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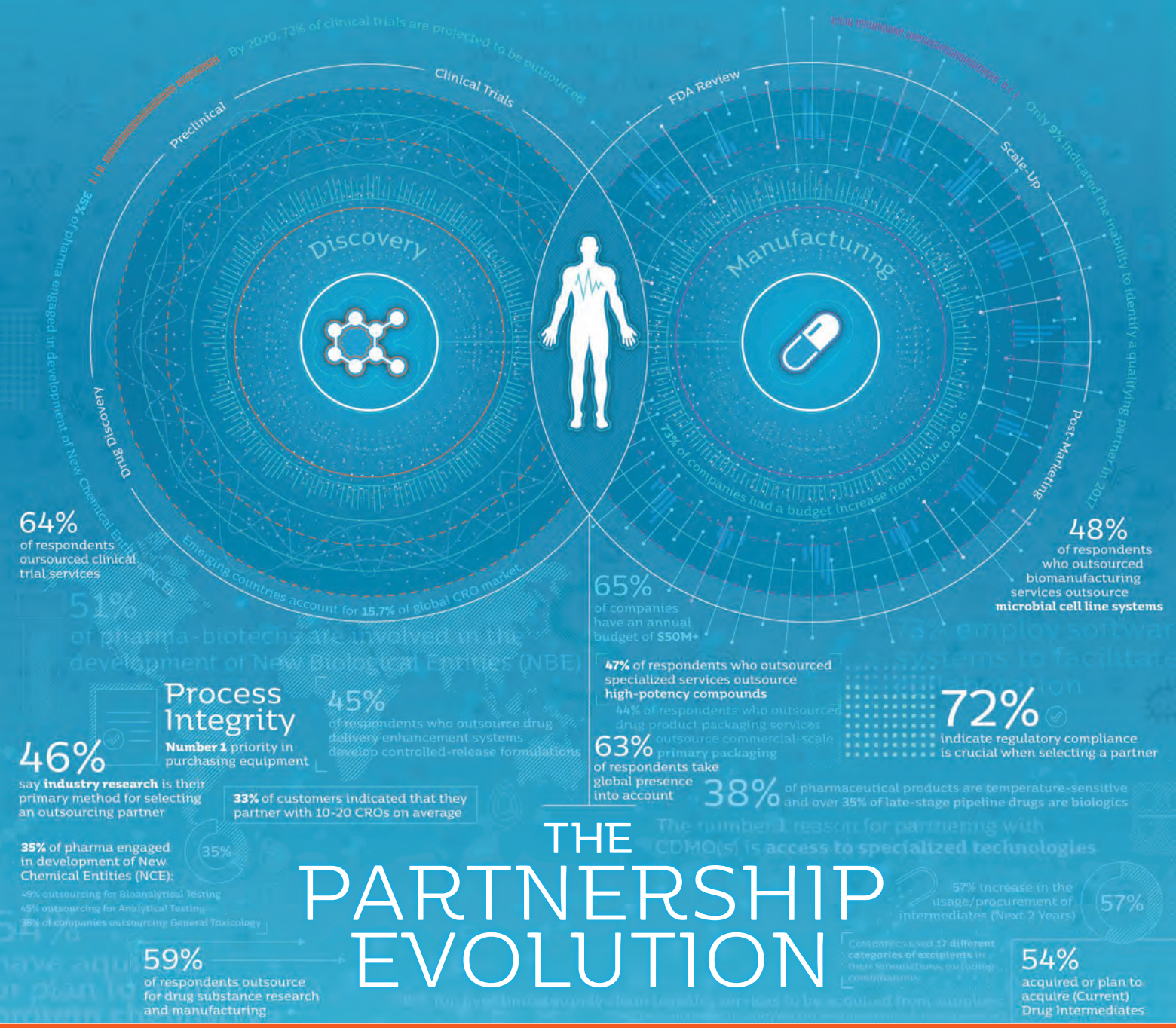
A NICE INSIGHT SUPPLEMENT

Q3 2017 EDITION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS

FUTURE PHARMA PARTNER MODELS



THE PARTNERSHIP EVOLUTION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS Q3 2017 EDITION

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→ A NOTE FROM THE EDITOR

A WORLD OF PARTNERSHIP

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

Like individuals, companies require strong relationships to thrive. This includes relationships with family (employees, 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 agility and technical expertise necessary to be competitive in the (bio)pharmaceutical 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.

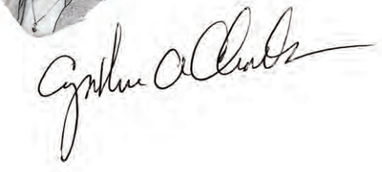
Consolidation within the pharmaceutical sector has an impact on relationships as well. There are fewer sponsors, and those that remain are looking to build strategic partnerships with contract service organizations that can support them throughout the increasingly complex and accelerated drug development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

Whether this is via *Pharma's Almanac* in print, www.PharmasAlmanac.com or the Trending Now e-newsletter, your voices are heard in Vienna, Zurich, Brussels, Gibraltar, Andorra, Rome, Kiev, Monaco, Baghdad, San Marino, Malta, Tokyo, Seoul, Kuala Lumpur, Dubai, Kathmandu, Bangkok, Taipei and many, many other places, as well as in all 50 of the United States.

Together, our reach is global, much like a robust supply chain must be. Please enjoy our 8th issue of Pharma's Almanac and join the conclusion with your family, friends and colleagues around the world. P



Pharma Contract Services Consolidation Wave Continues

Contract service providers to the (bio)pharmaceutical industry must help their customers speed the development of new drugs while reducing costs. **These new drugs are increasingly based on complex APIs, which can be challenging to formulate and often require global clinical trials.** To meet this demand, many CDMOs are gaining access to advanced technologies, expanding their breadth of capabilities and entering new geographic markets through the acquisition of other service providers.

Many Drivers for Consolidation

Deals involving contract service providers – 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 frequent 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;[1]**
+ **The contract services market is highly fragmented, with even the biggest players holding < 5% market share;[2]**
+ **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 converting themselves into contract development and manufacturing organizations (CDMOs). Others have extended their ability to support the full commercialization process with the addition of final drug product manufacturing 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 activities associated with clinical trials and/or analytical testing and build value.[3] 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.[4]

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. Larger contract service providers are in a good position to continue making purchases. Private equity firms are also looking to benefit from the healthy growth rate of the contract services market.[5] They are, in fact, facilitating a portion of the deals taking place.[2] 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 6-12 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 result directly in further consolidation of the CMO/CDMO space, the financial resources of these two PE firms, according to AMRI's President and CEO William Marth, "offer a compelling opportunity to accelerate our growth and enhance delivery of world-class solutions to our customers."[6]

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. Mullen has stated, he is "confident that our combined offerings and Thermo Fisher's proven track record of disciplined M&A and successful integrations will take our business to the next level."[7] The acquisition of Capsugel provides Lonza access to advanced capsule technology for addressing drug candidates with poor solubility.

There have been several big deals between CROs as well:

- **IMS Health acquired Quintiles Transnational;**
- **LabCorp acquired Covance;**
- **The Carlyle Group acquired Pharmaceutical Product Development (PPD);**
- **Huntingdon Life Sciences acquired Harlan Laboratories, now Envigo; and**
- **The merger of PRA and ReSearch Pharmaceutical Services (RPS) by KKR.**

The acquisitions of Quintiles and Covance were of a similar nature. In both cases the purchasers sought to benefit from access to patient data to improve efficiencies.

Activity in the CRO space, at least on the megadeal level, seems to have slowed recently. Only one possible deal was reported in the last several months: LabCorp was possibly negotiating for the purchase of PPD in February, 2017.[8] No further information has been forthcoming, however.

Don't Forget the Small and Medium Acquisitions

Megadeals get the headlines, but smaller, bolt-on acquisitions can ultimately have significant impact. For instance, AMRI, Patheon and LabCorp reached their current states only after the completion of multiple acquisitions: Euticals, Gadea Pharmaceuticals (Crystal Parma), Aptuit/SSCI, Cedarburg Hauser, Excelsyn, ComGenex, Hyaluron, OsoBio and Whitehouse Labs by AMRI; in addition to DSM Pharmaceutical Products, MOVA Pharmaceutical Corporation, Banner Pharmacaps, IRIX Pharmaceuticals, Agere Pharmaceuticals, Gallus BioPharmacetuicals and its Ferentino, Whitby and Cincinnati Operations by Patheon; and Esoterix, USLabs, Litholink, Tandem Laboratories, Monogram BioSciences, Orchid Cellmark, Genzyme's genetic testing business and Sequenom by LabCorp.

