pharma's almanac
A NICE INSIGHT MAGAZINE

Q1 2018 VOLUME 4 NUMBER 1

THE EXECUTIVE EDITION

M&A STRATEGY: STRUCTURING AND ALLIANCE

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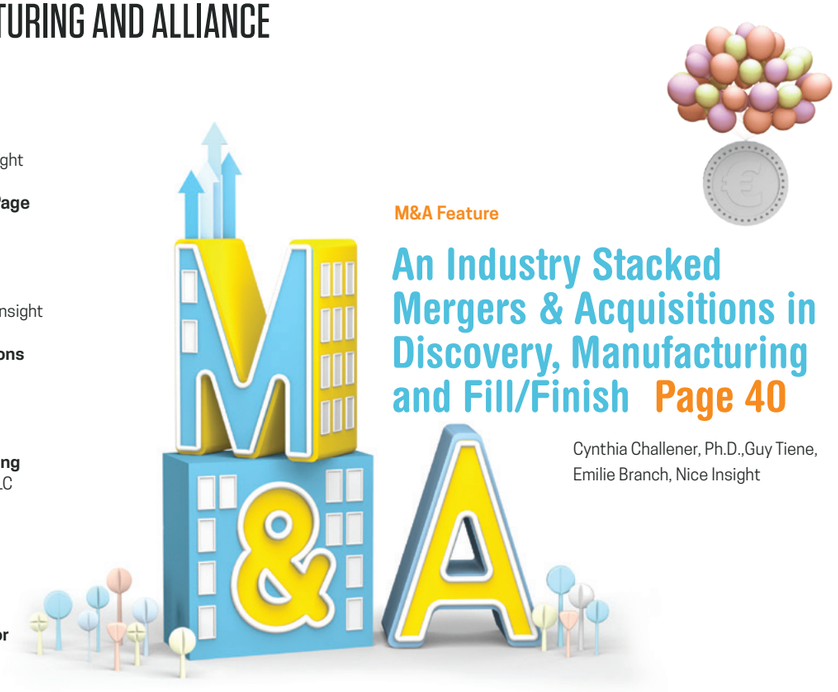

M&A Feature

An Industry Stacked Mergers & Acquisitions in Discovery, Manufacturing and Fill/Finish **Page 40**

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

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Nice Insight is the market research division of That's Nice LLC, A Science Agency, leading marketing in the life sciences.

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

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→ A NOTE FROM THE EDITOR

MARKET IN MOTION: LARGE TRENDS CONTINUE TOWARD CREATING OUR NEW INDUSTRY

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

Welcome to the first Pharma's Almanac edition of 2018, in which we take a look at the mergers and acquisitions, consolidation and specialization taking place in contract services, and the entire pharma-biotech industry. This is in the face of a surge in demand and mandated improvements in processes, efficiency and security of supply – we're talking "Pharmageddon."

We are excited to deliver this first edition of the year to you, our print readership comprising a select group of pharma-biotech professionals. Our new content marketing approach brings you valuable and insightful commentary from a variety of contributors.

This edition includes fantastic contributions from a great group of thought leaders at some of the best solution providers around the world, covering topics from viral vector manufacturing and parenterals to customer partnerships and clinical trial logistics, with more on serialization.

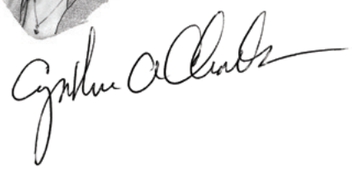
The pharma-biotechs are simplifying their supply chains, attempting to work with fewer contract service providers, such as contract development and manufacturing organizations (CDMOs), and doing so in more strategic and cost-effective ways.

The utilization of pathways for accelerated drug approvals requires agility and scalability from outsource partners. With the continued growth of antibody-drug conjugates (ADC) and other highly potent APIs (HPAPIs), as well as cell and gene therapies, specialty knowledge and capabilities are critical.

When it comes to contract research organizations (CROs), the top ten handle much of the market – and much of the North American market. Specialization in this sector is occurring around early-stage development services, late-phase clinical trials and central laboratory services.

We invite you to enjoy this, our "Executive Edition," with a feature article covering M&A activity at the research and discovery, contract manufacturing and finished drug-product levels. This topic is also addressed in our Roundtable, with both CDMO and CRO perspectives.

Welcome to the issue! P



Pharma's Almanac Publisher's Page

Outsourcing solution providers contributing to the global supply chain dialogue with compelling and insightful content.

BY THE NUMBERS 2017

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1,192+
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68,299
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938+
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Dear Pharma's Almanac Reader:

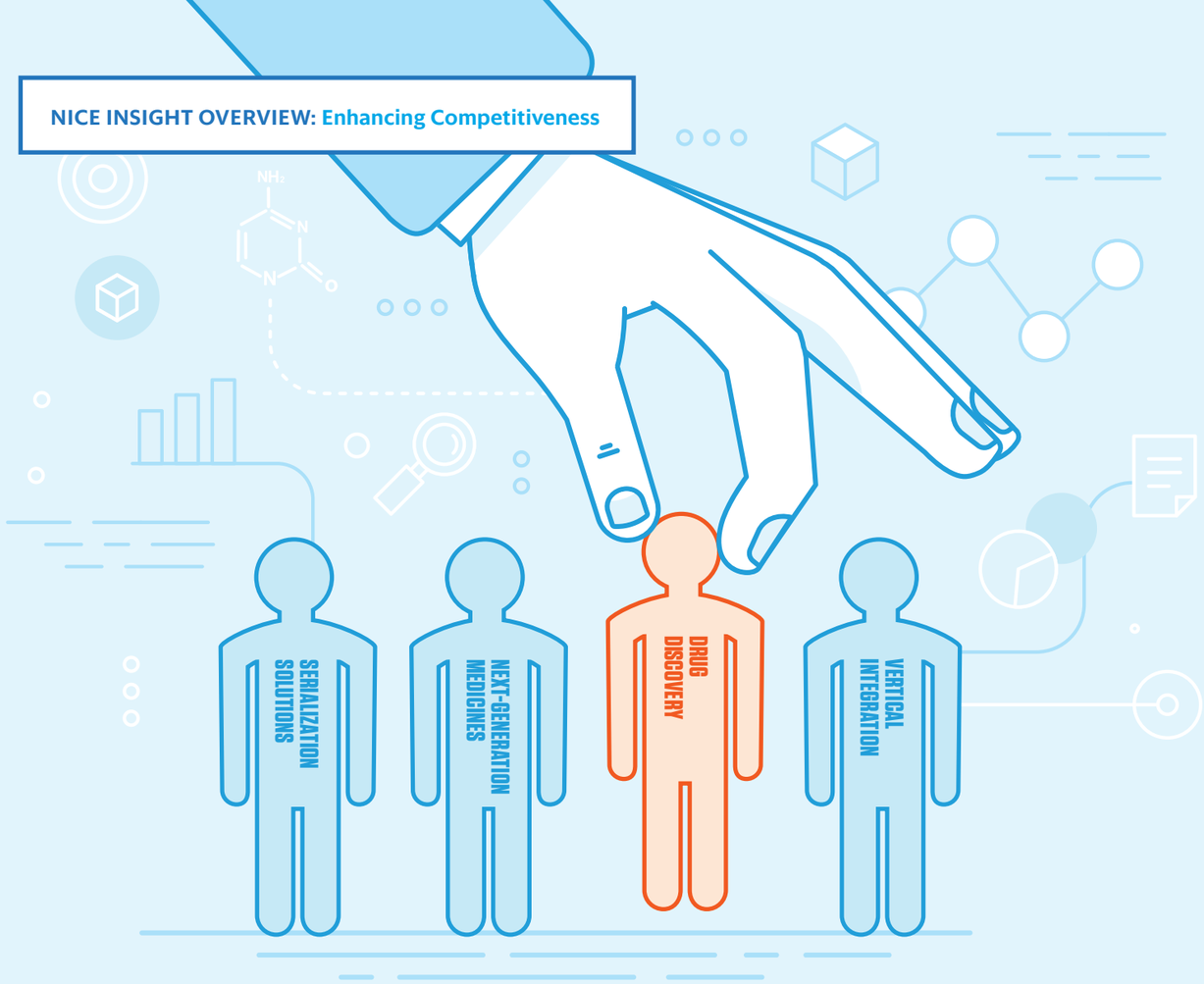
You are receiving this print edition of Pharma's Almanac at the request of one of our contributors, based on your organization, or your active role in the industry.

Nice Insight's Pharma's Almanac has grown into a premier content universe, recognized for offering in-depth analysis of pharma-biotech research and discovery, manufacturing, supply chain, regulatory and future technologies. This content universe includes a robust and highly active web portal that delivers content and data, as well as archives of all past issues.

In 2017, PharmasAlmanac.com had over 80,000 visits, with thousands of views of more than 1000 articles, blogs, videos and news pieces posted. To reach our audience, we send out "Trending Now," a tri-weekly e-mail newsletter that extends the reach and consumption of Pharma's Almanac content, which is sent to over 62,000 readers.

We invite you to **visit www.pharmasalmanac.com** to read more, examine our research section, review over 900 supplier company profiles, and sign up for Trending Now.

Sincerely,
The Pharma's Almanac Team



M&A ACTIVITY IN A FRAGMENTED CDMO MARKET

By **Nigel Walker**, That's Nice LLC/Nice Insight

While there has been a slowdown in M&A in the pharmaceutical industry, and particularly among pharma companies, the contract services market remains highly fragmented and players large and small continue to enhance their competitiveness through inorganic growth. Investment in facilities also continues apace.

The pharmaceutical contract development and manufacturing market is highly divided. According to one recent report by Ernst & Young, there are at least 600 different active CDMOs, including many international organizations and some firms that serve local markets.[1] It has also been reported that the major players in the CDMO market each have just 2%-4% market share.[2]

Several Drivers of Consolidation

With such extensive fragmentation, significant merger and acquisition (M&A) activity would be required to result in any measurable consolidation. Several notable transactions have occurred in recent years, leading to the formation of the current major players, which begs the question: what is driving this desire for consolidation among CDMOs? Outsourcing to CDMOs is increasing as biopharmaceutical companies look to cut costs while accelerating timelines. Sponsor firms are also concerned with rebuilding pipelines as many blockbuster drugs lose patent protection, focusing on drug discovery and relying on CDMOs for development and manufacturing activities.[3]

Some CDMOs are expanding in order to achieve more financial stability. Increasingly, private equity (PE) is playing a role in M&A activity in the CDMO sector, helping smaller companies to achieve this goal.[2] Others are looking to improve their global reach or add advanced and specialized technologies that enable them to offer innovative solutions. Of course, vertical integration – or the one-stop-shop strategy, which is evidenced in the conversion of contract manufacturers to CDMOs – continues to be a driver.[1,2] CDMOs continue to expand their capabilities across all phases of development and commercialization in order to eliminate the need for technology transfer, which increases both the time and cost of projects.

At the same time, pharmaceutical customers are simplifying their supply chains to reduce costs, forming strategic partnerships with fewer CDMOs.[4] In addition, more drug developers are looking to receive accelerated approvals from FDA and/or focusing on orphan drugs, which require more flexible, responsive manufacturing capabilities. The advent of antibody-drug conjugates (ADC) and other highly potent APIs (HPAPIs), as well as next-generation medicines such as cell and gene therapies, are also creating the need for contract service providers with specialized expertise. Even small-molecule drugs pose challenges, as the percentage of compounds that are poorly soluble with low bioavailability continues to increase.

Furthermore, it is worth noting that innovative therapies are often initially developed by emerging pharma companies that eventually get acquired by established biopharma firms once their technologies are proven – which requires extensive support from service providers that can offer a breadth of capabilities from discovery through late-stage clinical trials and sometimes beyond.[4]

The need to implement serialization solutions may also be driving consolidation in the CDMO space.[5] Many smaller service providers do not have the resources to meet track-and-trace regulatory requirements, while larger firms can incorporate these costs across numerous supply agreements. Some smaller CDMOs are expected to look to be acquired in order to achieve compliance.

A Bit of History

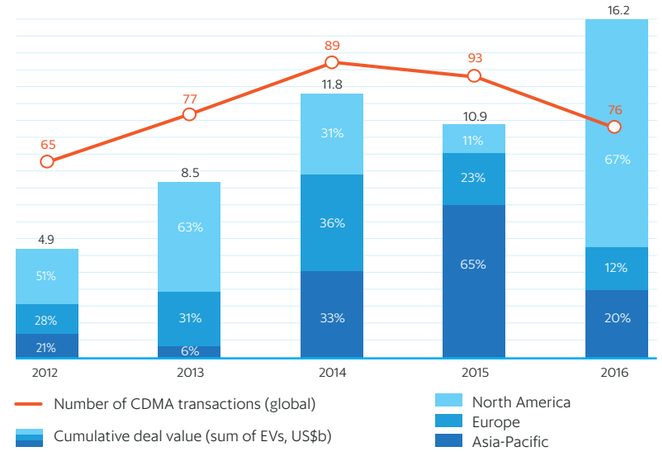
These drivers are leading to measurable M&A activity. One report estimates the small-molecule CMO market is consolidating at an annual rate above 10%; the value of transactions in the sector rose from $5.5 billion in 2014 to $12 billion in 2016.[2] Overall in the CDMO segment, from 2012 to 2016, the number of publicly announced M&A deals increased by approximately 12% per year.[1] At the same time, implied enterprise values of acquisition targets increased 35% per year, resulting in CDMO deal values more than tripling over the period.

The one-stop-shop concept has been around for some time, and clearly a number of leading CDMOs have adopted this model.

More activity has taken place in North America and Asia than in Europe.[1] In North America, over $23 billion worth of deals were completed from 2012-2016, with 43% of buyers domestic and the bulk of the remaining purchases from Europe. Notably, most of the deals in Asia take place between companies in the same country. There appears, however, to be growing interest among Asian buyers in European and North American targets.

Private companies (or their assets) accounted for 56% of all CDMO deals from 2012 to 2016. Sales by PE firms accounted

CDMO M&A Volume and Value



CDMO deal value and volume between 2012 and 2016 (only covering publicly announced M&A deals where more than 51% has been acquired).

SOURCE Ernst & Young

for just 22% of the transactions during this period, but represented 50% of the total value of all CDMO deals. The result of the recent M&A activity has led to a restructuring of the CDMO market.[1] Prior to 2012, 57% of the assets involved in deals were privately held; today 47% of remaining assets are under private ownership. In addition, PE firms now own just 12% of all assets, down from 22%. Overall, there has been a concentration of CDMOs into large, publicly traded strategic players. According to Ernst & Young, only three of 10 top players (Aenova, Amatsigroup and WuXi PharmaTech) are currently privately owned.[1]

Several Big Deals in 2017

The big deals that took place in 2017 reflect the variety of deal types that have been occurring in the CDMO segment, often resulting in companies with a greater breadth of capabilities. With its $5.5-billion acquisition of Capsugel from PE firm KKR, Lonza, which had capabilities in small-molecule and biologic API manufacturing, gained a position in drug product services. Thermo Fisher Scientific, through its complementary $7.2 billion purchase of Patheon, added drug substance development and manufacturing, formulation development and drug-product manufacturing capabilities to its products and services businesses. On a slightly smaller scale, Catalent acquired CDMO Cook Pharmica for $950 million, gaining capabilities for the development and manufacture of biologic-based drug substances and parenteral drug products. Albany Molecular Research (AMRI), meanwhile, agreed to a buyout by PE firms The Carlyle Group and GTCR for $922 million. AMRI sees the move as offering "a compelling opportunity to accelerate our growth and enhance delivery of world-class solutions to our customers."[6]

Many More Small- and Mid-sized Transactions

Many of the companies that participate in mega deals do so only after building their organizations through numerous smaller transactions. Patheon, AMRI and Capsugel are all examples. These smaller deals collectively often have a greater impact than the few large deals that take place each year.

