relevant patient population and therapeutic expertise. Under these agreements, different pharmaceutical units are established within a hospital facility to conduct phase I clinical trials, which are undertaken by a permanent dedicated on-site SGS team. This team works in close collaboration with hospital physicians, trial experts and investigators to ensure solid patient recruitment capability and rapid subject enrollment, and maintain high-quality data collection and on-time study delivery. These partnerships are beneficial in keeping the “partner hospitals” at the cutting edge of applied R&D, enabling their staff to gain enough experience in early phase clinical trials, but most importantly, patients benefit by having access to new therapeutic solutions as early as possible.

A s a provider of medicines that are destined to over 100 coun-
tries around the world, it is clear we increasingly operate in a global pharmaceutical market. While drug development has been traditionally concentrated in North America and Europe, emerging markets have grown considerably, in particular, in the Asia-Pacific region, which not only have the knowledge and experience necessary to bring new and effective medicines to patients, and to develop innovative and safe products.

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Collaboration and partnership are key to business success, regardless of the industry. Companies pursue international strategic partnerships since they consider it will lead to synergy and, therefore, economic benefits. It is an important strategy that offers benefits without adding costs.

For example, in a partnership between a pharma company and a CRO, some of these benefits are:

- Reducing the number of suppliers, therefore being able to project long-term goals
- Offering a single Quality Management System that allows choosing any location worldwide, thus making a strategic choice and not only a financial choice
- Taking on routine work while the client directs their focus on new discovery, thus helping growth and managing expertise and resources cautiously

Strategic partnerships are rising at a high speed year after year. However, these partnerships differ, whether they are between partners with the same business models (e.g., two biotech companies) or different business models (e.g., a biotech company and a CRO). In the pharmaceutical industry, international partnerships are essential in fighting diseases and finding a faster way of getting drugs to market.

Fadia Gadar

Vice President Global Business Development, Life Sciences, SGS

Today’s challenges in the industry are as complex and daunting as ever. Perhaps it’s speed to market for a new product candidate, operations and quality management of an existing facility in the face of downward pressure on its cost of goods, implementation of first-in-kind technologies and approaches without a precedent of regulatory approval, or loss of skilled resources to the robust labor market and baby boomer retirement.

Whether it’s a long-term relationship with a core client, a strategic alliance with a trusted service provider or a turn-key engagement with a proven vendor, partnerships have frequently provided compelling, value-added solutions to the industry’s problem statements and associated project opportunities.

With partnerships come shared successes and risks, which begs the question of who makes a good partner. From experience, good partnerships are about alignment of core values and culture, a shared vision for the desired outcomes, an agreed-upon distribution of goods, implementation of line of sight scale-up and decisive action when necessary. Corporate partnership must be an extension of the strategic choice and not only a financial decision.

Charles Darwin may have said it best: “Those who learned to collaborate and improvise most effectively have prevailed.” Partnerships are more easily formed and can effectively multiply talent, versus adding capabilities through development or acquisition, making them critical to responding quickly to changing markets and efficiently delivering “best in class” customer solutions.

International Partnerships are of the utmost importance for Grifols Partnership, mainly because these partnerships offer us a global understanding of the CDMO market, which is where we are focused, and consequently help us to provide the best service or solution for any request.

Identifying the right provider, supplier or firm is a critical factor to success. It is equally important to take the time to understand what each partner wants from the partnership. All companies receive approaches from prospective partners, and while this can lead to a positive and mutually beneficial relationship, it is also important to be proactive and identify your own preferred partners. As Grifols Partnership operates mainly at the international level, working with international suppliers allows us to be more agile, and accelerate time-to-market especially regarding a regulatory standpoint. Partnerships also help us accomplish international quality accreditations.

Marga Villos

Business Development Manager, Grifols
GLITTERING INSIGHT FROM INSIDE THE INDUSTRY...

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