Smaller and medium-sized service providers are also busy acquiring their counterparts with technologies and capabilities in order to better serve customers developing niche products. In some cases clients prefer these smaller firms over bigger providers because they can be more responsive, are often easier to work with and their production equipment is on a scale more suited to small-volume products.[5]

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

- **Par Pharmaceuticals' acquisition of JHP Pharmaceuticals;**
- **Siegfried Group's acquisition of Hameln Pharma and BASF's API business;**
- **Consort Medical's acquisition of Aesica Pharmaceuticals Limited;**
- **Piramal Enterprises' purchase of Coldstream Laboratories and Ash Stevens;**
- **WuXi PharmaTech's acquisition of XenoBiotic Laboratories;**
- **Recipharm's acquisitions of Corvette Pharmaceutical Services Group, Mitim S.r.l., Nitin Lifesciences, a Flamel Technologies facility in France, Lusomedicamenta and Kemwell in the US, Sweden and India;**
- **Capsugel acquisitions of Bend Research and Powdersize;**
- **Catalent's acquisitions of R.P. Scherer Eberbach, Rethly Labs, Micron Technologies, PharmaPak Technologies, Aptuit's Clinical Trial Supplies business and Redwood Bioscience;**
- **Lonza's acquisitions of Vivante GMP Solutions, Genentech's Porrino operations, UCB Bioproducts, Cambrex's bio businesses, Xcelience and recently PharmaCell (for cell and gene therapy manufacturing in Europe);**
- **JSR Life Sciences' acquisitions of KBI Biopharma and very recently Selexis;**
- **Packaging Coordinators Inc.'s (PCI) acquisition of Penn Pharma;**
- **Fujifilm's acquisitions of Merck & Co. biopharmaceutical operations in the US and UK and Kalon Biotherapeutics, forming Fujifilm Diosynth Biotechnologies;**
- **PolyTherics' acquisition of Warwick Effect Polymers and Antitope to form Abzena, which then acquired PacificGMP and The Chemistry Research Solution;**
- **Brammer Biopharmaceuticals acquisition of Florida Biologix to form Brammer Bio, which then acquired a cell and gene therapy manufacturing plant from Biogen; and**
- **The acquisition by CDMO Frontida BioPharm, which was formed by CRO Frontage 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 pharmaceutical customer base with expansion into the CDMO market.

There have been, of course, numerous small and medium-sized CRO-CRO acquisitions as well. A few examples in this area include:

- **Charles River Laboratories' (CRL) acquisitions of Galapagos NV, Celsis, Oncotest GmbH and WIL Research;**
- **INC Research's acquisitions of the Global Clinical Development business of MDS Pharma and Kendle International;**
- **Quintiles' acquisition of Novella Clinical;**
- **InVentiv's acquisitions of PharmaNet and i3;**
- **Chiltern's acquisition of Theorem Clinical Research;**
- **Icon's acquisition of Aptive Solutions;**
- **Evans Analytical Group's (EAG) acquisition of Analytical Bio-Chemistry (ABC) Laboratories; and**
- **SGS's acquisition of Quality Compliance Laboratories.**

Partnerships Are Important Too

One of the drivers for consolidation in the contract services market is the growing preference among pharmaceutical companies to form longer-lasting, more strategic partnerships with fewer providers. Indeed, over the past four years, respondents to Nice Insight's CDMO[9] and CRO[10] surveys have indicated that the percentage of projects contracted to strategic providers has increased, while those contracted to tactical and preferred providers have remained nearly the same or declined. In addition, the total number of respondents interested or very interested in forming strategic partnerships with CDMOs and CROs has increased from 2015 to 2017.

M&A isn't the only mechanism for establishing differentiation. The way in which service providers are willing to work with their customers is also changing – creativity is an important aspect of all relationships. CDMOs are "finding new ways to deconstruct their value proposition and reassemble the elements into new offerings more tailored to individual client requirements," according to Jim Miller of PharmSource.[5] Examples include offering dedicated suites equipped with client-owned systems; operation by CDMOs of pharmaceutical 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 long-term strategic partnership in the CRO space is that between Covance and Sanofi, which was established when Covance acquired two of Sanofi's European sites in 2010.[11] Another is the strategic alliance between MedImmune and WuXi AppTec to support biologic R&D efforts for AstraZeneca in China.[11] AstraZeneca also has the option to acquire the WuXi AppTec facility. In a third case, Siena Biotech took a minority stake in Aptuit's Italian operations and made Aptuit a provider of choice for its drug development efforts.[11]

Close collaborations between strategic partners can, in fact, lead to acquisitions. Catalent, for instance, acquired Redwood Bioscience after working with the company for approximately two 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-add.[12] 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.[1]

What Does It All Mean for the Pharma Industry?

The consolidation that has occurred to date has certainly changed the contract services market. Service providers that offer an integrated set of capabilities to support pharmaceutical clients regardless of their therapeutic targets, development needs, formulation and production requirements and intended markets can help their customers not only simplify their supply chains, but also benefit from economies of scale and gain access to differentiating technologies.[13]

Indeed, the fact that service providers are employing advanced, state-of-the-art technologies that in the past would likely have been kept in-house at pharmaceutical companies (and left unused) is increasing the level of innovation across the entire pharmaceutical industry.[13] 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 Catalent.[12] The rise of creative partnerships and collaborations has been another result, if indirectly, of consolidation that ultimately facilitates innovation and accelerated drug development and commercialization.

Consolidation is expected to continue at a heightened pace as the drivers outlined above remain in play. Some providers will continue to grow and transform, while others are consumed or exit the market. Private equity investors will continue to play a role as they seek to leverage their investments. The result: a market that 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. P

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

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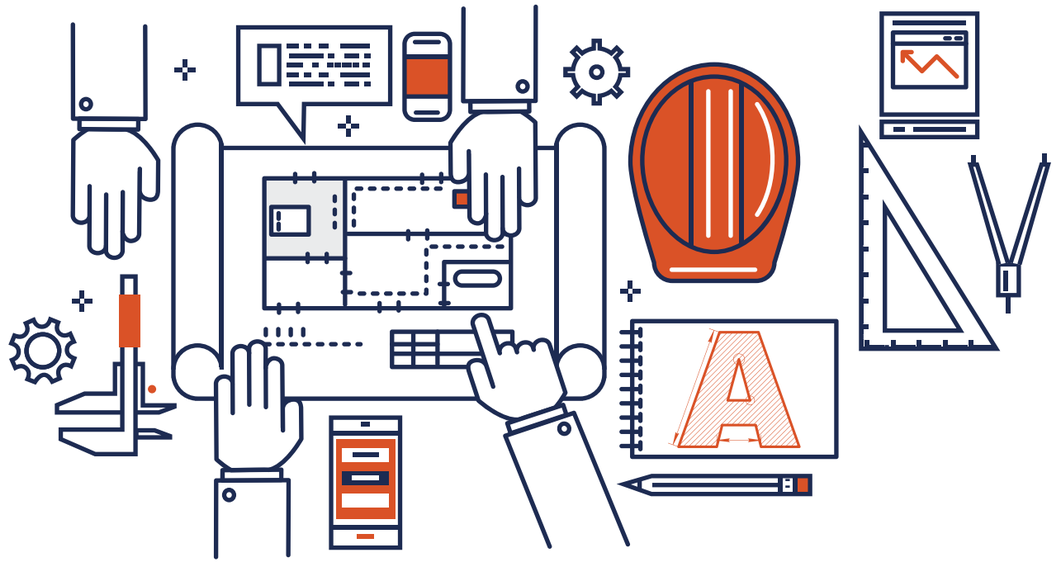
SYSTEMS INTEGRATORS AND TECHNOLOGISTS

EVOLVING ROLE OF THE PROCESS ARCHITECT

→ BY **PETER CRAMER**, M+W GROUP

Evolution 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.



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.

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.

IMPORTANTLY, **MODULAR SOLUTIONS** ARE BEING DEVELOPED FOR ALL ASPECTS OF LIFE SCIENCES MANUFACTURING.

THE MOVE TO MODULAR AND SKIDDED SYSTEMS

Equipment suppliers have responded to the evolving needs of the pharmaceutical industry with the development of flexible and compact modular solutions. No longer is it necessary to build from scratch; pre-engineered modular systems ranging from cleanrooms with complete air-handling systems to integrated single-use process skids are now available for most of the components making up a biopharmaceutical production facility.

There are many good reasons why a project delivery strategy will want to take advantage of today's modular offerings. Suppliers of modular systems are highly experienced and have the specialized expertise required to design and build their high-performance solutions. Modular suppliers are also able to control the cost and quality of the system they produce at their manufacturing site, which reduces the risks of work slowdowns due to labor issues or inclement weather at the construction site, while improving quality through construction in a controlled environment. At the project site, congestion is significantly reduced when fewer trades are needed to install the modular building systems, pipe racks and process super-skids. It is also important not to overlook the fact that most vendors today offering modular systems provide the in-house design capabilities that give them the ability to tailor their product in certain ways to meet project-specific requirements. It is up to the process architect to understand the range of flexibility a modular system vendor may offer, and demonstrate the additional value realized from integrating the solution into the overall design of the facility.

Modular solutions 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 delivery 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 are designed for ease of installation and use should be integrated into the process layout whenever possible.

EXPANDING HORIZONS

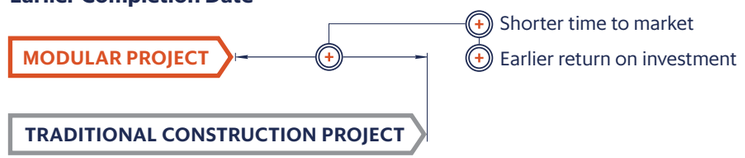
The constant introduction of new, innovative modular manufacturing solutions is creating significant opportunities for process architects to contribute their skills in ways that will have major impacts on the duration and cost of future manufacturing facilities. In fact, the term "process architect" may no longer adequately describe the role 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



Same Completion Date with Later Start Date

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.