In 2017, for instance:

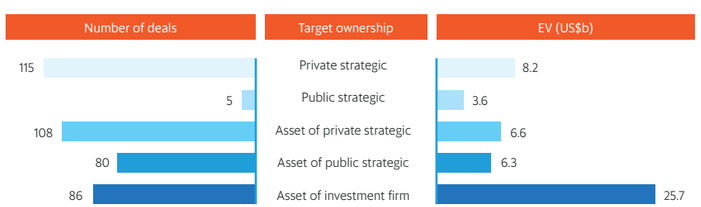
+ **Lonza acquired cell and gene therapy CDMO PharmaCell B.V and micronization services provider Micro-Macinazione**
+ **Germany-based drug discovery and development company Evotec finalized the acquisition of US-based CDMO Aptuit to enhance its capabilities as an integrated provider of drug discovery and development services**
+ **Biopharma testing services company Eurofins Scientific expanded into the CDMO space (multi-step syntheses, development of cytotoxic and high potency APIs) with the acquisition of Alphora Research**
+ **Ireland-based CDMO Almac Group acquired Ireland-based contract research organization (CRO) BioClin Laboratories to expand its analytical capacity and better serve its global customers needs**
+ **Catalent completed the acquisition of Canadian softgel manufacturer Accucaps Industries Limited**
+ **UK-based Quotient Sciences acquired the US-based Charles River Laboratories CDMO unit QS Pharma and UK-based CDMO Pharmaterials**
+ **Italy-based CDMO Olon S.p.A. gained US operations through the acquisition of the Chemical Division of Ricerca Biosciences**
+ **China-based CDMO Porton Fine Chemicals acquired US-based J-STAR Research**
+ **Chinese biopharmaceutical company 3SBio acquired Canadian biologics CDMO Therapure Biopharma**
+ **CMC Biologics was sold by PE firms Monitor Clipper Partners, European Equity Partners and Innoven Partenaires to Japanese glass, chemicals and high-tech materials manufacturers AGC Asahi Glass**
+ **Corden Pharma acquired an HPAPI manufacturing plant previously owned by Pfizer**
+ **Celonic, a specialist in perfusion biomanufacturing, acquired Glycotope's production facility in Heidelberg, Germany, gaining its complementary GEX human cell line platform**
+ **CDMO Avara Pharmaceutical Services purchased Pfizer's sterile manufacturing facility in Liscate, Italy, the fifth plant purchased in the last two years.**

Many of the key drivers of consolidation in the CDMO sector are elaborated in these examples. The first four represent deals intended to expand services to implement a vertical integration or one-stop-shop model. Lonza is clearly willing to make large and bolt-on acquisitions to realize its strategy. Eurofins Scientific and Almac are branching out beyond their original sectors to expand capabilities – CRO into the CDMO space and vice versa. Companies like Quotient Sciences and Olon furthered their capabilities in their areas of specialization. Others are building capabilities through the acquisition of sponsor facilities, which does not lead to consolidation but does reduce in-house capacity. The two acquisitions of North American operations by Chinese companies reflect the growing interest of Asian firms in expanding their global presence as their technical capabilities improve.

Lots of Investment Activity

M&A deals are not the only way that CDMOs are looking to increase their competitiveness. Investments in new facilities and technologies are occurring at a rapid pace, regardless of company size, location or areas of specialization. CDMOs are expanding both small-molecule and biologic drug substance (proteins, antibodies, cell therapies, viral vectors, etc.) process development and manufacturing, bioconjugation and highly potent manufacturing, formulation development, drug delivery, analytical testing and drug product manufacturing capabilities and capacities around the world.Examples include Alcami, Almac, Boehringer-Ingelheim BioXcellence™, Brammer Bio, Capsugel, Cambrex, Catalent, Cobra Biologics, Flamma, Fujifilm Diosynth Biotechnologies, Granules India, Grifols, KBI Biopharma, Lubrizol, Novasep, Pfizer CentreOne, Piramal Pharma Solutions, Recipharm, Vetter and WuXi AppTec.[7]

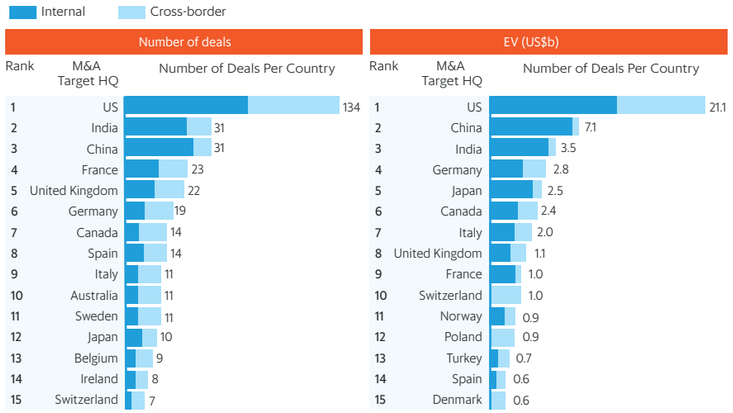
Targets of CDMO M&A Activity



Number of deals and EVs of publicly announced CDMO deals between 2012 and 2016.

SOURCE Ernst & Young

Country League Table – Targets of M&A



Top 15 target countries for CDMO M&A transactions based on number of deals and EV involved in deals, 2012-16.

SOURCE Ernst & Young

Will Vertical Integration or Specialization Dominate the Future CDMO Market?

The one-stop-shop concept has been around for some time, and clearly a number of leading CDMOs have adopted this model. Customers can theoretically benefit from reduced sourcing costs due to simplification of the value chain and accelerated development timelines due to simplified movement through the development cycle with elimination of the need for technology transfers from one partner to another. On the flip side, CDMOs benefit from the need to manage fewer customers with whom stronger relationships are established.

At this point, while many CDMOs have moved to build integrated offerings, evidence for the preference of this model among pharmaceutical industry customers has not yet surfaced. It is too early to draw any conclusions, however. The costs and time involved in switching projects are enormous, so use of integrated services will likely occur over time as new projects are implemented.[1]

It is also possible that larger pharmaceutical companies will be more likely to use integrated CDMOs than smaller sponsor firms. Smaller firms may be concerned that their projects will receive low priority compared to larger firms with multiple projects at multiple phases.[1] For smaller North American and European pharma companies, lower-cost options in Asia may also remain attractive. On the other hand, it has been suggested that access to integrated services may provide a competitive advantage to developers of biosimilars.[1]

It should be noted that with the increasing pace of innovation in the pharmaceutical industry – consider the rapid advance of ADCs, bispecific antibodies and cell and gene therapies – there will always be a need for third-party services based on the latest state-of-the-art, novel technologies. As a result, CDMOs that have adopted the specialist model will continue to be an important component of the CDMO market.

There is one conclusion that can be drawn: M&A activity in the CDMO sector – by PE firms, large and small privately held strategic buyers and large publicly traded companies – will continue. Each of these types of players seeks to achieve differentiation and gain competitive advantage in the eyes of drug developers looking for partnerships with high-quality, innovative, cost-effective service providers that accelerate the development of novel, safe and efficacious drugs. P

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Managing Director, That's Nice LLC/Nice Insight

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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PRECLINICAL, CLINICAL, MEDICAL DEVICE TESTING

CREATING COMPREHENSIVE SOLUTIONS **THROUGH LABORATORY TESTING**

→ BY **XIN ZHANG, Ph.D.**, WUXI APPTEC

WuXi AppTec has continued to build a comprehensive offering through organic growth and acquisition. Its Laboratory Testing Division is poised to play a key role in propelling the open-access capability and technology platform company forward with a full range of integrated testing services. As an organization, WuXi AppTec provides a broad and integrated portfolio of services to help our worldwide customers and partners shorten the discovery and development time and lower the cost of drug and medical device R&D through cost-effective and efficient solutions.

THE LABORATORY TESTING DIVISION

The Laboratory Testing Division covers nearly all testing capabilities involved in drug and medical device development, from early-stage R&D to clinical diagnostics. It was formed in December 2013, when all of WuXi's testing capabilities were combined into one powerhouse unit, adding a full range of DMPK, toxicology, bioanalytical, analytical and clinical diagnostics services to create a vast portfolio of IND- and NDA-enabling services.

Our progress since then has remained constant. Over the last four years, the Laboratory Testing Division has evolved to become a fully-integrated testing platform supporting customers across the full scope of drug discovery and development. We are continuously evolving to meet the ever-changing needs of our clients and global patient populations.

Acquisition is a key component of our expansion strategy. One of the most recent changes to our division has been the addition of the Medical Device Testing Unit, formerly referred to as AppTec. The company, which specialized in medical device testing, was acquired by WuXi in January 2008. At the time of its acquisition, it was one of the top three medical device testing companies in the US. In October 2017, WuXi AppTec acquired ResearchPoint Global, a US-based CRO, in order to continue to build a more robust clinical CRO offering.

PLATFORM TO PATIENT

At its core, WuXi is a platform company that is committed to enabling innovative therapies to benefit patients. The Laboratory Testing Division offers comprehensive solutions that stem from this commitment, enabling customers to take their projects from lab to patient on an accelerated timeline. Our "Platform to Patient" philosophy speaks to the many layers that comprise the organization's vision, as it emphasizes the value of consistently delivering high-quality study data from early through late phases of development, while also serving to connect the Laboratory Testing Division to the other areas of the WuXi business.

As an integrated testing platform, the Laboratory Testing Division is uniquely positioned to aid our customers in all of their testing and development needs. Our goal is to ensure our clients are able to deliver innovative medicines faster and more cost-effectively. To best address any request, the Laboratory Testing Division is divided into three key platforms—preclinical drug development, clinical drug development and medical device testing.

WUXI LTD AT A GLANCE

7	R&D Sites in the US and China
2,500+	Employees Globally
450+	Global IND Packages Completed
100+	Global NDA Packages Completed
30	Clinical Centers in China
430+	Validated Methods for Bioanalysis

ANALYTICAL SERVICE UNIT : TRACK RECORD OF SUCCESS

330	Customers for Discovery Chemistry & Separation, API & Clinical Trial Material Manufacturing
1,000	Stability Programs Conducted for 1,000 Batches of API & Drug Products
25	INDs / NDAs Submitted to FDA
20	CTDs / CTAs Submitted to CFDA

WUXI PLUS IND FORM WIND

Our preclinical drug development services support the testing, document preparation and regulatory submission for Investigational New Drug (IND) applications. Our commitment to meeting all goals within an accelerated timeline and hands-on program management, coupled with extensive expertise in both US and China-specific regulations, makes us fully equipped to support the full scope of any drug development program. WuXi and IND combine together to form our "WIND" program, which takes customers from the initial steps of document preparation all the way through to submission. Our IND-enabling services include CMC and analytical development, bioanalytical solutions, full-scale *in vitro* and *in vivo* ADME and PK/PD, as well as preclinical and clinical toxicology safety assessments.

WIND combines our open-access capability and technology platform, program management and regulatory support services to facilitate our customers' global IND applications, designing customized solutions that fit the needs of each individual project. Our team of regulatory experts support IND submissions to global regulatory bodies, including the CFDA and FDA.

COMPLETE CLINICAL DEVELOPMENT

The transition from preclinical to clinical studies should be seamless. As we provide support at all levels and across all phases, our goal is to ensure that regardless of when we take on a project, we are able to successfully progress it though each development stage, leveraging our vast range of technical capabilities. Our clinical development services include, but are not limited to: small molecule and biologics quantitation, generic/biosimilar and innovator study support, biomarker testing, PK Met ID, mass balance (hot & cold), CYP, Phase II enzyme and transporter substrate phenotyping, chronic and subchronic toxicology, Seg I-III DART studies, carcinogenicity studies, juvenile toxicology, four-week batch impurity testing, late-phase commercial analytical development, stability studies, regulatory CMC and project management.

PARTNERING THROUGH MEDICAL DEVICE TESTING

When customers work with us, they are working with a partner fully committed to the success of their project. We understand the challenges associated with getting a medical device to market, and our scientists have the expertise and experience to proactively support this endeavor within an ever-changing regulatory environment.

What definitively sets us apart – as an organization, business unit and testing platform – is our people. Our medical device testing experts not only serve on international standards committees as active participants, but as leaders. In addition to keeping us in tune with the shifting regulatory environment, our leading chemists work alongside our toxicologists to provide comprehensive toxicological risk assessments. We not only provide guidance but adopt a customized strategy for each individual program. The vast number of diverse products that our experts have tested makes us an unquestionable authority in this space.

A FORWARD LOOKING JOINT VENTURE: WUXI AND THE MAYO CLINIC

As part of our commitment to delivering value to patients worldwide and our vision that 'every drug can be made and every disease can be treated', in January 2018 WuXi AppTec Group formed a joint

WHEN CUSTOMERS WORK WITH US, THEY ARE WORKING WITH A PARTNER **FULLY COMMITTED TO THE SUCCESS OF THEIR PROJECT**.

venture with the Mayo Clinic to introduce testing capabilities and clinical diagnostic services to the Chinese market. This venture will bring novel esoteric tests to market faster, benefiting patients in both China and the US.

The partnership with the Mayo Clinic elevates our portfolio of diagnostic services and will serve to accelerate research in the lab. The outcome will be the transformation of discovery tests and the diagnostic landscape, as well as precision medicine – not only in China but also worldwide. Through the collaboration with Mayo, we're committed to building a leading diagnostic services operation in China and co-developing in ways that will benefit our patients, doctors, and innovative collaborators in all corners of the world.

LIFE, TECHNOLOGY, AND DISCOVERY

The Laboratory Testing Division is commonly referred to as "LTD" for short. We have made use of this internal acronym, developing it into the meaningful slogan: "Life, Technology and Discovery" – an all-embracing reflection of our capabilities as a testing platform. We stand for these three tenets, which truly summarize where we see our company in the future. Our focus is strongly on the US and China, and we have expansion plans for both. Specifically, the expansion of our New Jersey facility for DMPK and Bioanalytical services, with the opening of a new building in Cranbury, is taking place in early 2018.

OVERCOMING THE CHALLENGES OF A RAPIDLY PROGRESSING ORGANIZATION

Although our organization's growth is overwhelmingly positive, one of the challenges of growing so rapidly is addressing any doubts concerning where everyone fits, and how we can all work together to accomplish one overarching goal. Of course, our evolution is an ongoing process. Internally, we are relying on program management to play a key role in how our divisions are perceived.

Ultimately, the Laboratory Testing Division – or LTD – stands for just what we are capable of – our testing capabilities are limitless. Regardless of whether a client comes to us with one single compound, or hundreds of thousands of compounds, LTD can do the testing, evaluate that the targets are druggable, go through all the necessary preclinical testing and eventually conduct testing in clinical trials. It has been tremendously exciting to watch our Laboratory Testing Division's growth over the last four years into the integrated testing powerhouse it is today, and we are wholeheartedly looking forward to what lies ahead in the coming years. P

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Dr. Xin Zhang joined WuXi AppTec in September 2013. Prior to joining WuXi, Dr. Zhang worked for Charles River Laboratories, LabCorp (Tandem Labs) and Agilux Laboratories. After earning a degree in physical chemistry from Peking University and working in China for a few years, Dr. Zhang traveled to the US to pursue his graduate career and obtained his Ph.D. in organic chemistry from the University of Iowa. Dr. Zhang completed his postdoc training at Northeastern University, where he focused on new mass spectrometry applications including oligonucleotides, DNA adducts, and proteomics.

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→ MACHINE INTELLIGENCE

ARTIFICIAL INTELLIGENCE IN BIOPHARMACEUTICAL MANUFACTURING

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Artificial Intelligence (AI) has significant potential to change the healthcare industry, from the way patients receive treatments to the ways in which drugs are discovered and manufactured. In the first of a four-part series exploring the use of AI in biopharmaceutical manufacturing, we look at the challenges and opportunities facing early adopters of this game-changing technology.

FROM HYPE TO APPLICATION

As the hype around artificial intelligence (AI) has been growing, its promise to change healthcare has started to materialize: medical imaging classification algorithms have bettered a panel of experienced radiologists; new in-silico developed drugs are moving through clinical trials; wearables and smart phones produce data helping with mental disease treatment; and medical decision-support systems pave the way to revolutionize the entire healthcare provider model.

In biopharmaceutical manufacturing, however, we need to search deeper to recognize the victorious arrival of AI.

INTEGRAL COMPONENTS

Some low-hanging AI, or rather Machine Learning, fruit are ripe enough to fall in the hands of COOs and Directors of Manufacturing; machine learning-backed visual inspection and bacterial culture yield optimization are good examples. As with many other potential opportunities for the application of machine learning to achieve a predictable, high-quality, flexible, low-cost manufacturing process, we first need to look at the two integral components: the data and the data scientists.

Too often we collect manufacturing data with the hope of never seeing it again, i.e., for regulatory compliance purposes. The structure and content of this data is typically not designed for manufacturing optimization. As a result, the data generally does not help data scientists to clearly see how machine learning classification and predictive models can produce practical improvements.