Importantly, 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 process systems 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.

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**.

Modular Penthouse Solution

The benefits of employing modular solutions are clearly demonstrated in a recent project completed by M+W for a client building a drug development facility in Boston.

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 mechanical systems. In particular, there were height limitations and no penthouse. The company also had a budget limit, which had been exceeded by the proposed solutions under evaluation.

M+W Group, with its knowledge of modular penthouse systems for heating, ventilation and air conditioning (HVAC) systems (boilers, chillers and all control systems), was able to deliver a proposal that involved location of the central utility functions on the roof of the building. The systems were delivered and installed within a couple of weeks, rather than the 4-6 months required for building a traditional penthouse. The project schedule was also significantly reduced, allowing the company to begin critical research 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 having 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 such 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 most also be 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 system 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 are able to work in a small team 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.

PROVIDING THE BEST SOLUTION COST EFFECTIVELY

At M+W Group, the focus is on taking the very best solutions that the market has to offer and applying them in the most cost-effective manner for our clients. That means gaining as much knowledge as possible about what solutions are available, and applying them using a client-driven and client-focused approach based on technology integration. This approach is market driven; in today's competitive landscape, it is necessary to clearly define roles and goals in order to meet our

Technology Integration Group (TIG)

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 match a specific process output.

The TIG can be leveraged to produce and refine repeatable designs that lower overall engineering costs. It focuses on planning activities that use pre-engineered solutions where price, schedule and capacity can be defined earlier in the process. TIG platform designs are scalable and provide early feedback on overall project cost and schedule. TIG prototype designs are aimed at demonstrating the advantages of modular delivery method over conventional construction techniques that do not leverage what today's market has to offer.

clients' expectations. With our focus on the big picture from the start of a project, it is possible to identify fundamental, basic 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 solutions; 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. P

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Peter Cramer, AIA, NCARB, LEED AP, is VP Life Science Facility Design at M+W Group with more than 25 years of industry-leading experience in preparing conceptual and basis of design documents for pharmaceutical and biologics clients. He is a leader in designing cGMP-manufacturing facilities for clients around the globe. A facility design subject matter expert and contributing member to ISPE, Peter is a thought leader who specializes in the planning and design of facilities using disposable-single-use and modular technologies.

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MANAGING THE COMPLEXITY OF GLOBAL CLINICAL LOGISTICS FOR NEXT-GENERATION PERSONALIZED MEDICINES

BY **WES WHEELER** AND **ARIETTE VAN STRIEN**, MARKEN

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 (bio)pharmaceutical industry. The evolution towards evidence and value-based medicine, coming after a focus on blockbusters, 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 2000, 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. 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.

Continually Expanding Services

At Marken, we manage the largest portfolio of active DTP trials in the industry, including global trials with more than 15,000 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 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 regulatory requirements. In June 2017, we launched our DTP White Book Industry Guide, a client resource that provides clear logistics standards for DTP trials.

THERE ARE MANY BENEFITS TO DTP TRIALS, INCLUDING **IMPROVED PATIENT RETENTION AND INCREASED COMPLIANCE WITH PROTOCOLS**.[6]

PATIENT-CENTRICITY AND DIRECT-TO-PATIENT (DTP) SERVICES

The shift to patient-centric trials is perhaps one of the most significant developments impacting the nature of clinical trials. With access to a plethora of information at their fingertips, patients are more highly educated about their diseases than ever before.[5] They better understand the risks of trials and want, even expect, to actively participate in the determination of their treatment regimes and the clinical trials process.[6] The increasing demand for DTP delivery is a key consequence of this. With DTP trials, patients can receive treatment and have blood samples drawn and prepared for shipment at their homes, requiring the delivery of drugs and the pickup of laboratory samples.

There are many benefits to DTP trials, including improved patient retention and increased compliance with protocols.[6] This approach is particularly valuable for trials involving orphan drugs, indications for patients that are dependent on a legal representative or family members (certain CNS and oncology indications), pediatric trials and trials involving next-generation personalized medicines.

While it is challenging to map the supply chain and established delivery times for multiple materials from multiple patients in many different locations, doing so is essential to the success of the clinical trial. To meet these complex and continually evolving delivery needs, drug manufacturers are partnering with logistics providers that have the necessary knowledge, experience and supporting technologies to ensure risk minimization and secure delivery.

DE-RISKING CLINICAL TRIAL SERVICES WITH A PERSONAL TOUCH

Supply Chain Logistic 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 personalized clinical trial logistics services, including highly secure standard, specialty and hybrid services. Marken has been successful for more than 35 years by focusing on the evolving nature of the

BIOLOGIC SAMPLES AND DRUG PRODUCTS BOTH ARE BIO-HAZARDOUS MATERIALS **REQUIRING SPECIAL HANDLING UNDER CRYOGENIC CONDITIONS.**

pharmaceutical industry, developing and implementing innovative solutions that anticipate the changing needs of our clients. Our systems are designed specifically to reduce the risks associated with clinical materials supply and biological sample shipments, facilitate regulatory compliance, increase supply chain efficiency and productivity, and reduce costs. Our ability to innovate for the clinical trial industry results from the fact that we only serve pharmaceutical and life sciences clients, working strategically with our clients and all other external partners to identify unmet needs before they occur.

Marken's specialty logistics services include biological sample shipments. With a state-of-the-art GMP-compliant depot network and logistic hubs for clinical trial material storage and distribution in 46 locations worldwide, we manage 50,000 drug and biological shipments every month – at all temperature ranges – in more than 150 countries.

In May 2017, we introduced our new hybrid logistics service that leverages our position as the clinical subsidiary of UPS and the first company to offer both specialty and integrator services to ensure seamless integration, superior visibility and dedicated customer care. This hybrid service utilizes the global transportation network, including its expansive airline, to reduce the reliance on commercial aircraft for improved quality and value.

Marken's hybrid offering extends to its reverse logistics service for the efficient return of reusable packaging and tracking devices.

All standard, specialty and hybrid services from Marken are supported by cloud-based shipment tracking, from booking through delivery, via the use of 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.[6]

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 services 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. P

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ABOUT THE AUTHORS

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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 Glaxo (now 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 baccalaureate of modern languages and biological sciences.

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→ **REVIEWED**

NEW BRAND POSITIONING FOR **MARKEN**

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 life sciences industry, and that its offering has only grown stronger with the backing of a worldwide logistics leader.

→ **WWW.MARKEN.COM**

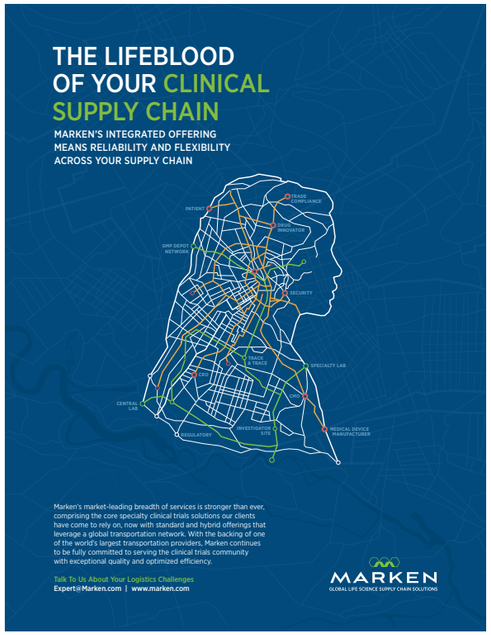
→ **FULLY LAUNCHING AT CPHI WORLDWIDE 2017**

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



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.

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.

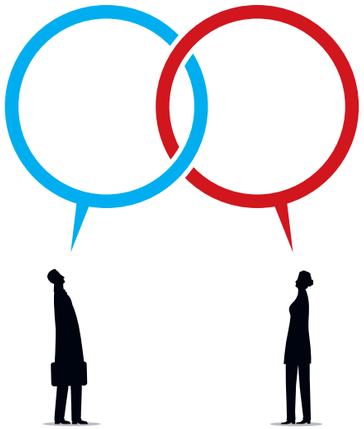
THE REVEAL

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. P

IN CONVERSATION

MERGERS & ACQUISITIONS: COMBINING MARKET SEGMENTS

→ BY **GUY TIENE,** NICE INSIGHT



NICE INSIGHT IS IN CONVERSATION WITH DAGO CACERES, MARKETING DIRECTOR, AND GARY LORD, GLOBAL STRATEGIC MARKETING DIRECTOR AT THE DOW CHEMICAL COMPANY, TO DISCUSS THE DRIVERS OF THE MERGER BETWEEN DOW AND DOW CORNING, AND THE POSITIVE IMPACT THE MOVE WILL HAVE ON DOW'S PHARMA CUSTOMERS.

In December 2015, The Dow Chemical Company announced that it would restructure the ownership of Dow Corning, which has shared ownership with Corning for more than seven decades. Dow became the 100% owner of Dow Corning on June 1, 2016, and has since been leveraging the synergies of its complementary silicone technology.

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 Lord 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 is 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 POWER OF TWO

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 Solutions 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, resourcing those that "have a sustainable impact for our customers, us and, of course, patients and consumers."

ABOUT THE PANELISTS

Dago Caceres
Marketing Director, Dow Pharma & Medical

Dago is the Global Marketing Director for the Pharmaceutical market of Dow Food, Pharma & Medical, the business unit of Dow responsible for the commercialization of all Dow and Dow Corning technologies and expertise focused on solutions serving the pharmaceutical, medical device and food manufacturing markets. In this role, Dago is in charge of developing and implementing the global pharma strategy for the business to achieve sustainable, long-term growth.

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Gary Lord
Global Strategic Marketing Director, Dow Corning

Gary's career with Dow Corning spans more than 25 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 1990 after working for BASF in Strasbourg. He currently manages all healthcare marketing strategies for Dow Corning's silicone-based solutions across the healthcare value chain.

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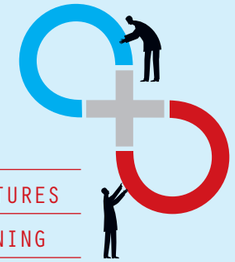

DOW RESTRUCTURES DOW CORNING

Until the recent restructuring and merger into The Dow Chemical Company, Dow Corning was a 50:50 joint venture between Dow and Corning Incorporated. In fact, the joint venture lasted for 73 years.

Today, Dow Corning operates as a wholly owned subsidiary of Dow and is headquartered with Dow in Midland, Michigan. Dow Corning has been integrated into Dow's existing operations, allowing the companies to benefit from the synergies and growth opportunities created by their joining together. Overall Dow anticipates capturing at least $400 million per year in cost and growth synergies.

"Dow Corning's world-leading silicone position brings complementary new chemistry and technology to Dow, with it being a hand-in-glove, strategic fit for our material sciences portfolio. As an owner of Dow Corning for more than seven decades, our deep understanding of the common and adjacent markets we serve will enable us to go narrower and deeper into high growth businesses where innovation is rewarded with value," said Andrew N. Liveris, Dow's Chairman and Chief Executive Officer. "By linking our two robust innovation engines, we will bring greater value to our shareholders and a wider range of differentiated, high value solutions to our customers."

Added Howard Ungerleider, Dow Vice Chairman and Chief Financial Officer and now Chairman of Dow Corning: "Dow Corning is a new element for growth for Dow. Bringing together these two industry-leading companies will drive exciting opportunities for our customers worldwide via more comprehensive product offerings, access to new technologies, and expanded R&D power to help quickly commercialize innovations."

With the added growth has come the potential for geographic expansion. "In certain regions, Dow has 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. P

BUILDING THE FOUNDATION OF JAPAN'S PREMIER CDMO

→ BY **JUN YOKOHAMA**, BUSHU PHARMACEUTICALS LTD. AND **TOSHIO YOSHIOKA**, SPERA PHARMA, INC.

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 2.8%.[1] 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.[1]

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.[2] 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 chemistry, manufacture and control (CMC) 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, including 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 R&D 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 Kawagoe, which specializes in drug product manufacturing and packaging, and Misato, which is focused on both oral solid dosage and injectables. The third facility is Spera's operation in Juso (Yodogawa-ku, Osaka city), which encompasses R&D and clinical trial materials. The combination of these facilities now propels the Bushu Group to its "Number One" CDMO status.

BRINGING EXPERIENCE SUPPLYING FINISHED GOODS TO MORE THAN 40 COUNTRIES, **BUSHU HELPS ITS CUSTOMERS OVERCOME CULTURAL AND OTHER BARRIERS TO ENTRY**.

Bushu Group **Manufacturing Facilities**

Kawagoe Plant

Originally constructed by Sandoz Yakuhin, forerunner of the present Novartis Pharma, the facility's design reflected western best practices when it was built. Branching off from a roughly 180m-long central corridor are interconnected buildings for manufacturing, packaging, warehousing, engineering/maintenance and QC testing. There is also a separate pharmaceutical laboratory for testing. The plant site covers approximately 65,000 square meters, with a total floor area of approximately 38,000 square meters, with plenty of scope for future expansion.

Misato Plant

Constructed by Eisai Ltd., the facility encompasses approximately 173,000 square meters of manufacturing space. This space is divided into a plant area for manufacturing pharmaceuticals and welfare facilities (including a gymnasium and playing field). The total floor space is approximately 57,000 square meters, and consists of a solid dosage production building, an injectables building, a warehouse building and QC area. Bushu operates much of its large-scale manufacturing here, with solid dose manufacturing capacity approximately twice that of the Kawagoe Plant.

Spera Facility

Located in Osaka, the Takeda Pharmaceutical Company, Ltd plant has a total floor space of 45,863 square meters in nine buildings and warehouse areas. The space is mainly for API manufacturing (process development and GMP manufacturing), formulation development and CTM manufacturing (solid dosage and injectable), packaging development, analytical development and QC area.

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 their Quality System further to adapt to other major pharma clients.

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 manufacture 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. P

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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 not passed on during cell division. It is effectively achieved using plasmid DNA, but high-purity and high-quality siRNAs, miRNAs, mRNAs and even proteins 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.[1] 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.[2] 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/infectivity due to the higher fragility and complexity of these megadalton molecules.[3] Transient transfection does present challenges for large-scale manufacturing where several factors can impact the process performance and product quality, including cell viability and density, the quality of the plasmid DNA, media and/or supplements, transfection reagent, and the cell line that is utilized in production. Different buffer systems and downstream purification methods are required. Product segregation, cleaning, changeover and line clearance are also essential and facilitated using well-designed facilities and procedures.

It is also worth mentioning that accelerated development under FDA's Fast Track and Breakthrough Therapy designations and Accelerated Approval program adds further challenges to the development of commercial viral vector manufacturing processes, given that timelines are significantly shorter.[4] In these cases, it is effective to initially develop a scalable process that will provide high-quality product and be practical and cost-effective to implement in compliance with current Good Manufacturing Practice (cGMP) guidelines at the intended commercial scale. While process changes may not be avoidable during scale-up, evaluating potential impact from raw materials, equipment and manipulations needed for transient transfection at larger volumes can significantly mitigate risks of scale-up and reduce time to the clinical and ultimately commercialization.

Transient transfection methods that utilize calcium phosphate ($CaPO^4$), cationic lipids or polyethylenimine (PEI) to deliver the DNA can be utilized in adherent or suspension culture. Identifying 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 m^2 of cell growth surface area, allows for transient transfection 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 (in-process materials before Drug Substance) typically are unstable, and the final vector product potency/infectivity may decrease significantly with increased processing 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.

FIGURE 1 The new iCELLis 500 bioreactor from Pall can in many cases overcome the need to scale-out plasticware processes due to its larger capacity. **PHOTO COURTESY OF PALL LIFE SCIENCES**

CHOOSING ADHERENT OR SUSPENSION CULTURE

As mentioned above, transient transfection can be achieved via either suspension or adherent cell culture. Suspension cell culture is typically performed in stirred tank or wave bioreactors, with which the biopharma industry has extensive experience. Approaches for scaling these processes present unique challenges (sourcing plasmid DNA that is suitable as a raw material for cGMP manufacturing, mixing times, cell density) to transition from development to clinical and commercial production.

Adherent cell culture, except when microcarrier beads are employed, requires 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 layers 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 to 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.[5] 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

using their legacy platforms due to financial or time constraints. Wherever possible, 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/baculovirus[6] or stable mammalian producer cell lines for vector production is also an area of expertise for Brammer Bio, and these plaforms 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 to transition 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 material and commercial quantities.

In January 2017, Brammer Bio acquired a 69,000-sq.-ft. manufacturing facility and nearby 49,000-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. P

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Dr. Snyder was the founder of Florida Biologix, which was spun out of the University of Florida in 2015 and merged to create Brammer Bio. Dr. Snyder has been investigating virus biology, vector development, cGMP manufacturing and analytical technologies, and viral vector–mediated gene transfer for over 30 years. Dr. Snyder received his doctoral degree in microbiology from The State University of New York at Stony Brook, and obtained his BA in biology from Washington University in St. Louis.

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RUSSIAN PHARMA MARKET OFFERS GREAT POTENTIAL FOR LOCAL MANUFACTURERS

→ BY **RENAUD BESSIÈRE**, SERVIER

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 $20.91 billion in 2016 and expanding at a compound annual growth rate of 13% to reach $38.56 billion by 2021.[1]

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.[2]

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 (ZHNVLP) 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.[3]

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.[3]

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 substation policy. In the last phase (2018-2020), the emphasis will be on increasing exports.[3]

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 ZHNVLP 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.[3]

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.

SERVIER OFFERS HIGH-QUALITY PRODUCTION GROUNDED IN 10 YEARS OF LOCAL OPERATION, COMBINED WITH THE DECADES OF EXPERIENCE AND KNOW-HOW OF THE INTERNATIONALLY RECOGNIZED SERVIER GROUP.

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.

Sevier 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 10% 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/or 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 tableting 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 10 years, and in that time has received only favorable reviews from Russian authorities (the 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 10 years of local operation, combined with the decades of experience and know-how of the internationally recognized Servier Group.