Mixed paper-electronic formats are another obvious issue. Even if the API and finished dose batch records, exception reports and development and QC analytical testing results are all in electronic form, there is a lot of semantic/relational database preparatory work needed before Natural Language Processing (NLP) algorithms can produce actionable insights.

Great value would come from combining data sets from different manufacturing organizations within a larger biopharma company, but business unit and facility-level data silos and the lack of clear data ownership do not make this job an easy one. The lack (or complete absence) of data scientists with dedicated machine-learning training within ops/manufacturing groups is another challenge, but one that is at least easy to explain.

SOME BAND-AID SOLUTIONS

To make machine learning effective in biopharmaceutical manufacturing, gargantuan an internal mindset and business process changes around data collection, analysis, and use are necessary. There are, however, some quicker Band-Aid solutions that can be initially deployed.

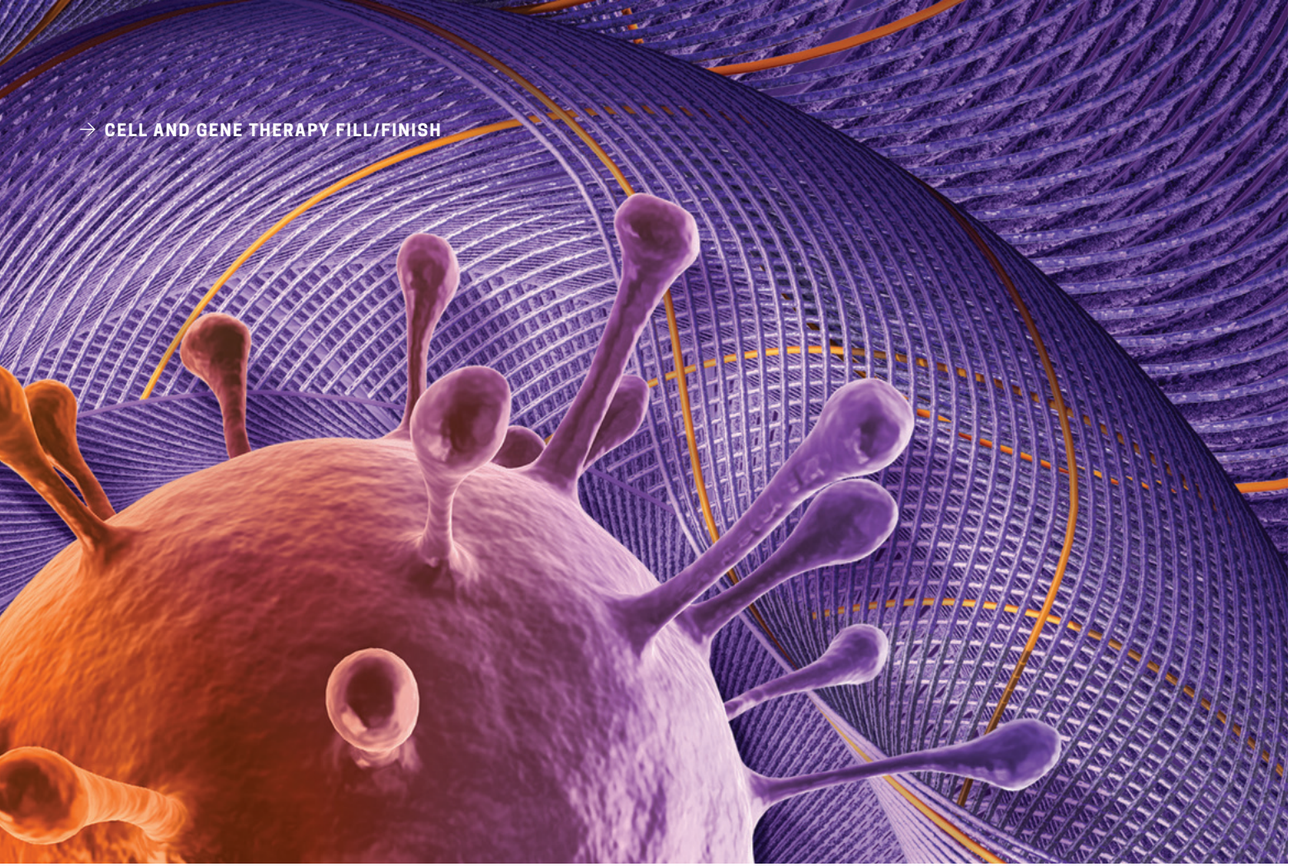
Machine-learning automation tools, for instance, perform reasonably well the activities of data cleaning, feature engineering, model/algorithm selection and hyper-parameter optimization. In-residence drug development and manufacturing scientists, who might not have deep machine-learning expertise but surely possess robust statistical analysis experience, can use these tools to take an initial dive into the data to determine if any practical insight can be gained.

An interesting AI approach for the biopharmaceutical industry, that requires less structural change in data collection routine, might be the application of Internet-of-Things (IoT) sensors, depth cameras for collecting and analyzing visual object movements, sound and speech recognition systems – all of the tools that allow shifting data collection in the background of manufacturing operations. In addition, new developments in deep neural network science, specifically Capsule Nets, have significantly improved the effectiveness of object visual recognition and classification from different angles. These neural nets can be trained using much smaller data sets, which is critical for environments with unique manufacturing processes.

EXCITING FUTURE FOR AI IN BIOPHARMACEUTICAL MANUFACTURING

The abovementioned solutions, although lacking the effectiveness of data-driven re-engineering that "smart manufacturing" might eventually require, are not disruptive to a high-quality cGMP-compliant manufacturing organization. They should be most interesting to those companies that see manufacturing as an important value-creating activity, such as contract manufacturing organizations, generic drug producers, and biologic drug substance manufacturers with high costs of goods.

Over the next year, MILS-Group will dive deeper into the most practical cost-cutting, quality-enhancing, predictability-improving applications of AI in biopharmaceutical manufacturing. We will explore applications being pursued by Big Pharma, analysis of data generated by automated production systems and much, much more. P



ENSURING CONFIDENCE IN VIRAL VECTOR MANUFACTURING

→ BY **CHRISTOPHER MURPHY** AND **MICHAEL WOURMS**, BRAMMER BIO

Cell and gene therapies are rapidly advancing to late-stage clinical trials and commercialization. Brammer Bio has expanded its capabilities to meet the growing need for flexible, high-quality advanced viral vector development and manufacturing services with an emphasis on providing the highest level of patient safety and reliability.

RAPIDLY GROWING MARKETS IN NEED OF VIRAL VECTORS

Most gene and cell therapies, like the first two chimeric antigen receptor (CAR)-T cell therapies (Kymriah™ and Yescarta™), and the first in vivo gene therapy (Luxturna™) approved by the FDA in late 2017, utilize viral vectors for transduction. Given the large number of cell and gene therapies in late-stage development/nearing commercialization, it is not surprising that demand for viral vectors is growing rapidly. According to Allied Market Research, the global viral vector and plasmid DNA manufacturing market (including viral and nonviral vectors and plasmid DNA) was valued at $262 million in 2016 and is expanding at a compound annual growth rate of 22.6% to reach $1.090 billion in 2023.[1] Viral vectors accounted for the largest segment.

The rapid growth in demand for viral vectors is challenging the sector, however.[2] The production of viral vectors requires advanced manufacturing facilities and equipment, and highly skilled and experienced operators. There are a limited number of biopharmaceutical companies and contract development and manufacturing organizations (CDMOs) with the resources in place across all stages of the drug development cycle. Both academic laboratories providing early phase support, and most CDMOs providing clinical and commercial development and manufacturing services are running at full capacity, typically with wait lists that extend months to years.

EXPANDING TO MEET DEVELOPMENT-SCALE NEEDS

Recognizing the growing need for viral vector production services on the development and commercial scale, Brammer Bio was formed as a highly specialized contract development manufacturing service organization focused solely on meeting the needs of the cell- and gene-therapy markets.

In March 2016, Brammer merged with Florida Biologix, an Ampersand Capital Partners' portfolio company based in Alachua, Florida that had a decade of experience and specialized expertise in the development and early clinical supply of all of the major viral gene transfer vector systems (Adeno-associated viral, Adenoviral, Herpesviral, Lentiviral and Retroviral). Brammer management had a strong track record of success supporting late-stage and commercial biologics manufacturing.

In September 2017, Brammer completed the expansion of clinical capacity at the Florida site, doubling the site's GMP manufacturing capacity supporting clients' clinical cell and gene therapy trials. In addition to increasing capacity for adherent and suspension cell culture using mammalian and insect cell host systems up to the 1000L scale, additional unidirectional flow manufacturing suites were built and a state-of-the-art isolator and integrated fill line were installed for drug product manufacturing in a range of formats, including up to 2000 vials per day.

Isolators are the most robust barrier systems available and provide a high level of assurance and reliability with respect to contamination control. Fill/finish is the last step in the manufacturing process, and the use of an isolator provides a high degree of safety for the drugs being produced. The new isolator system also meets tightening global regulatory requirements.

INVESTING IN COMMERCIAL MANUFACTURING

The second step in the establishment of Brammer as a full-service cell and gene therapy CDMO was the acquisition on January 1, 2017, of Biogen's biologics manufacturing and distribution facilities in Cambridge and Somerville, Massachusetts, including the on-boarding of an experienced team of 100 employees. The Cambridge facility was licensed by regulatory authorities to manufacture four commercial protein therapeutics.

Following a FDA Type-C meeting to review the design plans for the Cambridge facility, Brammer began renovations to support late-stage development and commercial launch of gene therapy products. The project was completed in late November 2017, and the facility now houses state-of-the-art equipment in cleanroom suites specially designed to accommodate a broad range of gene therapy manufacturing process technologies.

Multiple drug substance suites able to support small- to large-scale (up to 2000L) adherent and stirred-tank production, quality control laboratories and process establishment space were installed. The facility is also designed with an HVAC system for grade C clean rooms and unidirectional flow. A centralized vaporized hydrogen peroxide (VHP) system ensures suite sanitization. A fully automated version of the filling system at the Florida site that leverages similar isolator technology was also installed with capacity for nearly 10,000 vials per day to support late-stage and commercial gene therapy drug products.

Brammer's Cambridge facility also houses manufacturing science laboratories where processes can be run outside of GMP conditions, at or close to scale, in order to test them before moving to GMP production. In addition, it is important to note that beyond fill/finish operations, Brammer offers visual inspection and packaging and labeling services. The Somerville distribution center, which is located within one mile of the commercial manufacturing operations in Cambridge, is equipped for the storage of cell banks and viral banks, and labeling, storage and distribution of products as client needs dictate. In a separate project, Brammer plans to renovate a facility in Lexington, MA, increasing capacity to support late-stage clinical and commercial viral vector production. Construction is expected to start in early 2018 with capacity coming on line by year end.

FOCUS ON FLEXIBILITY, TRANSFERABILITY, QUALITY AND CONFIDENCE IN PATIENT SAFETY

Cell and gene therapies are next-generation medicines that require novel manufacturing technologies. As with any new field, needs and capabilities are evolving rapidly. Flexibility in both drug substance and drug product manufacturing is essential for effective support of client projects. Efficient and simplified scale-up and transfer from early- to late-stage clinical and commercial manufacturing allow for shorter time to market for enhanced competitiveness. Ensuring quality and patient safety are absolute requirements and standards.

The expansion projects in Florida and Massachusetts have enabled Brammer to evaluate state-of-the-art development and production systems. For instance, the Ambr® mini-bioreactor system from Sartorius, with the option for 24 or 48 single-use mini-bioreactors, allows high throughput scale-down modeling for efficient process characterization. Disposable technology has also been implemented at large scale in partnership with Pall Life Sciences. In addition to the new isolator systems, the implementation of

single-use product flow paths and the use of disposable technologies for drug product manufacturing provides significant flexibility with respect to the types of projects that can be completed and project scheduling, all while ensuring product quality.

Brammer also purposely incorporated manufacturing capabilities for both large- and small-volume production of viral vectors. For instance, at both the Florida and Cambridge facilities, Brammer can accommodate filling volumes down to 250 microliters with a high degree of accuracy – also leveraging single-use technologies.

Given the fill/finish operation is the last step before the product reaches the patient, we made a significant investment into technology that provides confidence in the environmental control for drug product manufacturing. In addition, because similar fill/finish equipment is installed at the Florida and Cambridge sites, scale-up and transfer of projects between the sites can occur rapidly and seamlessly, Notably, the isolator system at the Cambridge facility is equipped with a unique "L" flange design that enables rapid change out of different filling configurations (cartridges, syringes, closed vials, etc.) and the Florida site offers the same flexibility at clinical scales.

Furthermore, with the ability to perform development, process scale-up and establishment, clinical and commercial drug substance manufacturing, fill/finish, visual inspection, labeling and packaging, storage and final product distribution, Brammer is an end to end service provider for companies in this specialized field.

UNIQUE COMBINATION

Two key elements make Brammer unique as a cell and gene therapy CDMO. First is the deep level of expertise and experience we have in the development and production of viral vectors. Brammer's process and analytics development capabilities and manufacturing track record are based on our team's 11-plus years of experience gained through the successful execution of over 100 projects which have delivered over 150 clinical lots, many for first-in-human trials. Second is Brammer's understanding of the technical aspects associated with the production of many different vectors using a variety of manufacturing platforms. At the Cambridge facility, Brammer's team has successfully commercialized several biologic products, manufactured hundreds of product lots, and hosted numerous regulatory inspections.

AN INCREDIBLY IMPORTANT ROLE

The cell- and gene-therapy sectors are booming, and demand for viral vectors has only increased as a result. With Brammer's differentiating expertise in developing processes and analytics, and manufacturing of both drug substance and drug product, Brammer is positioned to catalyze the growth of the market. Brammer expects to rapidly fill our existing capacity and increase our staff; and we are already planning for additional expansions, as represented by the build-out of our Lexington facility.

Brammer's Florida location is a center of excellence for process and analytical development and early-phase clinical manufacturing. It is fast becoming an industry hub for the development and qualification of products, processes and methods, and early-phase clinical manufacturing. Smooth transfer to Cambridge (or Lexington in the future) allows for rapid scale-up and commercial production. Final drug products are further supported by the capabilities at the Somerville distribution center.

Perhaps most importantly, we recognize that the products we make at Brammer Bio are highly complex. We have great respect and humility for the fact that we are making viruses that are used to create unique and life-changing therapies. Our strategy is, in fact, underpinned by the recognition that we play an increasingly important role in advancing these new medicines with the goal of helping people. P

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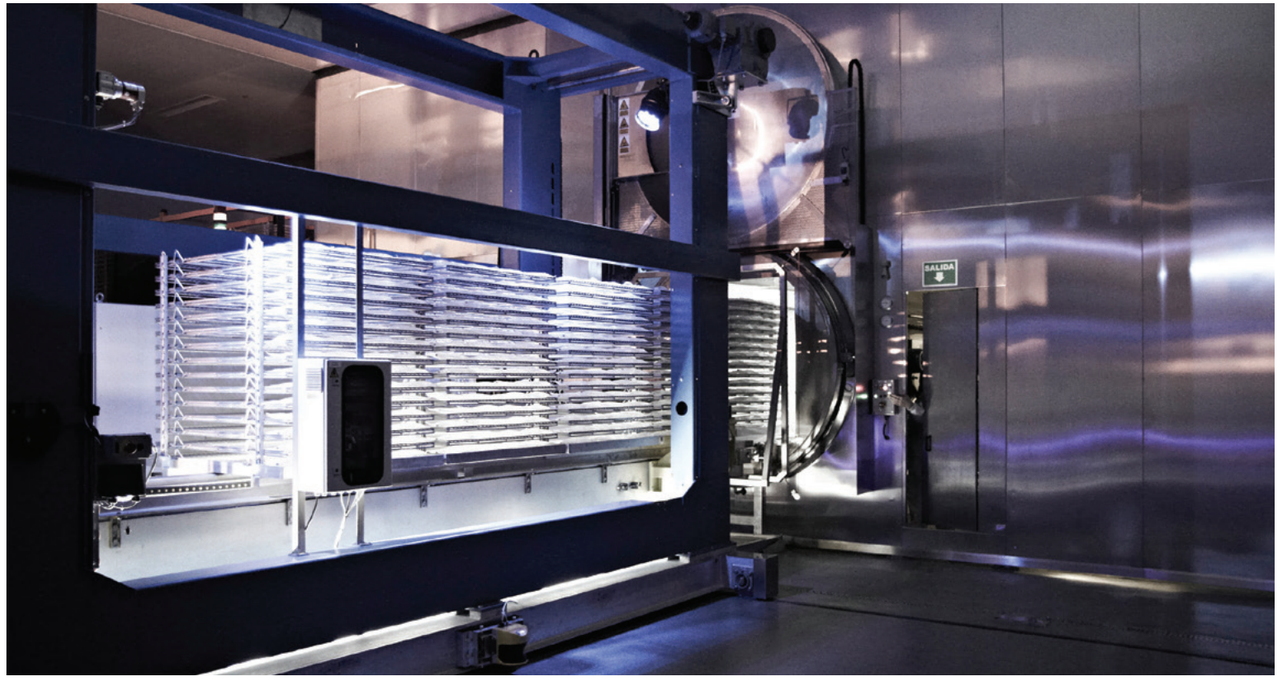
EXPANDING U.S. SUPPLY OPTIONS FOR LARGE-VOLUME PARENTERALS

→ BY **MARGA VIÑES**, GRIFOLS PARTNERSHIP



With limited numbers of producers supplying large-volume parenterals (LVPs) to the US market, shortages can result when natural disasters or manufacturing problems interrupt production operations. Grifols has implemented its vertical integration philosophy to ensure the consistent supply of high-quality sodium chloride 0.9% solution to its blood/plasma donor centers. The product will also be available to hospitals and compounding centers.