For the last three years, Sevier 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. P

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An engineer by background, **Renaud** has worked for more than 10 years in FMCG companies in Europe in managerial positions. He joined Gidy 10 years ago as Production Manager, before moving on as the Production Unit Manager for liquids and dry forms. Renaud has been responsible for the Serdix 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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THE PARTNERSHIP EVOLUTION

54% have aquired or plan to aquire protein chemistry

59% of respondents outsource for drug substance research and manufacturing

63% of respondents take global presence into account

The number 1 reason for partnering with CDMO(s) is **access to specialized technologies**

Sustaining Growth with Collaboration Worldwide

A well-thought-out and structured partnership can bring a sponsor organization both strength and agility. Whether with a CDMO, CRO, engineering & design firm or an equipment supplier, an ideal relationship must be defined to be successful. The importance of forging international relationships across the supply chain is evident from discovery to development, on to commercialization and through to packaging. Global presence is not only a factor for companies looking to partner, it can be *the* defining factor — especially as the industry's universe narrows. This issue's feature highlights how these types of organizations are creating bridges around the world and becoming ever more interdependent.

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The CDMO and the International Supply Chain

How Global and Local Relationships Are Guiding Sponsors and Providers

As 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; firms must consider international regulations, socio-political or economic conflict, and costs and benefits, and always be forward looking – taking a nation's growth, as well as the potential for social discord, into consideration. As CDMOs become more than just tactical service providers, edging ever closer into strategic partnership 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) have not always benefited 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 indicated that they outsourced to a tactical service provider, with 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."[1]

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 it or break it for CDMOs, 63% of respondents stressed that they take the organization's global presence into account when selecting an organization to work with.[1] 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 a competitor. "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.[2] 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.[2]

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 the Nice Insight CDMO Outsourcing Survey shows a positive correlation for CDMOs in emerging regions over the last few years.[1] 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 69% in 2016; it currently rests at 62%, which is still almost 20 points higher than it was three years ago. The number of trustworthy CDMOs in these 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 2017.[1]

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 market providers, 23% outsourced projects to the US and Canada, 14% outsourced 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 partnerships.[1]

Regulatory Concerns in Emerging Markets

Among those who did not wish to expand into foreign, emerging markets with partners, the top fear indicated was over 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 licensing and safety may not 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 19% indicated this was a fear in 2014. This number grew to 26% in 2015, and now rests at 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.[1]

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 Joachim 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 the pressure on CDMOs to remain ahead of the curve. "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, (bio-) pharmaceutical companies may have difficulty entering markets that are regulated by these authorities," he added.[3]

It's true; this is where the adage to "think global but act local" is applicable to CDMOs especially. A compliance officer that can 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 sanctions, and also as a way for Russia to assert self-sufficiency from a global standpoint.[4] However, that 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 serving the nation (including ZAO Servier, Serdix and EGIS).[5]

A Golden Regulatory Standard

We are far from having one set of regulatory standards dictate compliance on a worldwide scale; however, there are ethics codes that can be considered a step towards unification. For instance, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) code of practice is a set of ethical requirements and operations that must be upheld by all. In this code, the top priority is patients, followed by adherence. As the world shrinks and the supply chain grows, the need for a central, guiding system has become more apparent. Whether this manifests as a central patient database applied to clinical trial data or as a sole compliance standard that leaves little room for safety risks, unifying the pharmaceutical landscape should always be focused on the patient. P

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Building Strategic Sponsor-CRO Partnerships

The International Element Changing Clinical Trials

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 $59.42 billion by 2020 at a compound annual growth rate (CAGR) of 9.8% from 2015 to 2020, according to Zion Market Research.[1] Valued at $34 billion in 2014, clinical trial services accounted for over 70% of the market value; services for phase II to IV trials generated 60% revenue. By 2020, 72% of clinical trials are projected to be outsourced.[2] 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 (47%), followed by phase I (42%), pre-clinical (37%) and phase IV/post-launch (22%) in 2017.[3] Geographically, North America and Europe represent the two largest regional CRO markets, holding a 43% and 40% global share, respectively.[4] In addition, the clientele for CROs have expanded from traditional pharma, biotech and medical device industries to government institutions, foundations and universities.

The global CRO market is led by a number of large CROs (e.g., Covance, Quintiles, Parexel), which capture over 50% of market share.[5] CROs are under the constant pressure to expand their service portfolio and geographical presence. To meet this challenge, mergers & acquisitions, strategic alliances and joint ventures have become the norm in the CRO industry. In recent years, going public has become another strategy to achieve growth.[1] As a result, large CROs become larger with full-service capabilities and extensive global reach. Smaller CROs try to differentiate by focusing on niche area specialization or functional services such as bioanalytics, eClinical solutions and HEOR (health economics and outcomes research).[6]

> Selecting a CRO has become extremely critical to the success of an entire study.

The Rise of Emerging Markets

Currently, emerging countries account for 15.7% of the global CRO market.[2] Most of the worldwide population lives in emerging market countries and several of these countries have a rapid 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.[2] 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 pharma industry has been cautious in terms of engaging emerging market CROs. According to the Nice Insight 2017 Preclinical and Clinical Contract Research Survey, the willingness to consider emerging market CROs varies among different pharma/biotech sectors with big pharma/biotech showing the highest consideration rate of 62%, followed by small (54%), mid-sized (51%), 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 constitutes other major barriers.[3]

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.[5] Other features include the ease in patient enrollment, a skilled scientific research and healthcare working force, and government incentive programs (i.e., tax exemptions).[1] Consequently, more large-scale multi-site clinical trials have been conducted in these regions.

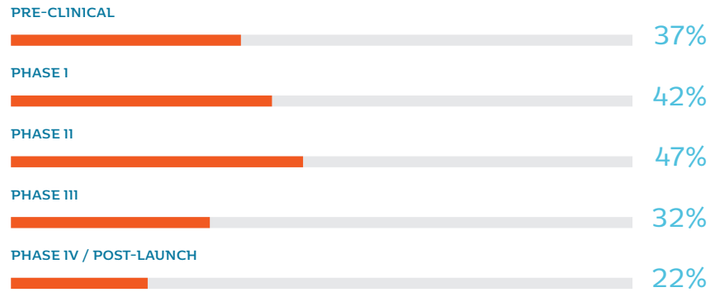
Globalization of Clinical Trials

One approach to improve clinical study efficiency has been to conduct trials in developing countries. As a result, clinical trials have been shifting 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 America/the 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.[7]

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 Pfizer's partnerships with Icon and Parexel as their strategic providers of clinical-trial implementation services in June 2010 and May 2011, respectively.[8] A recent alliance between Takeda and PRA Health in 2016 has taken the sponsor-CRO strategic partnership to an unprecedented level of integration of the two businesses, which may serve as a platform for future pharma-CRO partnerships.[9]

To meet sponsors' needs to conduct clinical trials efficiently within a tight timeline and deliver high-quality data, CROs are forming preferred provider relationships with investigation sites, investigator networks and site management organizations (SMOs).[10,11] The healthy working relationship between CROs and the sites can eventually translate into better enrollment forecasting, faster study startup, improved protocol and data quality. Parexel's Global Site Alliance Network and INC's Catalyst program are two examples of this proactive approach for nurturing CRO-investigator relationships.[10,11]

Phases of development during which outsourcing partners are engaged



Phase III is the most popular phase for outsourcing services, followed by phase I and pre-clinical phase.

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 outsourced projects; 25% are contracted to tactical service providers and strategic partners, respectively. For CROs, becoming a strategic partner is a gradual evolvement from tactical service 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 strong interest (84%) in establishing a strategic partnership with a CRO in the next 12-18 months.[3]

Key Elements for a Successful Strategic Partnership

A successful strategic partnership is mutually beneficial, requiring commitment from both parties to work together as a united team with integrated goals, structure and processes.[12] This partnership must be built upon a shared vision, as well as mutual trust and respect. It is important to clarify expectations, responsibilities, commitments and investments for each party at the very beginning of the partnership. Additionally, a governance structure is fundamental for communication, collaboration, escalation and risk management that enables the sponsor and CRO to function as an integrated team. Another key element for a successful strategic partnership lies in effective, open communication that promotes a high degree of cross-organizational transparency and information sharing. P

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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.

Relationships between Engineering Firms and Equipment Suppliers

Major trends in the pharmaceutical industry, from the growing emphasis on evidence- and value-based medicine and patient-centric drug development to the increasing focus on niche and personalized therapies rather than blockbusters, are driving significant change. Heightened M&A activity, a concentration of core capabilities accompanied by increased outsourcing and a drive to accelerate the development and commercialization of safe and cost-effective drugs are all part of the new normal for pharmaceutical manufacturers.

Engineering/design firms have been affected as well. Successful firms have deepened their expertise by adding key personnel with direct manufacturing/engineering experience in the pharma industry and often act as consultants, providing strategic advice.[1] Most have also developed new approaches that facilitate facility/process design, construction and validation through streamlining of activities. Examples include implementation of effective computer-integrated engineering systems[1] and collaboration with equipment and other suppliers.

New facilities must be flexible and incorporate state-of-the-art equipment that ensures increased efficiency with reduced downtime to achieve greater productivity.[2] Increased use of automation to improve quality and enable continuous processing will lead to further manufacturing improvements.[3] For instance, the concept of overall equipment effectiveness is rapidly gaining importance.[4] Pharmaceutical companies and their engineering/design firm partners must be skilled at acquiring and integrating equipment.[5] Next-generation manufacturing strategies are becoming imperative and are at least being considered by most pharmaceutical companies and implemented by leading players.[2]

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 "apparent" 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 start-up and transition to production that require administrative workarounds, leading 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 a continuing relationship with the buyer, and we need available information and pricing for the development of our plans and budgets, their useful 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 complex and customized, and therefore relationships between design firms and suppliers are quite important. In addition, "process equipment and technologies continually evolve to align with the changing needs and requirements of pharma operations, methodologies and newer drug administration devices. 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 somewhat symbiotic, according to Roy. "For example, based on an engineering firm'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.

Increased use of automation to improve quality and enable continuous processing will lead to further manufacturing improvements.[3] For instance, the concept of overall equipment effectiveness is rapidly gaining importance.[4]

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 within a facility, according to Stropoli. "It is counterproductive to involve a supplier any sooner, but their eventual participation is valuable," he adds. He also points out that involving suppliers in the early stages, 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 reasonable turn-around times on quotations, and design firms must be mindful of supplier workloads and availability. "Treat the suppliers like you would treat 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 highly productive and worthwhile for both parties," observes Roy. Stropoli adds that proposals should clearly address the items contained within the specifications relative to performance requirements, testing, 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 substances and drug products of the future. P

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ACHIEVING A HIGH LEVEL OF CUSTOMER SERVICE THROUGH LEAN QUALITY MANAGEMENT

→ BY **WARREN HORTON**, AVARA PHARMACEUTICAL SERVICES

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.

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 programs without impacting process 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."[3] 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.[1]

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

matter experts. 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 jobs 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 level of customer service we are in turn serving the patients that rely on the medicines we produce. P

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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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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.

able technologies. CRB customers are also implementing direct blend and tablet compression systems, in which the main ingredients are fed directly through gravimetric feeders into an in-line blender and on to a tablet press.

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 mixer, 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 closed transfer are much preferred. Equipment manufacturers are also continually introducing improved systems to meet these needs. For example, high-shear granulating machines now include drying capabilities, allowing two processing steps to be completed in one contained piece of equipment without having to transfer or expose material to the environment. Once dry, the material can be transferred into a blender and then to a tablet press.

Engineering and design firms like CRB, often design customized containment solutions. For instance, we had a request from a customer looking to perform Wurster coating of one-millimeter sugar spheres containing an API with a tri-coating needed for a controlled-release formulation. CRBs engineers designed a containment system that included the fluid bed, vacuum 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 provide their clients with enhanced services. CRB, for example, uses project management software to carefully track time and effort, allowing any potential scope creep 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 P

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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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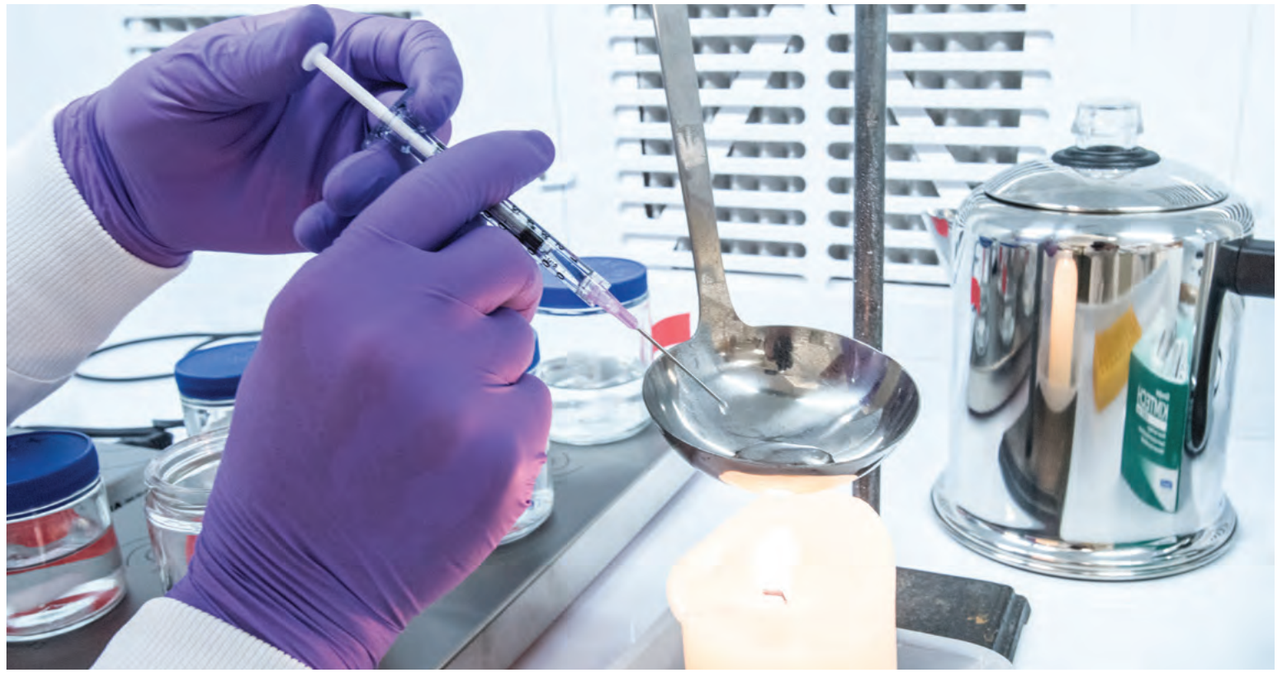
FIGHTING PRESCRIPTION DRUG ABUSE WITH DEMONSTRATED ABUSE-DETERRENT FORMULATIONS

→ BY **ANGELA MOORE, M.Sc., SCIENTIST**, ALCAMI CORPORATION



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.

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, 20,101 overdose deaths were related to prescription drugs and 12,990 to heroin.[1] In addition, four out of five new heroin users switched from abusing prescription opioids.[2] 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).[3]

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. The most commonly abused prescription drugs are opioid painkillers, including oxycodone, 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 opioid drugs, this approach is a key element of FDA's strategy to combat the problem.[4] The agency issued a final guidance in April 2015 on the evaluation and labeling of abuse-deterrent opioids.[5] 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, pharmacokinetic 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.[6]

MANY DIFFERENT 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 can 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 ideally 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 and realistic methods that can be used to abuse the drug product. The physicochemical properties of the API and excipients used in the formulation should dictate the types of extractability and solubility studies to be performed. An awareness of the sophisticated techniques employed by recreational abusers is necessary in order to include all reasonable approaches. The choice of valid comparators must also be

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 testing using laser light-scattering or sieve techniques should be performed to fully characterize drugs that can be crushed or inhaled. For drugs that can be injected, their behavior in syringes should be investigated along with extraction of API in small volumes of injectable solvents.

Clinical Pharmacokinetic Studies

Clinical pharmacokinetic studies involve comparison of the pharmacokinetic (pk) profiles of the manipulated formulations investigated during the *in vitro* studies with the intact abuse-deterrent formulation. The goal is to understand the *in vivo* properties of the abuse-deterrent formulation. Prior to executing pk studies, it is crucial to thoroughly evaluate the *in vitro* manipulation characteristic to avoid having to repeat studies. In these pk studies, the behaviors of the manipulated and abuse-deterrent formulations can also be compared to those of the selected comparator drugs using at least one route of administration.

Clinical Abuse Potential Studies

The next step is to determine the abuse liability or abuse potential of the abuse-deterrent formulations through the performance of clinical 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.[7] 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 these 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 determination with particle size analysis, syringeability and small-volume extraction studies, and large-volume multi-solvent 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. P

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Scientist, Alcami Corporation

Angela Moore is a scientist at Alcami with over 11 years of experience performing analytical testing in the pharmaceutical industry for both branded and generic products and their active pharmaceutical ingredients. She has considerable experience successfully executing Category 1 *in vitro* abuse-deterrent studies. Angela holds a masters of science degree and bachelor of science degree in chemistry.