THE IMPORTANCE OF LARGE-VOLUME PARENTERALS (LVPs)

Drugs administered as parenteral solutions are prepared as either small-volume or large-volume products. Large-volume parenterals (LVPs) include intravenous solutions sold in bags or bottles containing 100 mL or greater (250 mL, 500 mL, 1 L). They are packaged in these large volumes because larger quantities are typically required. Common LVPs include solutions needed to correct electrolyte and fluid imbalances, provide important nutrients or act as a vehicle for the delivery of other drugs. The most common examples include sodium chloride solution, dextrose solution, Ringer's solution, and lactated Ringer's solution, as well as combinations of dextrose and sodium chloride.

The market for LVPs is expanding due to an increase in the numbers of surgeries performed and the growing numbers of patients with chronic and other lifestyle-related diseases requiring hospitalizations.[1] LVPs provide a faster method for administering drugs to patients during surgery and when in the hospital. A growing preference by patients for single-dose administration of vaccines and drugs to treat chronic diseases is also driving demand for LVPs.

THE CHALLENGES OF LVP SHORTAGES

Despite the growing interest in LVPs, only a few manufacturers produce these important products for the US market. In fact, increased demand in combination with manufacturing delays and other problems has led to shortages of key LVPs in the United States.[2] Some manufacturers have also discontinued production of products in certain packaging or withdrawn from the market altogether. In its second report on national drug shortages in the US, the Council of Science and Public Health stated that quality problems, manufacturing delays, limited production capacity – particularly for generic sterile injectable products including LVPs – and product discontinuations accounted for more than 80% of the drug shortages in 2014 and 2015.[3]

Currently, there are shortages of sodium chloride (saline) and dextrose solutions sold in large-volume bags for injection.[2] These shortages began in early 2014 and at the time were expected to be resolved by the summer.[4] According to an Infusion Nurse blog post in March 2014, "Not having IV Saline solution available is like not have bread and milk at the grocery stores."[4]

A VERTICAL INTEGRATION STRATEGY

Production of sterile injectable drugs must occur in highly controlled environments in accordance with current good manufacturing practices. Extensive process understanding is required to ensure the consistent manufacture of high-quality products. Advanced quality programs combined with state-of-the-art automated aseptic processing systems are essential.

Grifols has been manufacturing parenteral products, including LVPs such as sodium chloride 0.9% solutions, for more than 50 years. To ensure the highest quality, the company has adopted a vertical integration model for control of the entire manufacturing process and implemented automation technologies (robotics) and advanced process controls (e.g., artificial vision) to reduce human interactions with injectable products and thus further minimize the potential for contamination.

Grifols' pharmaceutical production plants, processes and machinery are designed by Grifols Engineering, which – because it is a Grifols company – is knowledgeable about the quality and compliance requirements for parenteral manufacturing. The bag molding process, often a source of particle generation, has been integrated into Grifols' filling operations through the adoption of Form-Fill-Seal technology. This approach allows Grifols to ensure complete control of this critical process.

This vertical integration philosophy is being extended to the production of LVPs for the US market. Grifols is one of the top three players in the plasma-derived proteins market. The company operates blood/plasma donor centers across the US. Each blood donor receives 500 mL of sodium chloride 0.9% solution, which currently is provided by another supplier. The shortage for several years of this important LVP has presented Grifols with an untenable situation. The company's blood donor centers, which are part of its core business, are at risk of being without this essential product. Vertical integration through the internal production and supply of LVP saline solutions eliminates this risk.

BACKED BY DEMONSTRATED QUALITY AND EXPERTISE

Grifols has successfully manufactured sodium chloride solutions for the European market at its Spanish manufacturing facilities for more than fifty years. Both its plasma-derived proteins and parenteral manufacturing businesses, and in fact all activities from non-biological injectable products to reagents and instrumentation for clinical diagnosis, are operated within a quality culture founded on a commitment

to continuous improvement and ongoing achievement of the highest quality levels.

As a result, the company has never experienced any quality problems with its blood derivative products due to virus contamination or any recalls of its parenteral products due to particulate contamination. An FDA audit in June 2015 generated zero 483 observations. In addition, Grifols was one of the first companies in Europe to obtain approval for the parametric release – which requires historical demonstration of excellent sterility test results and highly consistent quality system performance – of parenteral solutions in glass and flexible containers from its EMA- and FDA-certified production plants in Barcelona and Murcia, Spain.

ENTERING THE US MARKET

To implement its vertical integration philosophy for large-volume solutions used at its blood donor centers in the US, Grifols required FDA approval. An application for a 500-mL product was submitted to the Center for Biologics Evaluation and Research (CBER) within the FDA, with which Grifols has a long-standing relationship. FDA approval was received in May 2017.

Production of sodium chloride 0.9% solution for the US market in 500-mL bags was initiated at the Grifols manufacturing plant in Murcia, Spain in late 2017, and export of the product began in early 2018.

A fourth, completely automated Form-Fill-Seal line will be operative in the coming months to guarantee that it has sufficient production capacity to supply to blood donor centers, hospitals and compounding centers. With these automated lines, the operator uploads the polypropylene rolls and the bags are formed, filled and sealed and then sent for overwrapping; interactions between the operator and the process are avoided, minimizing any risk of contamination and human error. Inspection of injectable products for particulates is also automated using artificial vision systems developed in collaboration with Diagnostic Grifols.

CONCLUSION

Production of high-quality, sterile parenteral products involves complex processes. There are few manufacturers willing to take on the challenges associated with parenteral manufacturing for inexpensive, basic generic parenteral solutions to be marketed in the US. Natural disasters, quality issues and other manufacturing problems have resulted in shortages of saline, dextrose and other widely used solutions that are offered as LVPs.

With its long history of LVP production for the European market, Grifols has demonstrated its ability to implement cost-effective processes for the consistent production of high-quality LVP solutions. The company has determined that internal supply of LVPs is essential for reducing the risk to its US blood/plasma donor centers posed by ongoing shortages of important LVPs.

The company will supply these centers with 500 mL solutions during 2018. Grifols is also offering this important LVP to hospitals, pharmacies and compounding centers in the US. Minibags (50 mL, 100 mL and 250 mL) will be available soon.

If the US market responds in the way Grifols expects, the company plans to submit additional applications to FDA for 5% dextrose IV solutions in volumes of 100 mL, 250 mL and 500 mL. P

Minibags are Coming Too

In addition to shortages of LVPs offered in large plastic bags, there are shortages of smaller "minibags" in volumes of 50 mL, 100 mL and 250 mL. The hurricanes that devastated Puerto Rico earlier this fall have affected production of these products.[5] Such shortages are having an impact on hospitals, home infusion pharmacies and infusion centers. The greatest shortages exist for 50- and 100-milliliter minibags of sodium chloride 0.9%, dextrose 5%, and IV nutritional products, according to the American Hospital Association.[5]

To address the shortage, FDA is allowing the temporary importation of products from overseas, including minibags of sodium chloride 0.9% injection bags, dextrose 5% injection bags, and metronidazole injection.[5] The agency is also expediting the review of any new product applications that will help resolve the shortages.

Grifols will submit the approval of its saline solution in 50 mL, 100 mL, 250 mL and 1000 mL to the FDA. In addition to hospitals and pharmacies, compounding centers use saline solutions in minibags to reconstitute lyophilized antibiotic and oncology therapies. The company will be marketing the minibags to all users throughout this year.

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OVERCOMING CHALLENGES IN THE COMPLEX MARKET FOR CLINICAL TRIALS AND CLINICAL LOGISTICS

→ BY **WES WHEELER**, MARKEN

Increasing complexity, evolving treatment strategies, advancing technologies, data security challenges and the growing focus on patient centricity are all impacting the way in which clinical trials are conducted. One outcome of this has been the expanded outsourcing of clinical trial supply and logistics. These trends are expected to continue for the next several years. As a dedicated, one-stop, full-service clinical supply chain solution provider, Marken provides insights to help customers overcome numerous and interconnected supply chain challenges.

EVOLVING TREATMENT STRATEGIES

As clinical trials have become increasingly complex and expensive, drug developers are relying on external service providers to source clinical trial materials and deliver them to investigator sites and to the patient. Further reliance on outsourcing of all clinical trial supply and logistics tasks will drive strong growth in the market, which encompasses logistics, storage and transport of clinical trial materials – including investigational drugs, ancillary supplies and biological specimens – to and from clinical trial sites or patients' homes directly.

Cell and gene therapies, immunotherapies and other personalized medicines have brought new hope to patients fighting cancer and other previously untreatable diseases. However, they present significant challenges for the clinical trial supply setup, as transit times are stringent and patient identification, visit scheduling and full end-to-end visibility at all times are critical to the success of these trials.

In addition, patient recruitment for clinical trials has become increasingly challenging in recent years.[1] Drug developers racing to market with the first compound in a therapeutic class must recruit the statistically required number of patients as quickly as possible, particularly if other pharmaceutical companies are conducting competitive trials. As the industry has shifted its focus to orphan and other specialized drugs targeting narrow indications, finding patients in the US and Europe that meet trial criteria has become quite difficult. There has, as a result, been tremendous growth in patient recruitment in places such as Mexico, Russia, Ukraine and South Korea.

ADVANCING TECHNOLOGIES

Technological developments are also impacting clinical trial logistics, both on the inbound and outbound sides. As more Point of Care (POC) diagnostic technologies are developed, there will be a shift in the future towards performing more and more local analyses and transporting less blood, tissue, urine and other samples to a central location for analysis. Data transfer and management of the devices will become critical factors to the success of clinical trials. These new POC devices can be potentially designed to analyze blood from a finger prick and transmit the data over the internet. If (or when) this happens, our market will be revolutionized. Central labs will rely less on blood collection, and will specialize in high-end esoteric analysis. The manner in which clinical data is collected will clearly be disrupted.

On the outbound side, the value of our shipments has increased dramatically as the number of expensive biologic drugs in development has grown. Some of these drugs can take up to two years to produce and are very difficult to replace. A single shipment of sterile vials can be valued at more than $10 million. Effective management of these shipments has, therefore, become more crucial than ever.

Advances in smart packaging solutions, including active and passive thermo-regulated products, ensure shipments remain within proper temperature ranges while en route and in storage to safeguard the shipment's contents. GPS-enabled devices, including SENTRY, perform real-time tracking of a shipment's location and condition, including motion, shock, battery life, and light exposure, all while sending SMS messages of any excursions or deviations. SENTRY is accepted on over 95% of commercial airlines with technical acceptance by Civil Aviation Authorities in all regions. Our Global Control Center (GCC) in Mumbai monitors shipments to all of our regions across the globe. The Center transmits data through its proprietary MAESTRO operating system.

Because of our SENTRY technology and GCC, we have, on numerous occasions, saved shipments that were misplaced or lost by commercial airlines. When a sample is lost or a patient misses a dose because a drug is not delivered in time, that patient may be removed from the trial. Marken's advanced monitoring and track-and-trace technologies have therefore had a significant impact on patient retention and trial success rates.

Sponsor companies are also expecting third-party logistics providers to implement good distribution practices (GDP). In Europe, supply chain solutions must be aligned with requirements outlined in Annex 15, Chapter 6 regulations. Implementing best practices is achieved when manufacturers of clinical drug products work closely with supply chain solutions providers.

AT MARKEN, WE ARE COMMITTED AS AN INTEGRATED CLINICAL TRIAL LOGISTICS PROVIDER, **TO SUPPORT OUR CUSTOMERS WITH VALUE-ADDED SERVICES**.

We are now required to validate and document the mapping of shipping lanes and develop contingency plans. Additional scrutiny is also being given to the temperature-controlled supply chains for clinical drug distribution. Supply chain safety, shipment integrity, and risk management/contingency planning are other important factors to be considered.

PATIENT CENTRICITY

Patient centricity continues to be a real factor in designing trial protocols, with a focus on maintaining patient convenience. Patient surveys, patient groups, opinion leaders and enhanced tools to collect data will drive clinical trial reporting design, feedback, and ongoing data collection that is multi-directional and allows the definition of new endpoints at any given moment. The rapid acceleration of patient-centric home care is also presenting new challenges, as growing numbers of clinical trials include in-home patient visits. Mobile applications are common, and devices such as Apple Health are revolutionizing the way patients access their health records.

The complexities of a global direct-to-patient (DTP) program, particularly in the last mile, require a supply chain solutions provider with the ability to anticipate potential points of risk, that has proven contingency plans in place, and offers complete tracking transparency to monitor shipments in real time as

PATIENT CENTRICITY CONTINUES TO BE A REAL FACTOR IN DESIGNING TRIAL PROTOCOLS, **WITH A FOCUS ON MAINTAINING PATIENT CONVENIENCE.**

part of an end-to-end visibility solution, while respecting all applicable patient privacy laws.

Because of the sensitivity and value of clinical drug products, end-to-end visibility is extremely important, particularly for DTP services, to ensure that the administered drug is safe for the patient. We have plans for further technology development to ensure tighter control and end-to-end visibility, variations of GPS trackers and smart packaging solutions.

We have experience with thousands of DTP shipments since starting this service in 2012. We are currently managing and coordinating DTP/Direct from Patient (DFP) services for over 80 clients around the world. In addition to our Patient Communication Center – a 24-hour, 7-day-a-week call center based in Philadelphia (USA) dedicated to the logistics needs of patients who participate in home-based clinical trials – Marken recently introduced an online interface, **Viseo**, which offers patients the ability to track their home deliveries of clinical trial materials and the pickup of their biological specimens via their mobile devices or personal computers.

With a simple click, patients can view the driver's name and follow his/her progress right up to their front door. A photo of the driver shows exactly who will ring the doorbell with the Marken delivery or pickup. The on-screen rating option after delivery provides direct and immediate feedback on the service and experience of the patient. This type of real-time driver traceability can translate into improved patient expectations and confidence with DTP or DFP trials and reduce the number of rescheduled deliveries and delays.

MAINTAINING DATA SECURITY

Compliance with data protection laws is another challenge. The General Data Protection Regulation (GDPR) goes into effect in the EU on May 25, 2018. The regulation has strict rules about how personal data may be used and how it must be protected and sets a 4% administrative fine, up to the *greater* of €20 million or 4% of global annual turnover in the prior year for noncompliance. Many organizations will need to make significant investments in basic tools to comply with GDPR requirements. We have actively ensured that all of our data protection, privacy, and IT infrastructure are in full compliance with not only the GDPR regulations but all patient privacy rules and guidelines worldwide.

Recent ransomware attacks show a increasingly important threat to pharma and logistics companies. A leading pharmaceutical company was hit by the rapidly spreading Petya ransomware in 2017. Several other attacks throughout the year impacted manufacturing and formulation operations, shipment tracking, data collection and time-sensitive services, and even just this month, another global logistics company was impacted by a significant data breach. In this instance, we were able to rescue hundreds of shipments from that provider's warehouse. Our ATA transmission and IT infrastructure are designed to withstand such attacks.

MARKEN IS MAKING A DIFFERENCE

At Marken, we are committed as an integrated clinical trial logistics provider to supporting our customers with value-added services. For instance, as the independent, wholly-owned Clinical Supply Chain subsidiary of UPS, we have launched a hybrid service in 2017 that combines our expertise and capabilities in managing deliveries over the last mile with UPS airline and ground operations. The hybrid service enables the booking of shipments in Marken's proprietary MAESTRO operating system, managing them from origin to destination while using the UPS network in a seamless and effective manner.

We also continue to further develop our position as the dedicated one-stop, full-service clinical supply chain solution provider for the pharmaceutical industry. Just recently, we announced the opening of an additional kit-building facility in Shanghai, China and a new operational hub in Stuttgart, Germany. In December 2017, Marken announced the opening of our 6th location in India (Ahmedabad). We continue to expand, grow and extend the services and additional value that we provide to our clients and the clinical supply chain. The next step in our DTP journey will be the development of our own nurse network. We are also investigating the possible future application of autonomous vehicles, drones and block chain technology to continue on our innovative path. P

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

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FACILITATING IMPLEMENTATION AND CUSTOMER SERVICE WITH OFFLINE SERIALIZATION

→ BY **TYLER EWALD** AND **JOSEPH QUALES**, UPM PHARMACEUTICALS

Even though the FDA has extended the deadline for compliance with unit serialization requirements, UPM Pharmaceuticals serialized its first commercial product in May 2017, well ahead of time. The use of an offline serialization system facilitated implementation and provides numerous benefits to our company and our clients.

RISING INCIDENCE OF FRAUDULENT MEDICINES

Drug counterfeiting is a global and growing problem. In 2010, the World Health Organization (WHO) estimated that the incidence of counterfeit drugs is less than 1% in developed countries and much higher in developing countries.[1] As of November 2017, the WHO estimate that 1 in 10 medical products in low- and middle-income countries is substandard or falsified.[2] Its Global Surveillance and Monitoring System, founded in 2013, had issued 20 global medical product alerts and numerous regional warnings and provided technical support in over 100 cases.

In the US, between 2010 and May 2016, close to 1,400 adverse reactions related to counterfeit drugs were reported to FDA.[3] This data does not include incidences of counterfeit or compromised medications that do not lead to any adverse reactions or have no effect. As a result, the true extent of the problem is unknown.

SERIALIZATION EXPECTED TO HELP

Governments around the world have responded to the increasing presence of fake medicines in the drug supply chain by passing regulations requiring that pharmaceutical manufacturers implement systems that allow for the track-and-trace of drug products throughout the supply chain. Compliance is already required in some countries, while deadlines are fast approaching in others. The detailed expectations vary from country to country, and even over time within individual countries. They are also constantly evolving.

In the US, serialization requirements were established in the Drug Quality and Security Act (DQSA), which became law in November 2013. The law applies to manufacturers, repackagers, wholesale distributors, dispensers and third-party logistics providers. Title II of the DQSA outlines the requirements for supply chain members with respect to the implementation of track-and-trace systems for prescription drugs in three phases over 10 years. The sharing of lot-level information was completed in 2015. The serialization of all product units and the sharing of this data were to be completed by November 2017; and the sharing of aggregate data linked to unit data to establish chain-of-ownership throughout the drug supply chain from the manufacturer to the patient was initially set for 2023.

TRACK-AND-TRACE MORE COMPLEX THAN ANTICIPATED

Most large pharmaceutical companies and a select few CDMOs have taken an aggressive approach to implementing comprehensive internal serialization solutions.[4] Many companies, particularly smaller and medium-sized firms with limited resources, have adopted a "just-in-time" approach, implementing only those elements of the system needed to meet specific deadlines in different countries.[5] There are still a large number of smaller companies that are just beginning to initiate internal track-and-trace programs. Others have elected to forego any internal efforts, preferring to rely on outsourcing partners. A few companies also remain that have not taken any action with regard to serialization.

Implementing serialization solutions has, in fact, proven to be more complex and challenging than many pharmaceutical producers – both sponsor firms and contract development and manufacturing organizations (CDMOs) – expected. Companies must establish bi-directional data exchange connections with a wide range of suppliers and other partners (including clients and distributors for CDMOs), grapple with a dramatic increase in the quantity of data that must be generated and managed, stay up-to-date with evolving regulations in numerous countries, and implement their solutions without any disruption in the supply of their drug products.[5] The FDA responded by extending the deadline for compliance with the establishment of unit serialization by one full year, to November 2018.

ADDITIONAL CONSIDERATIONS FOR CONTRACT MANUFACTURERS

For any serialization system, definitions and formats for serial numbers must be determined. Sufficient space must be available on the product packaging to apply the serial number and other relevant data. A management system must be in place to allocate the serial numbers and link them to larger groups of unit packages, such as boxes and pallets (parent/child relationships) and to orders, shipments, etc. A system for handling other issues – repackaging, rework, returns, etc. – is also necessary.

Implementing an effective serialization solution is, therefore, challenging for any type of drug manufacturer. In addition to being quite costly, serialization impacts many different company operations and thus requires input from representatives of many different groups. Labels must be redesigned, and large quantities of new data must be properly managed and shared with appropriate partners in the supply chain. The new system must be implemented without negatively effecting production operations. Serialization cannot result in reduced efficiencies.

Contract manufacturers have the added challenge of needing to serialize different drug substances and/or drug products for many different clients, each with its own understanding of serialization and related set of expectations. In addition, contract manufacturers do not control the labels that they must use, but have to work within the capabilities of their serialization equipment. It is essential for CDMOs to make sure their customers understand those printing limits to ensure that mandated information is appropriately included on product labels.

FLEXIBLE STRATEGY AT UPM

UPM has always had strict procedures and specifications in place for labeling of drug products. We work closely with our clients and their product management teams to ensure that all labeling is correct and products are branded and otherwise labeled as they are supposed to be. We also have an extensive vendor approval process to ensure there are no mix-ups with labels or diversion of artwork to people trying to produce counterfeit versions.

When embarking upon our serialization project, we recognized the need to maintain this high level of security while implementing a flexible track-and-trace solution that allows for tailored customer service combined with robust and reliable performance. We wanted to be able to serialize bottles, cartons and cases, without disruption of production while maximizing the capacity on each of our packaging lines.

IN THE US, BETWEEN 2010 AND MAY 2016, CLOSE TO 1,400 ADVERSE REACTIONS RELATED TO COUNTERFEIT DRUGS WERE REPORTED TO FDA.

Our solution was to adopt an offline serialization strategy. At UPM, our serialization workstations are not associated with a packaging line. This approach provides the greatest amount of flexibility to serve our three packaging lines. Rather than having to set up the packaging equipment for printing, verifying and applying labels that will be serialized during packaging, we preprint the serialized labels/cartons in advance, electronically grading and verifying the information offline, and then apply the labels or fill the cartons during production.

Serialization offline affords us the flexibility to rapidly respond to customer requests for trial serialization runs. Often smaller customers aren't confident their labels will have sufficient space. Rather than needing to wait for time to be available on a packaging line, we can conduct trial runs on our offline workstation to determine if a label is ready. Offline serialization also provides the ability to troubleshoot problems without tying up a packaging line. As a result, we are able to maintain production efficiencies and maximize capacities.

In addition, while UPM selected TraceLink – the world's largest cloud-based provider of serial codes – as our serialization software partner, TraceLink is capable of working with whichever serialization codes are used by our clients with an interface built between other serial code providers and TraceLink. The transmission of data with TraceLink has proceeded without any issues. Since the link was established, we have consistently received codes and sent them back

to TraceLink for commissioning. All lot statuses can be verified on TraceLink's website once code transmission is complete.

CROSS-FUNCTIONAL EFFORT

A core cross-functional team was involved in establishing UPM's serialization strategy and bringing the project to fruition. Representatives from our information technology, technical service, manufacturing and quality groups formed this core team. The IT department worked closely with the equipment manufacturer and TraceLink to understand all of the system specifications as well as hardware and software requirements needed to manage and maintain our serialization operation.

Label control is an essential component of pharmaceutical packaging. The addition of a serialization component added another layer of complexity to label control. It was thus determined that a labeling department would be created to control all serialization activities and manage new clients. This department is within the quality assurance group and is responsible for generation of serial codes, generating and issuing serialized labeling, and reconciling completed batches once production is finished.

STAYING AHEAD OF SCHEDULE

The goal at UPM was to be six months ahead of the regulated implementation date for serialization, allowing for enough time to ensure a seamless serialization process. UPM management was committed to making sure the capital was available to acquire and install the necessary system components ahead of the curve. We also benefited from partnership with a client that used UPM as a beta site before bringing a similar serialization system into its own facility.

The first commercial batches serialized by UPM were produced in May 2017 – well ahead of the original November 2017 deadline for unit serialization. Despite the one-year extensions granted by FDA, we have remained committed to our timeline for serialization of all batches. We currently meet the requirements that will go into force in November 2018. In addition, we have procedures and processes in place for on-boarding new clients and new products from existing clients, 75% of which we are currently serializing.

THE FIRST COMMERCIAL BATCHES SERIALIZED BY UPM WERE PRODUCED IN MAY 2017 – WELL AHEAD OF THE ORIGINAL NOVEMBER 2017 DEADLINE FOR UNIT SERIALIZATION.

CONCLUSION

Serialization, when used in conjunction with tamper-resistant packaging and other fraud-prevention methods, is expected to provide greatly increased security for the pharmaceutical supply chain. The transparency provided by the ability to trace the movement of a product unit throughout the supply chain, from the manufacturer to the distributor – and on to the patient, should provide a mechanism for the identification of both authentic and questionable medicines.

We are also building a base of understanding and preparing to respond to the unexpected when it happens. For instance, we have established complaint procedures and validated communications between UPM and our clients. In addition, we are evaluating current solution providers as we look to the next phase of serialization – aggregation. Labeling, including printing, application, verification and aggregation will be required to be done online. We are already preparing for this next level by considering the lessons learned during the first phase of serialization implementation at UPM. P

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Mr. Ewald serves as UPM's Associate Director of Manufacturing. He brings a broad knowledge of the pharmaceutical industry, having managed operations from intravenous to solid dose products. He served as the packaging department lead for UPM's procedural development and implementation of serialization. Mr. Ewald holds a Bachelor of Science in pharmaceutical sciences from Campbell University and a Masters of Business Administration from East Carolina University

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DRIVING CHANGE IN THE PHARMA INDUSTRY AND BIOTECH ONE RELATIONSHIP AT A TIME

→ BY **SYED T. HUSAIN** AND **CATHERINE H. HANLEY**, ALCAMI CORPORATION

Although small and medium-sized pharma and biotech companies are driving the growth of the industry, they often don't receive the attention and assistance that are essential to their success. Changing the industry's mindset is critical. Alcami is establishing many different relationships intended to facilitate and accelerate just that.

SMALLER FIRMS ARE DRIVING GROWTH

Historically, growth in the pharmaceutical industry has been driven by large pharmaceutical companies developing blockbuster drugs. That is no longer the case. Many companies today are focused on the development of treatments for diseases that afflict much smaller patient populations. A majority of these firms are founded by academic researchers that have discovered new molecules with desirable biological activities. Indeed, the success rates of smaller firms are often higher; the Tufts Center for the Study of Drug Development reports that smaller firms developing small-molecule drugs have higher clinical approval success rates than large companies.[1]

WHY RELATIONSHIPS MATTER

There are nearly 3000 pharmaceutical companies in the US with revenues of $500 million or less. Despite the fact that these firms often have very limited resources and sometimes little knowledge of the regulatory approval process, approximately half can be found in locations with minimal outsourcing support. This presents a challenge for innovators. This significant sector has, until recently, largely been neglected by the rest of the CDMO industry.

Alcami, through the establishment of many different types of relationships, is seeking to address this issue. The company was built to serve thriving new drug innovators also known as "two persons and a patent." Given the unique needs of this segment of the industry, Alcami has implemented a commercial strategy guided by an educational approach that seeks to address the needs of these smaller firms.

One element involves investment in industry trade associations. In many cases, these industry groups still place a heavy emphasis on large pharma. However, Alcami is serving as the voice for small and emerging pharmaceutical and biotech companies to drive change and positively impact the industry, and creating forums for this. Driving these efforts is the recognition that small and medium-sized firms are the innovation engine of the pharmaceutical industry and represent its future.

The second aspect of our commercial strategy is to provide companies that aren't familiar with the drug development and approval process with the information they need to be successful. Through various physical and digital events, we bring crucial knowledge about everything, from what data is needed to meet CMC requirements, to submitting regulatory applications, to ensuring robust process development, scale-up and supply chain solutions to support clinical trials and launch.

ROLE OF CDMOs

Why would a CDMO want to take on this role? Small and emerging pharmaceutical firms rely extensively on third-party services across the entire drug development and commercialization cycle. CDMOs that can provide integrated, end-to-end solutions and support these companies throughout the entire process can contribute to their success. As importantly, CDMOs with knowledge about the potential range of indications for a new drug substance, possible synthetic routes, efficient approaches to process optimization and regulatory pathways – and how to pull all of these components together – can provide the best possible service.

At Alcami, we believe that the success of small and medium-sized pharmaceutical companies is essential for continued growth of the industry. We have established integrated capabilities, combined with educational programs, specifically to meet the needs of these important customers. In addition, we treat every customer – whether a first-time, emerging pharmaceutical firm preparing for clinical trials or a small/midsize pharma company gearing up for launch and commercialization with multiple projects – equally. Each and every customer deserves the same amount of respect and attention – delivering on project objectives is important for all projects, regardless of size.

ASSOCIATION CONNECTIONS

Associations are an integral part of the pharmaceutical industry. On the global, national and regional levels, these organizations bring members of the entire value chain together using a variety of mechanisms, from trade shows to educational conferences and workshops. Regional associations, in particular, provide local forums where CDMOs like Alcami can learn more about small and medium-sized pharmaceutical developers and the local markets in which they operate. They provide a means for showcasing new ideas and reveal to the rest of the pharmaceutical community which universities and startups are driving innovation.

At larger trade shows, however, smaller firms have found it difficult to garner attention from pharmaceutical companies and larger service providers. With the launch of our first-to-market Alcami After-Hours™ networking events at conferences including BIO International and CPhI Worldwide, Alcami is alleviating this problem. These networking sessions are specifically designed to foster personal connections between Alcami experts and the scientists and executives (often the same people) from small and medium-sized pharmaceutical companies. We want to make sure that potential customers get to know the people behind Alcami.

EDUCATIONAL EFFORTS AND EVENTS

As smaller pharmaceutical firms have limited resources, it is often not possible for them to attend valuable events. Alcami, as part of its educational approach, has developed alternative outreach efforts to ensure that all firms seeking to learn about the drug development and approval process have access to the information they need.

Quarterly educational events are held at our sales offices globally, in order to bring the CDMO concept *to the customer* – a key step in the educational process of turning their concepts into medicines. These educational forums and other custom events will focus on critical topics related to the development and launch of drugs within the US. Educational opportunities range from structured workshops to informal discussions on what is needed to take a drug through the development process. They include participation by both Alcami scientists and external

DCAT Week 2018

DCAT Week, the annual event held by the Drug, Chemical & Associated Technologies Association, is different than most other pharmaceutical shows in that it provides opportunities to bridge the large and small pharma worlds. Startups and virtual companies are given a platform for communicating their ideas to potential investors and service providers. For that reason, Alcami continues to expand its participation in the association, which is a 501(c)6, not-for-profit, member-supported, global business development association with members comprising branded and generic drug makers and their suppliers. Alcami's President, Chairman and CEO, Dr. Stephan Kutzer, was first elected to the DCAT Board of Directors in November 2016 as the Third Vice President and is currently serving a second term as the Second Vice President. Chief Commercial Officer Syed T. Husain was also appointed to the DCAT Advisory Council and has held previous leadership positions as Chair of the Education Committee and Task Force lead for the DCAT Sharp Sourcing forum.

Catherine Hanley, Brand Development and Awareness Leader at Alcami, serves on the planning task force for the DCAT Sharp Sourcing forum, which brings suppliers engaged in the pharmaceutical manufacturing value chain together with customers of all sizes. The event includes the presentation of solution-based practical insights from leading industry experts, round-table discussions with notable thought leaders, specialized educational forums for buyers and suppliers, and networking opportunities. Importantly, this event enables communication between innovator companies performing development and large pharmaceutical companies that are more focused on commercialization. It also serves as an important venue for suppliers to share industry knowledge and learn from one another.

To meet Alcami at DCAT Week, contact marketing@alcaminow.com or find us in the DCAT member lounge at The Palace Hotel, and Pre-Annual Dinner reception at The Hilton.

experts and are intended to provide existing and potential customers with the information they are seeking.