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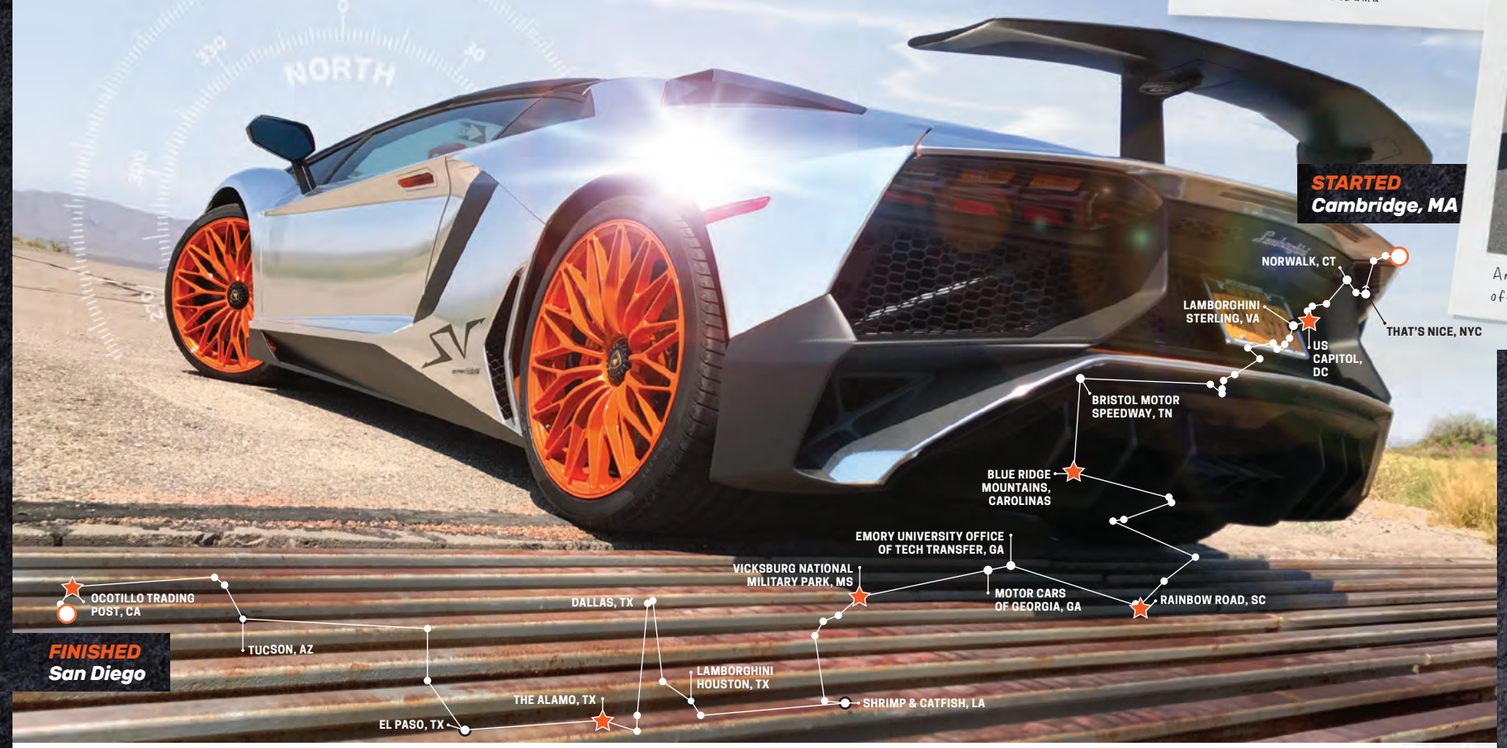
THE ROAD TO BIO

Barber Vintage Motorsport Museum, Leeds, Alabama

Road to BIO Team

On I-90 to Boston

An Army convoy travels from one base to another off I-81 South in Virginia.



THE ROAD TO BIO CHALLENGE — COMPLETE

- **4,746** Miles Driven
- **100** Hours of Driving
- **33** Gas Stations Visited
- **418** Gallons of Gas Purchased
- **19** State Lines Crossed
- **0** Speeding Tickets Issued
- **0** Flat Tires Changed
- **114°** Highest Thermometer Reading
- **UNDISCLOSED** Highest Speedometer Reading
- **19** Number of Sponsor Interviews
- **0.25** Hours Spent Driving in the Rain
- **9** Average Hours Driven Per Day
- **396** Average Miles Driven Per Day

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

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, bionano, 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 Bridge, currently under rapid reconstruction to meet the safety and demand of its over 10,000 daily commuters, BioVectra'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 rebuild.

Visiting Celanese in Irving, Texas

Unither interview set-up in Cambridge, Massachusetts

Overhead in Bristol, Tennessee

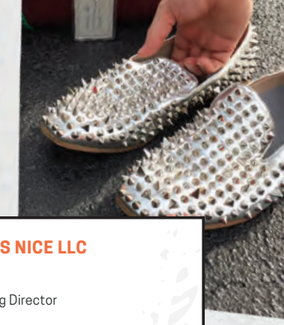
Broadcasting from Atlanta, Georgia, Todd Sherer, Ph.D., explained how Emory University's Office of Technology Transfer is driving promising therapeutics to patients.

Vicksburg, Mississippi

Roadside Dinosaurs, Arizona

Ocotillo, California

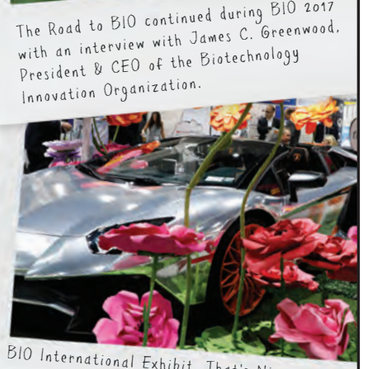
Little Miss Patriotic, El Paso, Texas



Dutch yoga instructor in Houston, Texas

Moms with their young sons in Willcox, Arizona

The Road to BIO continued during BIO 2017 with an interview with James C. Greenwood, President & CEO of the Biotechnology Innovation Organization.



BIO International Exhibit, That's Nice

The Divide Volunteer Fire Department in Mountain Home, Texas, welcomed us with generosity (and generous portions) at a charity cookout.

Safely over the bridge and through the verdant pasture land of New Jersey's greater Princeton area, we were greeted by Envigo's Joe Bedford with some sound advice on putting early development on the right road by meeting regulatory guidelines. Facing a minor run-in 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 CRO 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 CRB team are empowering customers to make smart manufacturing investment decisions with FutureFacility™ concepts.

FLAGGING CHEMICAL IMPURITIES

After circumnavigating the streets of Washington, DC, home to the Biotechnology Innovation Organization (BIO), we made our first pit stop in Sterling, Virginia, where the concept of safety and speed were not lost on Dave, our service technician at Lamborghini Sterling. Detecting micro-particles of metal in the vehicle's fluids, Dave had us safely back on the Road to BIO in just over two hours, a job that under normal circumstances should have taken eight.

SPEEDWAY 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 Alcami'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.

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.

BIOTECHXAS

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.

CALIFORNIA BY WAY OF TUCSON

An organization usually involved in the earliest stages of the development journey was the penultimate stop on ours. Broadcasting from Icagen's Tucson site, Dr. Kenneth Wertman shared what it means to be a truly integrated partner in early discovery, employing interdisciplinary teams that have long-term, collaborative 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 Blakely 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. P

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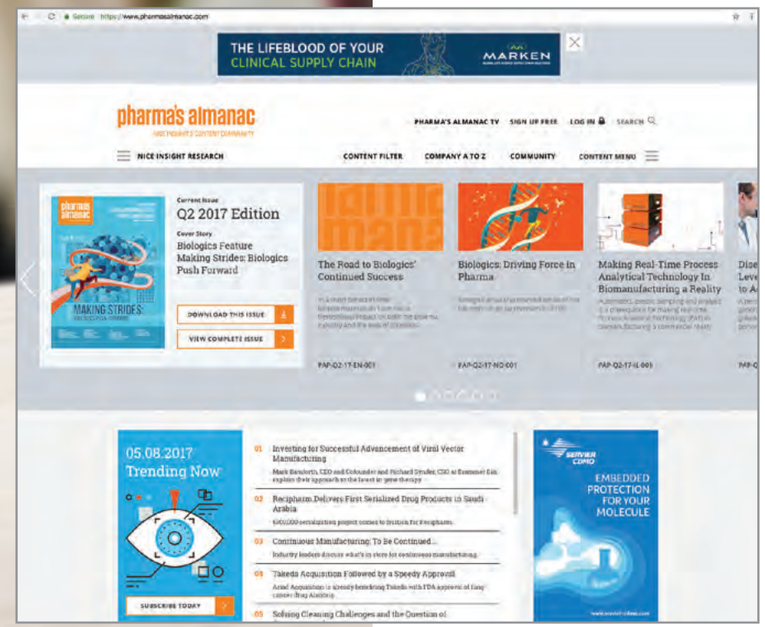

Insightful Integration

Combining Content and Research **in a Single Website Platform**

BY **EMILIE BRANCH** AND **KSHITIJ (TJ) LADAGE**, NICE INSIGHT WWW.PHARMASALMANAC.COM

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.**

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.

Nice Insight **Market Data**

www.niceinsight.com

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.

Nice Insight Market Segments Include

1. Preclinical and Clinical Contract Research Organizations
2. Contract Development & Manufacturing Organizations
3. Pharmaceutical Excipients Suppliers
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+ 146 original pieces of content published and posted per quarter.
+ 165 authors, contributors and commentators from a range of specialty service providers to date.
+ Printed quarterly, Pharma's Almanac includes a combination of 26 original articles, features, roundtables, reports and interviews, distributed to 20,000 industry readers.
+ Over 100,000 industry readers in total.

Stretching the limits of content in our heavily technical realm, and building a viable content enterprise, our editorial guidelines are simple:

+ Be informative and fact-based.
+ Speak from experience and knowledge.
+ Address current needs and advances in the industry.

COMPANY PROFILES

Nice Insight and the Pharma's Almanac editorial team would like to thank all the companies participating in this quarter's edition. The following are the profiles of the industry-leading companies that have appeared in this issue. These are companies that make it their business to energize pharma's increasingly complex supply chain, and pursue excellence every day in support of the industry's overall quality, health and safety goals.