SCIENTIFIC PARTNERSHIP

In the US, Alcami is involved in an academic partnership with the University of North Carolina Wilmington (UNCW). Since July 2016, we have collaborated to develop two courses designed to enhance workforce education and prepare students for a career in pharmaceutical sciences. In Spring 2017, an elective course designed to provide students with an overview of the drug development process from concept to commercialization, focusing specifically on current good manufacturing practices (cGMP), was co-taught by the Alcami team, while a laboratory-based course was offered in the fall. We are also involved in co-research with UNCW at the Marine Biology Center (MARBIONC) in Wilmington, North Carolina. This partnership reflects our commitment to building and maintaining strong relationships with the communities in which we operate. We feel privileged to be able to share our expertise with the university's students.

LISTENING TO THE CUSTOMER

Effective relationships can make a difference. Industry-related partnerships, relationships with consultants, collaborations with universities, internal relationships that enable truly integrated customer support, educational relationships with potential customers and strategic partnerships with existing clients are all crucial. Anticipating customer needs is the ultimate driver of business growth. The relationships we establish across the pharmaceutical community are designed to connect us to clients at every level and facilitate the implementation of our "customer are a privilege, not a right" approach. In addition, our company size and culture, end-to-end offerings and commitment to education contribute to our responsiveness and ability to deliver on time, every time. P

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Syed Husain, the commercial leader for Alcami, leverages in-depth experience in sales, business development, marketing and operations for the development and manufacture of small molecules, antibody drug conjugates, peptides and large molecules covering drug substance and drug product. Syed earned a BS in chemical engineering from New Jersey Institute of Technology in 2003 and an MBA from Cornell University in 2009.

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Catherine Hanley, Alcami's brand development and awareness leader, has 13 years of commercial and operational experience. Integral to her function are the continuing efforts toward expanding Alcami's global presence, thought leadership, customer experience, first-to-market initiatives, and the implementation of the Inbound Marketing & Sales strategy along with service launch design to ensure Alcami stays connected with its clients at every level. Catherine holds a BA from Franklin & Marshall College and an MBA from the University of Maryland, Robert H. Smith School of Business.

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First-to-Market Initiatives

Providing small and medium-sized drug developers with knowledge is not the only way Alcami is helping this important sector of the industry. We are also committed to introducing first-to-market initiatives designed to enhance the customer experience, particularly for smaller clients with limited resources.

For companies that lack full-scale laboratories, Alcami offers the Extended Workbench Program, a full-time equivalent (FTE) program tailored to each client's needs. The program includes dedicated lab space and scientists along with dedicated project management and technical leadership, 24/7 digital access and flexible resources. The goal is to provide customers with a seamless solution integrated with their own operations.

Alcami has also developed a customer portal, Alcami OnDemand™ that serves as a single source for customer project and order management with shared views to manage orders, libraries of compounds, test results and accounting information. It meets the market need for a simplified sample submission process, real-time tracking of sample submissions and projects, customer access to historical data and transparency. Alcami OnDemand™ gives our clients and prospects rapid access and visualization into ongoing projects.

In 2017, Alcami launched a fully interactive virtual tour experience for clients and potential customers to see our sites before visiting them. Alcami's Virtual Lab addresses our prospects' needs to save time and resources when deciding on a partner. The virtual experience is available online at www.alcaminow.com/virtual-lab, linked from our website, and has been featured at industry events throughout the year, with our Igloo Vision Ltd. viewing theater. We are now expanding the experience into virtual glasses so we can take the experience on the road to our clients and into our sales offices.

Those companies looking to implement a dual sourcing strategy but who lack the resources to secure a permanent second sourcing option can turn to Alcami's industry leading offerings like Protect Your Brand. Subscribers to this program can quickly bridge unexpected gaps in supply without the need to commit to a long-term supply agreement. Alcami will validate a product, maintain the required capacity and be ready to rapidly begin production in accordance with US and international regulatory compliance requirements if needed. Three options are available to prevent disruptions during the concept phase through post-commercialization.

WHY BUSINESS CONTINUITY MANAGEMENT IS IMPORTANT FOR CDMOs

→ BY **MAYEUL CAUVIN**, SERVIER

Members of the pharmaceutical industry have a responsibility to guarantee both the supply of high-quality medicines and the safety of their personnel. Servier has implemented a global business continuity management strategy to reduce the likelihood of incidents and minimize any consequent impact on its operations.

UNDERSTANDING BUSINESS CONTINUITY MANAGEMENT (BCM)

Business continuity refers to the ability of a company to continue to perform critical business functions in the case of disruptions such as natural disasters, fires, computer system crashes and geopolitical events. Business continuity management (BCM) involves the development and implementation of a management strategy to ensure that the necessary infrastructure and procedures are in place and personnel are prepared to appropriately respond when incidents do occur. A business continuity plan includes elements of emergency response, crisis management, disaster recovery, supply chain security and organizational/operational relocation.[1]

BCM matters because it impacts a business' competitiveness and provides assurances to the buyers of contract services. Companies that are recognized as resilient to potential disasters will be able to attract new customers and those that continue operating in the event of a disruption will retain their existing customers. Having an effective BCM strategy also ensures a company can continue operating – and thus keep its employees working.

BCM activities typically fall under the aegis of quality and risk management departments, but also involve governance, information security and compliance groups. Commitment from top management is essential to implementation of an effective BCM strategy. The effort begins with performance of a business impact analysis (BIA) to identify the critical operations, facilities and equipment that may be vulnerable to disruptions, determine what the potential impacts are, and reveal gaps in the ability to overcome these losses.[2]

There are global, regional and country-based business continuity standards that can be used to guide the development of BCM strategies and programs. For instance, ISO 22301:2012, "Societal security – Business continuity management systems – Requirements"[3] and related ISO 22313:2012, "Societal security – Business continuity management systems – Guidance"[4] support the development of formal BCM strategies.

There are also over 100 regulations relating to numerous industries including the healthcare sector[1] that demand some level of Business Continuity Management.

BCM AND THE PHARMACEUTICAL INDUSTRY

Business continuity planning can be particularly challenging for pharmaceutical manufacturers. It is not often feasible to move regulatory-approved, GMP manufacturing operations to another site in the event of a physical disaster. Ensuring a secure supply chain can also be difficult given that each supplier must be audited and validated, which often results in the use of a limited number of suppliers for even critical raw materials. On the other hand, the consequence of disruptions – such as shortages in the supply of crucial medicines, for instance – can be life-threatening.

Pharmaceutical manufacturers, including contract development and manufacturing organizations (CDMOs), have a social and patient responsibility to ensure that the production of drug substances and final drug products are not disrupted. Beyond the need to ensure the ongoing supply of important medicines, drug companies have a responsibly to mitigate threats to their business operations and assets in order to protect their employees, the environment and the local community.

Business continuity management is an effective structured approach to meet these obligations. It is also an effective method for achieving competitive advantage for contract service providers. CDMOs with a successful BCM strategy can demonstrate to potential customers the long-term sustainability of their business. Clients have greater confidence in manufacturing partners that have organization and resources in place to rapidly respond to potential threats to their operations. Projects are more likely to be successful and stay on schedule even if unexpected incidents occur.

BCM AND THE EMBEDDED CDMO

As an embedded CDMO within a large, global pharmaceutical company, Servier has over six decades of know-how and a strong record in quality, combined with empathy with our innovative customers. Our long-tenured, deeply experienced leadership team has an understanding of the needs of our clients and recognizes the importance of business continuity management.

Our BCM strategy has been developed and implemented to complement other key company initiatives, including our Lean Six-Sigma program, continuous improvement activities applied to equipment and processes, mitigation of operational risk through our "Safety-First" approach, and a quality culture that has supported more than 50 commercial launches.

BUSINESS CONTINUITY REFERS TO THE **ABILITY OF A COMPANY TO CONTINUE TO PERFORM CRITICAL BUSINESS FUNCTIONS** IN THE CASE OF DISRUPTIONS SUCH AS NATURAL DISASTERS, FIRES, COMPUTER SYSTEM CRASHES AND GEOPOLITICAL EVENTS.

SERVIER'S COMMITMENT TO BCM

Overall, we have two main goals: **[1]** to reduce the probability, as much as possible, that a disruption of our operations will occur, and, **[2]** in the event of an incident, to reduce the impact.

We recognize that not all incidents can be prevented. But with a BCM plan in place, we are prepared with equipment, procedures and strategies designed to reduce any impact and ensure continuity or at least rapid resumption of operations. The result is the protection of our people, the environment and Servier's business. This commitment to business continuity sets us apart from other CDMOs, underscores our acceptance of our responsibility to the patients, our employees and clients, and makes Servier CDMO an excellent strategic partner.

PROJECT MANAGEMENT STRATEGY

Our approach to business continuity management at Servier is very much a project management strategy. All of the business units within the Servier group are involved. An overall coordinator ensures that all business units work together to assess the risks – taking an operational approach and considering the key drivers for the company.

SERVIER'S MANAGEMENT HAS COMMITTED TO FUNDING BUSINESS CONTINUITY EFFORTS **THROUGH A GLOBAL FUND RATHER THAN HAVING EACH SITE FUND ITS OWN ACTIVITIES.**

The first step of the project is to identify the key products driving the turnover and margins. In the second stage, product mapping is performed using innovative methodology; this allows us to follow the volumes and costs of materials that flow through the buildings and equipment at our 15 global facilities. Based on this information, at the third stage, we are able to model several loss scenarios and evaluate the impact (in terms of disruption time, financial impact, etc.) for any situation. Finally, at the fourth step, we identify mitigation solutions to reduce our exposure.

Wherever possible, multiple suppliers are approved. The supply chain not only includes raw materials for API synthesis, but all elements involved in the manufacture of products – whether APIs or formulated drugs. Packaging suppliers are equally important, for instance. It is essential to ensure that suppliers in diverse locations (i.e., North America and Asia) with exposure to different risks are validated for all aspects of the production process to mitigate risk. This goal can be achieved by using two sources of supply for materials, or by using one supplier with multiple facilities.

RESOURCE CHALLENGES

Companies typically face three key challenges when developing and implementing business continuity plans: **[1]** finding the time to conduct evaluations and generate actions plans, **[2]** gaining access to the appropriate resources, and **[3]** appropriation of the necessary funds. Servier's management made a commitment to ensure that all three of these issues are continually addressed. The business continuity team has the ability to access external resources when needed. The area of fire protection is an important example. While our internal experts can identify the need for improved building protection, they might not have the ability to determine the best specific protective measures to implement.

External resources and suppliers are used to bring in the best knowledge and skills, ensuring that the investments being made are appropriate and adequate to address the identified risks. In this case, these resources include engineering firms, prevention specialists from insurance partners and other such experts. Servier's management has committed to funding business continuity efforts through a global fund rather than having each site fund its own activities. The decision-making process and prioritization of projects takes place at the corporate level.

EMBEDDED BUSINESS CONTINUITY

Successful BCM is not static – rather, it constantly evolves to meet changing market and customer needs. Servier CDMO is no exception. Each year, we not only have new projects, new customers and new suppliers, but new equipment and technologies as well. Business continuity management at Servier is, therefore, also a constantly evolving process. Each year the BIA is updated and this could result in a new BCM strategy, including the generation of a new action plan.

We focus on the implementation of backup solutions for key pieces of equipment and processes, protection of our equipment and facilities, and extensive auditing and management of our suppliers. The overall goal is to ensure the quality, safety and security of our manufacturing operations.

Notably, our BCM strategy often drives our operational strategy. Process mapping is performed whenever moving or changing equipment is proposed or when taking on a new project. This approach allows us to determine the choice that provides the least risk for the entire Servier group – anytime risk is reduced, performance is improved.

Finally, having a business continuity strategy has provided our employees with more transparency regarding risk within the company. While there was some resistance initially due to the additional effort required when first implementing the BCM strategy, today the thorough mitigation of risk is embedded within Servier's culture. Every employee recognizes his/her responsibility to protect the patient, the business, our customers and the broader community. P

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Mayeul Cauvin is in charge of Loss Prevention and Protection for all Servier's sites located in the world. He joined Servier in 2016, with more than 15 years of experience in Loss Control. Mayeul developed his expertise in Supply Chain Risk Evaluation, Business Continuity Management and Property Damage and Business Interruption evaluation and mitigation. Mayeul has encountered many different loss prevention approaches & requirements with different industry types, and with such experience, he is able to propose comprehensive and optimized solutions to reduce risk exposure.

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OVERCOMING FORMULATION CHALLENGES WITH LIQUID-FILL CAPSULES

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Solid oral dosage forms remain the preferred route of administration for many reasons. Many drug candidates today, however, cannot be formulated as tablets due to their poor solubility, high potency or sensitivity to processing conditions. For these complex APIs, liquid-filled hard-shell capsules enable formulators to overcome these issues while also achieving improved efficacy and safety.

COMPLEX MOLECULES MAKE FOR DIFFICULT ORAL SOLID DOSE FORMULATIONS

Increasingly complex small-molecule APIs are presenting a new set of challenges to drug formulators. Approximately 40% of current market drugs and 80% of pipeline candidates meet the Biopharmaceutical Classification System (BCS) definition of poorly soluble (classes II and IV).[1] In addition, the percentage of drug candidates that are classified as highly potent (highly potent active pharmaceutical ingredients, HPAPIs) is expanding. The global HPAPI market is expected to reach $34.8 billion by 2025, according to Grand View Research.[2]

LIQUID-FILL CAPSULES OFFER MANY BENEFITS

For APIs that cannot be formulated as powders into traditional oral solid dosage forms – either due to toxicity concerns, issues with abrasiveness, hygroscopicity or sensitivity to degradation from light and heat – encapsulation of a liquid in hard-shell capsules is an attractive alternative that still allows formulation as an oral solid dosage drug.

Formulation as a liquid can overcome many troubling physicochemical properties for APIs, giving formulators much greater flexibility. In fact, liquid-fill capsules can provide drug manufacturers with the opportunity to create formulations not previously possible. Both the drug formulation and the polymer composition of the capsule can be customized to accommodate APIs with many different properties and desired dissolution profiles.

As importantly, the dissolution of liquid-filled capsules is generally superior to that of other oral solid dosage forms. For two-part hard capsules, dissolution can start in as little as five minutes and be completed within 15 – and is often more consistent when compared to other solid dosage forms. Hard-shell capsules can also be designed to dissolve under different pH conditions, allowing controlled drug delivery in the gastric fluids or intestine, for instance.

Furthermore, the use of lipid-based solutions as liquid carriers increases the bioavailability of liquid-filled capsules compared to solid oral dosage forms. Lipid carriers are readily metabolized and provide for optimized absorption of the API. It is also easier to achieve homogeneity across low- and high-potency API formulations.

JOINING TOGETHER

The connecting of two-piece hard-shell capsules containing liquid formulations is advantageous over forced sealing methods using sprays to fuse the two halves together. With the latter approach, it is possible to compromise the integrity of the shell, which may lead to leakage of the contents – something that is unacceptable for HPAPIs.

In the banding process, on the other hand, the material used for banding is customized to work with the composition of the hard shell used to produce the two parts of the capsule. The band material seeps into the inseams of the capsule, drying and hardening at the same time, which allows for complete unibody fusion.

CUSTOMIZING AND OPTIMIZING

At CapsCanada, we specialize in liquid-filled hard capsules (LFHCs). Over the last three decades, we have perfected the technology to optimize LQ-CAPS® Liquid Formulation Capsules for our customers. In addition to standard capsule compositions, we develop customized capsule solutions to address the formulation needs of highly complex APIs with the goal of optimizing their performance. We are continually innovating to develop proprietary polymer formulations that provide the most stable capsules and hold the greatest quantities of API possible.

These special capsule polymer formulations require custom banding solutions that ensure protection of highly potent and otherwise sensitive APIs. CapsCanada's custom banding technologies create a custom seal, made with the raw material used to form the capsule (gelatin, HPMC, etc.), creating a secure seal that is both leak- and tamper-resistant.

Faster and more consistent dissolution inevitably improves the bioavailability of liquid-filled capsules, which provides enhanced efficacy overall. When combined with the greater security of hard-shell capsules, the result is better products that benefit manufacturers and patients alike. P

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An Industry Stacked Mergers & Acquisitions in Discovery, Manufacturing and Fill/Finish

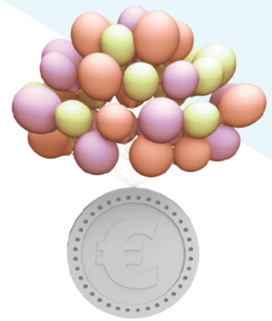
As the supply chain shrinks, it has grown far denser. There is no segment of the industry that has been untouched by the deep internal layering caused by M&A activity. In this Executive Issue feature, we explore how research, manufacturing and packaging have shifted with consolidation.

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

Contract Research Organization Mergers and Acquisitions

A New Landscape: M&A in the Discovery & Research Sector

The CRO market is condensing while experiencing rapid growth.



Mergers and Acquisitions have served to both shrink and expand the landscape of the pharmaceutical industry. The industry is more powerful with more merger and acquisition activity, as the supply chain inevitably becomes more robust. A set of standards and internal organization takes over after a merger and permeates the company, so it is in alignment with the umbrella organization. Perhaps this is most imperative in the drug discovery and research stage of drug development, when the groundwork is being laid in support of the next blockbuster.

The contract research organization (CRO) space has been one of the most active for mergers and acquisitions over the last several years and especially this past year. In the current arena of pharmaceuticals, strong players are becoming ever stronger. As of now, the top ten dominant CROs capture more than half of the total research market.[1] This market is highly valued, with predictions showing a clear upward trend for research organizations. According to Zion Market Research, the contract research market is expected to grow to $59.42 billion by 2020, with a predicted CAGR (compound annual growth rate) of 9.8% in the latter half of the decade.[2]

The United States is currently leading in the market; North America captured a 50% market share in 2014.[2] In spite of this, there is a growing global segment in research organizations, especially in developing nations. Emerging countries in the Asian Pacific, Latin American, and Eastern European regions have proven attractive for a number or reasons, including a large patient pool, low labor and manufacturing costs, and a skilled workforce.[2]

The contract research market is further segmented based on stage of drug development, from early-stage development services primarily focused on discovery, to late- and last-stage development services, which include phase II-IV clinical trials and central laboratory services. Also according to Zion Market Research, later stage development services are the greatest segment for the end-user in the CRO market. As such, this segment accounted for over 70% of the total market share in 2014; growth is expected to be especially present in this area for years to come, according to the survey.[2] 2017 was unprecedented in terms of mergers and acquisitions in the discovery phase – here are some of the most high-profile unions in the industry, and what they mean for the future of pharma.

IMS Research and Quintiles Becomes IQVIA

As CRO companies condense and we reflect on the trends going forward in CROs, it's interesting to note that some of the most influential mergers have included a global element. Global expansion seems to be a reoccurring theme when analyzing the effects of past mergers and predicting what is sure to come. To this point, one of the most headline-grabbing mergers over the past 18 months was that of Quintiles and IMS. Quintiles, a CRO based in North America, expanded into European territory by merging with information and technology consultancy group IMS Health.[1]

After briefly becoming Quintiles IMS Holdings Inc., the firm became IQVIA – The Human Data Science Company.[3] IQVIA is now a player in real-world data and has the potential to alter the way clinical trials are conducted. The company describes itself as "exploring a new discipline – Human Data Science – to unleash the power of data science and human science to improve health outcomes."[3] In mergers in general, there is usually a need or a gap in the market that the merger fulfills. As with IQVIA, the applied data is the key to progression in clinical trials, and for extending life outcomes for patients, and in all

major therapeutic areas. This particular merger paid off for both organizations; the company predicts to generate $200 million in 2019 and sustain 1%-2% annual growth.[1]

LabCorp Expands with Covance and Chiltern

In 2015, CRO conglomerate Covance was acquired by LabCorp, a testing laboratories company. The merger followed LabCorp's acquisition of Covance's genomic lab.[4] The acquisition was valued at $6.1 billion. The acquisition was meant to improve trial efficiency and patient recruitment, as well as deliver data faster to all parties – from drug sponsors to physicians and patients.[1] Commenting on the merger and the added value of both firms together, LabCorp Chairman and CEO David King explained that the merger was leading the charge of the industry to consolidate for the better. "As a combined company, we will be well-positioned to respond to and benefit from the fundamental forces of change in our business, including payment for outcomes, pharmaceutical outsourcing, global trial support, trends in pharmaceutical R&D spending, personalized medicine, and big data and informatics," King stated.[5]

Shortly following this decision, LabCorp set out to further solidify their position by acquiring Chiltern in a deal valued at $1.2 billion in cash.[6] In the press release for the acquisition, which took place on July 31, 2017, it was announced that the merger would yield a CRO with "significant global scale" as well as an expanded workforce of more than 20,000 employees. The merger also provided LabCorp with Chiltern's extensive oncology expertise, as well as expanded functional service provider (FSP) solutions.[6] Again, Chairman and CEO David King spoke on the expanded capabilities that accompanied the merger. "Our acquisition of Covance has demonstrated the value of combining diagnostic and CRO capabilities, expertise, data and leadership. The addition of Chiltern furthers our strategy and will provide us with enhanced capabilities across a broader client base as we continue to innovate and grow."[6] After the dual mergers, LabCorp's global reach has been greatly magnified, a key element in mergers and acquisitions.

INC Research Joins with inVentiv Health

On August 1st, 2017, INC Research Holdings, Inc. – a global research organization focused on Phase I-IV – merged with inVentiv Health, Inc., which was a privately held global CRO and Contract Commercial Organization (COO), to form Syneos Health. The combined entities are valued at about $7.4 billion.[7] Penetration of the global market was a byproduct of the merger, similarly to LabCorp. Syneos has over 22,000 employees in 60 countries, and reach over 110 countries.[7] Alistair Macdonald, Chief Executive Officer of Syneos Health, commented on the global expansion, stressing the worldwide reach of the new conglomerate: "Customers are increasingly seeking simultaneous approvals and product launches in multiple markets worldwide. The combination of INC Research and inVentiv will expand our global scale and add capabilities to grow our addressable market."

As demonstrated, global opportunities are a tremendous motivator for contract research and contract development organizations to edge into a merger. Directly correlated to this is the growing commercial trend of outsourcing; demand for outsourcing is nowhere near slowing, demand will only increase – as will the need for specialized knowledge and expertise. An additional driver of merging is the acquisition of a company that bolsters, enhances or adds capability. Buying a company is perhaps the easiest way to acquire expertise without having to build it up. As for INC Research and inVentiv, both were leaders in oncology and the central nervous system, which netted a total combined revenue of $1.2 billion in 2016; the proficiency in these areas makes Syneos an attractive outsourcing candidate, as buyers are looking for proven skill before taking on a contract.[7]

Icon Meets MAPI

Mergers work to accelerate growth. When ICON, a top global CRO in its own right, acquired MAPI in July of 2017, a consultancy specialized in late-phase research, the CRO became the second-largest CRO to specialize in late-phase research on a global scale.[1] This includes post-approval research, language services, consultancy, and pricing & market access.[8] With the acquisition of MAPI, ICON gained the company's access to Mapi Research Trust, the industry's most subscribed library of clinical outcome assessments. Engaging in the growing trend of a move toward real-time and the implementation of Big Data in clinical trials, ICON is making the move toward useful implementation in trials at all phases.[1]

Enter Private Equity

In June of 2017, private equity (PE) firm Pamplona Capital Management agreed to acquire Parexel, which was ranked as a top ten CRO, for $5 billion.[1] The company focused on drug development, clinical logistics, regulatory consulting and commercialization for life sciences at the time of the acquisition. In a statement on the acquisition, CEO Josef von Rickenbach noted that "Pamplona is an ideal partner, with deep healthcare expertise and a strong track record of investing in market-leading companies in the healthcare sector." The buyout suggests that private equity is the third variable to consider; not only are attractive firms being taken over by other, larger firms seeking their capabilities, but that the PE sector views outsourcing as a prime space for investment. This was echoed in the same month, when Albany Molecular Research agreed to be sold to the Carlyle Group LP and GTCR LLC for $922 million.[9]

The movement of CROs over the last few years suggests that this is the trend of the industry; we anticipate the CRO landscape will shrink further as CROs give way to each other and as private equity gets a firmer grasp on the industry (and its major players). With that in mind, the early/drug discovery area is ripe for growth. Well into the next five years, continuous growth is predicted with no sign of slowing down.[2] P

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Contract Development and Manufacturing Organization Mergers and Acquisitions

What's Driving M&A Among Pharma Sponsors?

M&A activity among pharmaceutical companies reached a peak in 2014-2015. It has slowed somewhat in 2016 and 2017, but companies remain active. They are seeking access to new technologies, looking to expand their pipelines and therapeutic expertise and reach both new patient populations and geographies.

Many Reasons for M&A

Merger and acquisition activity is, overall, driven by a need to improve competitiveness.[1] For public companies, shareholders expect a certain level of growth. For some, achieving those levels of growth organically is a challenge, leading to growth through acquisition. Many blockbuster drugs have lost or are soon to lose patent protection. At the same time, investment in R&D has decreased at large biopharmaceutical companies and they are faced with shrinking pipelines. The majority of new drug candidates have, in fact, been developed by small and emerging specialty pharma and biotech companies in recent years. Consequently, these innovative organizations are being acquired by big pharma and biotech firms to expand their portfolios with next-generation technologies.

In addition, those numerous patent expirations, combined with increasing pricing pressures from governments and insurance companies have led to reduced revenues for many large biopharmaceutical companies. Acquisitions can provide access to new revenue streams, particularly for companies with significant cash reserves.[2]

Financial factors can come into play as well, such as access to cheap financing and potential tax savings, although so-called tax inversion deals are no longer on the table for US companies. There is, however, under the current Trump administration, potential for US corporations to pay reduced taxes on money they repatriate into the country. Reduction of costs through achievement of synergies and the acquisition of new technologies (instead of making internal R&D investments) is also an important driver. In some cases, companies divest only part of their portfolio in order to streamline operations, leading to improved bottom lines for both deal partners.

Historical Perspective

Mergers and acquisitions have been an important activity in the pharmaceutical industry for many years. Over the past decade, the industry spent over $2.4 trillion on M&A deals, accounting for on average 9% of total global M&A activity, according to Mergermarket.[3] The highest value for M&A deals in the pharma industry in those 10 years – $392.4 billion – was reached in 2015, with North America accounting for nearly $300 billion of the total.

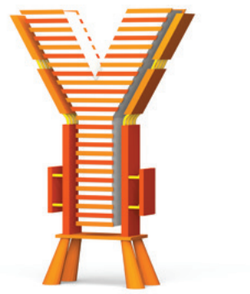
While most of the truly megadeals – Pfizer's acquisitions of Warner Lambert in 1999, Pharmacia in 2002 and Wyeth in 2009, Glaxo Wellcome's purchase of SmithKline Beecham in 2000 and Sanofi's acquisition of Aventis in 2004, for instance took place earlier, large deals continue to take place.[3] Teva Pharmaceutical's purchase of Allergan's generics division in 2015, Shire's acquisition of Baxalta and Bayer's purchase of Monsanto in 2016 and Johnson & Johnson's takeover of Actelion in 2017 are more recent examples.

Deals made by generic drug manufacturers accounted for 9.3% of the value of all pharmaceutical M&A activity from 1996 to 2016 (345 deals valued a total of $160.3 billion).[4] The vast majority of deals took place from 2014-2016 (2014: 22 worth $1.86 billion; 2015: 34 worth $33.56 billion; 2016: 42 worth $44 billion). Notably, in 2015 and 2016 many of these deals occurred in the US, accounting for nearly 90% of the value of generic deals in those two years. In addition, it is worth noting that both the number and value of M&A deals involving generics companies increased.[4]

Changing Headwinds in 2016

Despite the increase in M&A deals by generic pharmaceutical firms, the overall M&A activity among pharmaceutical manufacturers declined in 2016 compared to 2014 and 2015. In 2016, the value of pharmaceutical M&A activity fell to $274 billion from $392.4 billion in 2015.[3] Interestingly, deal activity increased in Europe and Japan in 2016, with total value growing from $33 to $57 billion in Europe and from $2.9 to $7.3 billion in Japan. In the latter case, the purchase of Toshiba Medical Systems Corporation by Canon accounted for $5.9 billion.[3]

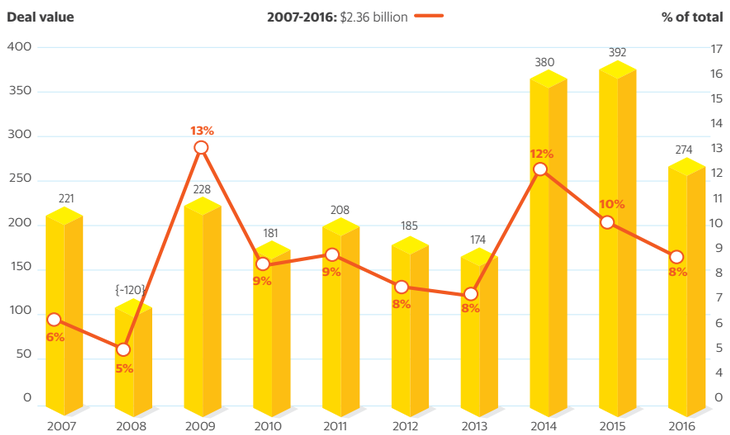
Rather than acquire an early-stage company and take on the further development of unproven candidates, big biopharma companies form collaborations that include the option to acquire the target molecule if performance milestones are achieved.



Top deals in 2016 included Shire's acquisition of Baxter spinoff Baxalta, Pfizer's buyout of Medivation and purchase of Anacor Pharmaceuticals, AbbVie's acquisition of Stemcentrx and Mylan's purchase of Meda.[5] The nature of deals also changed in 2016. Rather than being driven largely by specialty pharmaceutical firms (e.g., Allergan, Valeant Pharmaceuticals International and Endo International), big pharma and biotech companies started to lead the way again. Compared to 2014, valuations of specialty pharma companies declined by 34% in 2016, limiting their ability to make deals.[6]

There has also been a shift in interest away from companies with approved products to early-stage development firms.[3] In 2016, just under 20% of the companies acquired offered approved products, down from 49% in 2011. Possible reasons include reduced competition and thus valuations/prices, a desire to expand technologies and drug options for specific diseases, and the desire to bring next-generation technologies in-house. However, eight of the largest 10 deals completed in 2016 were for companies with approved products or products close to commercialization, suggesting that the biggest biopharma companies have a reduced tolerance for risk-taking.[5] It could also reflect lower valuations. It is worth noting that "option-to-acquire" deals became more common in 2016. In this case, rather than acquire an early-stage company and take on the further development of unproven candidates, big biopharma companies form collaborations that include the option to acquire the target molecule if performance milestones are achieved.[3]

VALUE OF M&A IN THE GLOBAL PHARMA INDUSTRY ($ / BILLION)



Source: Consultancy.uk analysis, Mergermarket data

Continued Slowdown in 2017

Through October 2nd, the total value of deals in the pharma, medical and biotech sector was $207.6 billion, representing a decline of 9.9% in value (and 106 fewer deals) compared to the same period in 2016.[7] Private equity deals were also notably lower than expected.[8] Pharma deals have been the main culprit; biopharma transactions have remained fairly healthy. A slowdown in biotech IPOs may be part of the reason for the higher M&A activity in this segment of the biopharma industry.[9] The overall slowdown is attributed by some analysts to the uncertainty created by the presidential administration.[8]

Notable deals have included J&J's takeover of Actelion, Gilead's buyout of Kite Pharma (which recently received FDA approval for the second CAR T-cell therapy in the US) and the merger of Impax Labs and Amneal Pharmaceuticals (to make the 5th largest generics firm in the US).[10]

Other companies looked to divest, not acquire, as a way to focus on core businesses and provide opportunities for growth for the divested operations.[11] One example is Biogen, which spun off its hemophilia business in 2017 as Bioverativ. Teva sold its intrauterine copper contraceptive ParaGard to CooperSurgical and its contraception, fertility, menopause and osteoporosis products to CVC Capital Partners Fund VI to pay down debt in the face of significant price declines for many of its generic products.[12] The company continues to seek a buyer for its European oncology and pain assets. Novartis had its one-third share of Roche on the block for more than a year, but decided to keep it given a lack of interest. It has also been reported that the company is looking to sell a $496 million portfolio of central nervous system meds, some respiratory drug rights and potentially its Alcon eye drugs business.[13]

THE 10 LARGEST TRANSACTIONS IN THE PHARMA INDUSTRY

Year	Buyer	Seller	Deal size ($ / billion)
1999	Pfizer	Warner Lambert	84.3
2000	Glaxo Wellcome	Smithkline Beecham	71.3
2002	Pfizer	Phamacia	63.8
2004	Sanofi	Sanofi-Aventis	58.6
2016	Bayer	Monsato	58.2
2014	Actavis	Allergan	52.2
2009	Pfizer	Wyeth	48.9
2011	Shareholders	Abbvie	43.1
2009	Merck & Co.	Schering-Plough	37.3
2015	Teva Pharmaceutical	Allergan-divisie	35.6

Source: Consultancy.uk analysis, Bloomberg data

For emerging and smaller pharmaceutical companies, initial public offerings can serve as an effective alternative to M&A for achieving growth.[11]

What's on Tap for 2018?