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, clinical and commercial finished dosage-form manufacturing (oral solid dose and parenteral), packaging and stability services.

www.alcaminow.com
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2320 Scientific Park Drive
Wilmington, NC 28405

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.

www.avara.com
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Marken maintains the leading position for direct-to-patient services and biological sample shipments, and offers a state-of-the-art GMP-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.

www.marken.com
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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 1912 and headquartered in Germany, M+W now has locations in over 30 countries worldwide.

www.mwgroup.net
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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.

www.servier-cmo.com
+33 1 55 72 60 00
50 Rue Carnot
92284 Suresnes, France

Brammer Biopharmaceuticals LLC is a contract development and manufacturing organization dedicated to cell and gene therapy. The company specializes in in-depth biologics manufacturing, which enables large pharma and biotech clients to accelerate the delivery of novel medicines. Founded by Mark Bamforth (CEO) and Steven Kasok (CFO), previously cofounders of Gallus Biopharmaceuticals, the company is positioned to accelerate the development of these emerging technologies. Brammer Biologics is building a facility in Lexington, MA.

www.brammerbio.com
+1 386 418 8199
45 Hartwell Avenue
Lexington, MA 02421

The Bushu Group currently operates three advanced cGMP 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.

www.bushu-seiyaku.co.jp
+81 49 233 4651
1 Takeno, Kawagoe-shi, Saitama,
Japan

For over 30 years, **CRB** has specialized in delivering high-quality bioprocess 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, fill/finish design and aseptic processing to operations improvement solutions.

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SSCI, now a division of Albany Molecular Research, Inc.

INTERNATIONAL PARTNERSHIPS

How important are international partnerships (with sponsor firms, service providers, engineering firms, equipment vendors, raw material suppliers, etc.) to your success?

Success in international markets is fundamental to the progression and growth of our pharmaceutical business. This demographic is driven by the geography of the market itself, in terms of current global pharmaceutical consumption and predicted regional growth, as well as the regulatory requirement for regional testing to support global and local product registration.

Key to driving this success across multiple international locations are the partnerships we develop with internationally based clients and sponsors, 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 solutions to global clients and sourcing equipment or materials from international partners as we look for innovative approaches to meet the growing analytical challenges and increasing regulatory requirements that are encountered by our clients who are developing evermore complex products.

Ashleigh Wake
Director of Biological Services, Intertek Pharmaceutical Services

Ever-increasing pressure on healthcare cost, a prevalent patent cliff, disharmonization of regulatory systems, increasing insolubility of new APIs, growing importance of generic and emerging market trends, etc. — the pharmaceutical industry is facing a variety of major challenges. We at BASF acknowledge the responsibility, which the pharmaceutical industry holds in curing and keeping a growing and aging population healthy. Therefore, working together across value chain steps and company borders gains more and more importance to develop reliable, sustainable and risk-mitigated solutions in a cost-effective and fast way. BASF has a long and successful history of actively partnering across company borders. An example is BASF's multi-level cooperation with Catalent. On the one hand, in the field of omega-3 fatty acid, Catalent offers custom encapsulation of the purest, high-quality molecules with best-in-class oxidation stability. On the other hand, the development of new, more effective and patient-compliant dosage forms for pharmaceutical and nutritional use is part of joint developments. BASF helps to develop solutions that support Catalent's goals to bring high-performance, cutting-edge products cost-efficiently to the market. International and domestic partnership will remain more than ever a key to the success of this industry.

Kai Sievert
Director Global Marketing, BASF Pharma Solutions

Working with an aim to foster strong partnerships with suppliers, service providers and other business parties makes 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.

Erik Haeffler
Vice President, Manufacturing Services, Head of CSR, Recipharm

International partnerships and collaborations are certainly critical for the success of Almac. Our customers are worldwide, with our business more or less evenly split between Europe, North America and Asia. Our suppliers are worldwide also. As an example, we are managing a diverse biocatalysis business that uses enzymes developed at Almac to produce multi-tons of chiral building blocks, complex advanced intermediates and APIs. These projects require both a supply of raw materials delivered to Ireland and REACH compliance. We have built an audited and reliable network of partners throughout continental Europe and in India for supply of raw materials and for manufacture of early synthesis steps.

A recent project involved a six-step process including an evolved lipase enzyme. To meet customer timelines and to utilize Almac reactor capacity most efficiently, the first step of the process was tech transferred to our Indian partner. An Almac chemist went to India to ensure the process was tech transferred seamlessly and the Step 1 product was delivered to Ireland, where it was then forward processed. This business model of using an evolved enzyme developed at Almac combined with manufacturing in India, Ireland and the UK provides our customers compelling economics for chiral building block and API supply.

Michael Cannarsa, Ph.D.
Director of North American Business Development, Almac Sciences

In order to constantly serve its clients better and meet their ever-evolving needs, SGS Clinical Research has set up R&D partnership agreements with hospitals across Europe to enable access to relevant patient populations and therapeutic expertise. Under these agreements, dedicated clinical pharmacology units are established within a hospital's facility to conduct phase I inpatient 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 capacity 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 greater expertise in early phase clinical trials, but most importantly, patients benefit by having access to new therapeutic solutions as early as possible.

Florent Hédiard
Marketing Director, Life Sciences, SGS

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 formulated drug product.

Federico Pollano
Global Business Development & Contract Manufacturing Director, Polpharma Biologics

As a provider of medicines that are destined to over 100 countries 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 recent years, particularly for commercial medicines. This has certainly changed the scope of our operations. Similarly, clinical investigational studies are increasingly global in nature; we rely on expert logistical partners around the world to get clinical materials to investigational sites reliably and safely. From a plant and manufacturing perspective, we have been fortunate to be supported by excellent world class and yet localized material suppliers, alternatively supported by more global equipment manufacturers who are largely concentrated in regional centers of excellence, including geographies such as Europe, often Germany and Italy, with companies such as Bosch, GEA and Gerteis in drug manufacturing and Uhlmann, IMA and Marchesini in packaging. We also see excellent companies thriving in the US, companies such as Micron Pharmaworks, MGS and many others. With the advent of serialization as a market requirement, we have been very fortunate to partner with Italian companies Antares Vision and Marchesini as we rapidly expand our global capacity in advance of the November deadline.

Justin Schroeder
Senior Executive Director, Global Marketing and Design, PCI Pharma Services

SSCI provides best-in-class solid-state and analytical services for **over 250 global clients annually that are engaged in developing new life-saving medicines** and require release testing of commercial product. Given the global registration strategy of these products, our laboratory is regularly audited by various regulatory authorities and has maintained an exemplary record of regulatory compliance with current Good Manufacturing Practices (cGMP).

Over the past quarter century, our reputation has been built on providing exceptional customer service and the highest-quality data. To maintain this standard, SSCI has sought leading multinational vendors, including Malvern (United Kingdom), Mettler Toledo (Switzerland), PANalytical B.V. (Netherlands) and Rigaku Corporation (Japan), that share these same core values. We value vendors that are truly committed to the design and support of their technologies over its service life cycle, which allows us to provide a consistent and reliable service offering. In cases where analytical methods are transferred to other testing laboratories, there is additional confidence gained in working with multinational vendors that maintain the technology at the receiving laboratory to the same high standard. Use of these technologies in a cGMP environment, and the heightened expectation on software and data integrity by global regulatory authorities, make the collaborations with our existing vendors and the selection of new vendors even more important.

David Engers
General Manager at SSCI, now a division of Albany Molecular Research, Inc.

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

The development path for University College London's (UCL) magacizumab highlights Abzena's integrated offering that enables its partner to progress from discovery to manufacturing utilizing Abzena's international capabilities across its sites in the UK and US. UCL supplied a novel sequence for an antibody therapeutic candidate, magacizumab, for the treatment of neovascular age-related macular degeneration.

Starting in Cambridge, UK, Abzena's protein engineering group utilized Composite Human Antibody Technology™ to generate antibody sequences devoid of significant T-cell epitopes. Abzena's cell line development group then cloned the optimized lead variant sequence into a vector system and transfected it into Abzena's Composite CHO™ cell line. Research cell banks of the best performing cell lines were then assessed for use in bioreactors to identify the best cell line to move forward to Abzena's San Diego cGMP manufacturing facility. The qualified candidate research cell bank of the highest producing cell line is currently in the process of being used to produce a GMP Master Cell Bank ready for cGMP manufacturing. Abzena's integrated platform allows customers to accelerate and de-risk their development process by allowing manufacturing expertise to feed into early product development to address any manufacturing concerns and select the best cell line for production in their facility early on.

Jim Mills
Senior VP Technical Operations, Abzena

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 turnkey 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 means to measure progress and a value proposition whose worth is greater than the sum of its parts, to name a few. Furthermore, identifying the "best" partner(s) requires a constant understanding and pulse of the ever-dynamic marketplace.

John Lagodney
Biotechnology Core Team Leader, CRB USA

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.

SP Scientific has earned a reputation for line of sight scale-up in freeze drying technology and equipment, and partnerships with thought leaders and those with complementary technologies such as TDLAS have been instrumental to our success. For large projects such as new pharmaceutical production lines, the ability to work collaboratively is imperative and usually assumed. SP often works with companies such as engineering firms who are integrating equipment from a number of suppliers to deliver a turnkey customer solution. SP's aseptic processing equipment portfolio allows us to deliver key elements, such as the sterile fill and finish capability, while other partners may provide isolators or bioreactors for production of a biological drug that are not currently within our portfolio.

Zak Yusoff, PMP
Senior Product Development Manager, SP Scientific

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 may 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 Viñes
Business Development Manager, Grifols

GLITTERING INSIGHT FROM INSIDE THE INDUSTRY...