With much uncertainty continuing, it is difficult to predict what level of M&A activity will take place in 2018. Following the failure to repeal the Affordable Care Act, however, biopharmaceutical stocks did begin to increase in value again.[14] Earnings per share are also on the rise. The increased rate at which the FDA is approving drugs – 46 in November 2017[15] compared to just 22 in 2016[16] – is also likely contributing to the improved stock prices. Some predict a return to higher M&A levels as a result.[14]

M&A activity in 2018 could also pick up. According to one report, there is $1.3 trillion in overseas cash that could be brought back to the US and used by pharmaceutical companies to pay for deals.[17] Despite continued uncertainty, it appears that M&A activity in the pharmaceutical industry will remain reasonably strong and could potentially increase to the higher levels in 2018. P

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Fill/Finish and Packaging Mergers & Acquisitions

Getting to the Finish Line

The industry's accelerating development of biopharmaceuticals, as well as the demand for other parenterally delivered formulations, has put tremendous pressure on the entire supply chain to focus organizational and financial strategies to improve and modernize fill/finish operations.

Demand for Fill/Finish Soaring

The major driving force behind the demand for operationally excellent sterile fill/finish operations is the accelerating pace behind biopharmaceutical development and the rise of biosimilars. Regardless of category, outsourcing the complexity and risk of aseptic sterile filling tasks to experts is the real trend in the fill/finish story.

Researchers at Evaluate Pharma project the global market for drugs will continue to expand at a compound annual growth rate of 6.3% until about 2022, with biologics accounting for 50% of the top 100 products by the end of the study period.[1] Based on input from more than 700 pharmaceutical industry professionals, representing all tiers and segments of the pharma business (41% large, 36% medium-sized, 20% small and 3% emerging) from around the world (Europe 38%, North America 33%, Asia 29%), results of the 2017 Nice Insight CDMO Survey revealed the top reason survey participants engage CDMOs and contract services providers is "access to specialized technologies."[2]

Similarly, respondents said they also seek improving quality and gaining expertise in areas their organizations lack. Nice Insight CDMO study data revealed that more than half (54%) engage contract providers for liquid dose form clinical-scale and commercial-scale drug product manufacturing services. Further, roughly a quarter of respondents engaged CDMOs for clinical-scale and commercial-scale filling of prefilled syringe and injectable dose delivery forms.

Innovation's Impact

It's obvious that this segment of the pharma contract services supply chain has become increasingly dynamic, partially because of advances in integrated enterprise IT, barrier technologies, environmental conditioning systems, robotics and automation, and control strategies.

According to Philippe Mougin, founder and Chairman of Cenexi Group, a CDMO specializing in injectables, patient safety relies heavily on error-free fill/finish operations. Citing inherent complexity of manufacture and finish, biopharmaceuticals are propelling the use of parenterals, which Mougin explained are expected to make up approximately 17% of the packaging market in the coming years.[3]

"A sterile product is only as good as the fill/finish line through which it must travel," noted Mougin, who explained that to assure biopharmaceuticals and parenteral quality remains high and product purity is maintained throughout processing, an aseptic fill-finish process is critical.

Noting that requirements of the Drug Supply Chain Security Act (DSCSA) and the larger Drug Quality and Security Act (DQSA) are ramping up, Mougin points out it is now an "opportune time" for CDMOs to implement fill-finish improvements globally.[3]

Investments in Capability, Capacity and Quality

Sterile fill/finish services providers are clearly responding to the demand for capacity and technical ability. It is likely that investment and capital allocation strategies will be ongoing, supporting those goals through a variety of means. These include acquisition and capacity additions, geographic positioning of assets, and strong moves technologically to achieve market niche or "no molecule barred" goals and other advantageous operational synergies.

Cenexi, for example, integrated extensive experience in sterile drug products, expanding into needle-free injection systems, galenical drug forms and cytotoxic (including antibody drug conjugates, or ADCs) and lyophilization capabilities. In 2017, Cenexi gained its fourth manufacturing site, a sterile operations facility located in Hérouville-Saint-Clair, France.[4]

Expansion and Development

Building momentum through 2017, several companies announced plans to expand, acquire or collaborate in an effort to develop their fill/finish operations in order to fulfill their business goals. Feliza Mirasol highlighted the energy and growth the sector is generating in a report for DCAT *Value Chain Insights*, noting that CDMOs and CMOs were very active, growing organically and "expanding operations to support the development and manufacturing of parenteral drugs." Mirasol reported that by March 2017, 18 companies across the sector had announced enhancements to parenteral operations.[5]

AB Bio Technologies, Alcami and AMRI all announced their plans to investors for adding aseptic filling and lyophilization lines and systems during the past 18 to 24 months. Alcami not only made strategic and critical acquisitions to add capacity and depth, but also moved fast to add new lines and focus on prefilled syringes. At the end of 2016, Grifols announced construction of a new plasma fractionation plant in Clayton, North Carolina, adding some 6 million liters of annual fractionation capacity. Construction began in early 2017 and the facility is scheduled to start production by 2022.[6]

Pfizer's CMO Pfizer CentreOne announced in February 2017 the successful expansion of its fill/finish services at the company's Kalamazoo, Michigan site. Along with vial-filling of small molecules and biologics, the new Michigan operations expand Pfizer CentreOne's service portfolio and provide new capacity for filling sterile suspensions.[7] In August 2017, Ajinomoto Althea announced it was launching a high-performance sterile vial filling line. According to the CDMO, the new line strengthens its product manufacturing capabilities and supports a broader range of drug substance APIs, as well as enabling larger batch sizes and a broader range of filling volumes.[8]

Thinking Big

One of the biggest announcements of the year came in September 2017, when Catalent announced the acquisition of Cook Pharmica for $950 million. The company explained the move was intended to bolster its biologics capability and extend its "capabilities in sterile formulation and fill/finish across liquid and lyophilized vials, prefilled syringes, and cartridges."[9]

The major driving force behind the demand for operationally excellent sterile fill/finish operations is the accelerating pace behind biopharmaceutical development and the rise of biosimilars.

In 2016, Vetter articulated its manufacturing strategy, announcing continued investments to expand fill/finish – including a $320 million investment over 10 years in its Des Plaines, Illinois site and plans to expand packaging operations.[10]

Outsourcing Continues

Outsourcing pharma packaging is logical due to complex nature of pharmaceutical packaging operations. In the report "Pharmaceutical Contract Packaging Market: Global Industry Trends, Share, Size, Growth, Opportunity and Forecast 2017-2022," management strategy analysts from IMARC Group found the global pharmaceutical contract packaging market reached a value of approximately $9 billion in 2016, and that it maintained a CAGR of more than 7% during 2009-2016.[11] The contract packaging market is expected to reach a value of nearly $15 billion by 2022.[11] This rise can be attributed to rapid and sustained growth in the pharmaceutical industry. Pharmaceutical contract packagers, explained analysts, invest tremendously in R&D to ensure innovation and introduce technologies that ensure product quality.

Expansion and Capital Spending Activity

A report by packaging industry group PMMI issued at the end of 2016 explained that, faced with the regulatory challenges of serialization, unique device identification (UDI), as well as pressures to produce at low cost, healthcare and life sciences manufacturers are looking at purchasing new equipment to replace outdated production lines. Nearly half of healthcare manufacturers interviewed "continue to replace legacy equipment and buy new equipment, while two-thirds of participating companies predict spending more on capital equipment in the next two years."[12]

For example, PCI Pharma Services made two significant announcements: one covering the acquisition of Millmount Healthcare, near Dublin, which before the acquisition opened a new, state-of-the-art high-potent, high-containment packaging facility; and the other announcing significant expansion to its global serialization capabilities.[13,14]

UK–based Sharp Packaging Services announced capacity expansion projects in the US and the UK in 2017, announcing the purchase of Daiichi Sankyo's 146,000 square-foot pharmaceutical packaging facility in Bethlehem, Pennsylvania, for $14 million, including all equipment and employees.[15] Vetter also announced a major expansion of its secondary packaging capacities – in response, said the company, "to rising customer needs and market demands for complex packaging solutions." The expansion will add approximately 32,000 square feet of new packaging capacity and include new fully-automated packaging lines, space for manual and semi-automated packaging processes, and assembly equipment for a wide variety of formats.[16]

For 2018 and beyond, the prospects for fill/finish and packaging market players will remain robust. The overall demand for drugs and the rise of parental-form biopharmaceuticals/biosimilars ensures the industry will see growth. P

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UNITING THE INDUSTRY FOR THE PREVENTION OF "PHARMAGEDDON"

→ BY **TIMOTHY C. TYSON**, AVARA PHARMACEUTICAL SERVICES

Revolutionary change is occurring in the pharmaceutical industry. The old model of discovering and delivering pharmaceuticals is under attack. The rising cost of medicines, the reduced productivity and the increased regulatory requirements have driven companies to seek alternative means. Significant efforts to reduce operating expenses, to share in the risks/costs of failure and to provide reasonable returns to investors are leading to the destruction of the industry as we have known it. This "Pharmageddon" isn't going to happen sometime in the future – we are currently in its midst.

The industry must respond by developing a win-win-win approach that allows investors, pharma companies and their suppliers to collaborate to continue to deliver life-saving and life-improving medicines to patients in need and to share in fair and reasonable profits. Otherwise, a time will come when new life-saving and life-improving medicines will no longer be developed.

DESTRUCTION ON THE HORIZON

Revolutionary changes are occurring in the pharmaceutical industry. The public perception of drug companies has reached an all-time low. And it's not just concerns about drug pricing. Drug manufacturers, distributors and pharmacies are also under scrutiny due to the escalating opioid crisis. States are suing drug companies based on the costs associated with responding to this serious health issue.

In addition to these challenges of public perception, the industry is struggling to contend with the impact that the loss of patents, the reduction in R&D productivity, the increased regulatory oversight and the rapidly rising cost of developing a new drug are having. All of these reasons have driven the industry to revolutionary change in all sectors to overcome these market dynamics. This has caused the realization that Pharmageddon isn't coming at an abstract date – it is here. Although it may seem dramatic, if no actions are taken to change this current landscape, the pharmaceutical industry is at risk of destruction – meaning that we will no longer have the ability to develop and produce life-saving medicines. When the next pandemic occurs, hundreds of millions of people could die because the needed new medicines and innovations will not be available to treat them.

THE NEED FOR RESPONSIBILITY

If the pharmaceutical industry is to survive this impending Pharmageddon, the industry must step up to be positive, be productive and solve these significant challenges. Our traditional operational model, which in the past was all too comfortable, is being challenged from every direction. The answer is revolutionary change; we need a new model that will drive the industry towards the necessary outcomes. We must take the initiative, rather than sit back and wait for someone else to do it.

As professionals, it is our responsibility to stand up and face these current pressures. We must address the concerns of the public – and eliminate financial and economic waste so that we can deliver medicines at fair prices. As an industry, we need to conduct business in a fair and transparent manner so that we can charge reasonable prices and still make fair returns for investors and everyone in the industry.

The first step is to take control of our processes to increase productivity and efficiency. We need to optimize all of our activities to provide the best value. Second, the industry needs to address the overcapacity situation. The branded pharmaceutical industry is running at approximately 30% capacity utilization, with the generics sector around 50%. The consumer goods industry operates at 85%-90% capacity utilization due to lower profit margins. The pharmaceutical industry must adopt this same mentality and deal with the excess capacity.

Though it may be difficult to accept, that means that some manufacturing and R&D facilities must be closed. The industry has not really tackled this problem previously because it is very difficult to do. Closing facilities creates job losses and infrastructure rationalization, which are strongly opposed by governments that often push hard for implementation delays. Moving drug production is also costly, and risky for the supply chain. Change requires a review of regulatory dossiers, which once opened up can be reevaluated entirely. There is a potential risk that additional work will need to be done, potentially threatening a product's survival in the marketplace.

It is, however, no longer an option for companies to sidestep and ignore overcapacity issues, inefficiencies and lack of productivity. Both branded and generic drug manufacturers and their contract manufacturing partners must dramatically increase efficiencies and better utilize capacity. Rationalization of facilities and firms is essential. The number of contract manufacturers must be reduced from the approximately 500 that exist today to 50 or 100. It will take 10-15 years for these changes to occur, but they must. And they will have a major effect on everyone. Those who understand the dynamics of today's market and adjust will end up winners.

A WIN-WIN-WIN SOLUTION

Winners post-reformation of the industry will be winners a different context; they will be winners in an industry where *everyone* wins. If the industry is to survive Pharmageddon, we need to create a mindset of generating value across the entire supply chain – we can no longer think that winning must occur at the cost of others losing. We must seek new ways to fund innovation, continue to seek productivity and efficiency improvements, and price the drugs of the future fairly so that society can afford them. Pharmaceutical companies

will continue to challenge what their core competencies are and will increase their reliance on partnerships with valued suppliers. Rather than look to pressure suppliers to achieve cost savings, drug companies must work with their suppliers to create a system in which everyone – patients, pharma companies, suppliers and investors – benefits.

Partnerships amongst all of the players must be created, in which everyone invests together to deliver valuable life-saving and life-improving medicines to patients at fair and reasonable prices. In spite of pricing concessions, pharma companies and suppliers will still be able to make a reasonable profit and investors will be able to make a reasonable return. We must all work together to get the current system – which is a system out of control – into control to establish a long-term win-win-win approach, in which everyone has a vested interest and from which all parties can assure a sustainable, profitable growth business.

NEED FOR GREATER EFFICIENCY

Creating these win-win-win relationships will require dramatic improvements in efficiency and productivity. The time to discover, develop and deliver medicines in the future must be reduced. There is also a need to continue to assure product quality. There are many opportunities to improve efficiency, reduce costs and enhance supply chain security, as well as regulatory compliance, across all phases of the drug lifecycle for branded, generic and over-the-counter medicines.

WHAT CDMOs CAN DO

Simplification of the supply chain is occurring as both outsourcing and consolidation occur at an accelerated pace. These market forces are creating a positive environment and more opportunities for contract development and manufacturing organizations (CDMOs) supporting both APIs and drug products to contribute positively to these market changes.

The greatest opportunities exist for CDMOs who seek to become true partners with their customers. CDMOs must understand the cost pressures facing the industry and recognize what they can do to play a role in improving customers' cost structures by finding new ways to drive efficiencies, providing security of supply, enhancing regulatory compliance and building long-term confidence by delivering on commitments to customers.

The consolidation occurring in the industry is not only fundamental to its success but will lead to an entirely new industry structure where CDMOs, as a part of a strategic partnership, deliver technical expertise and support to their customers to assist in drug development, offer new technologies and deliver more efficient and cost-effective manufacturing support.

TAKING ACTION AT AVARA

Avara's strategy, first and foremost, is to deliver on our commitments to our customers. We do that by focusing on, and caring for, our people. They really are our greatest asset. Each and every one of them realizes that what we do will impact the lives of people we may never know. Our people have passion and always focus on meeting or exceeding customer expectations and regulatory requirements – they understand the consequences are extreme if they do not. They also recognize the need for an operational approach that maximizes efficiency, productivity and quality.

IF THE INDUSTRY IS TO SURVIVE PHARMAGEDDON, WE NEED TO CREATE A MINDSET OF GENERATING VALUE ACROSS THE ENTIRE SUPPLY CHAIN — **WE CAN NO LONGER THINK THAT WINNING MUST OCCUR AT ANOTHER'S EXPENSE.**

Forming long-term strategic partnerships with our customers is an equally important component of our strategy. We want to help our customers succeed by providing security of supply and meeting regulatory compliance requirements at a fair price. We commit to certain guaranteed long-term benefits to our customers as a means of sharing the leverage that we realize from increased volumes or improved efficiencies.

As an integrated supplier of API and drug product services, Avara also helps simplify the supply chain. We reduce the number of handoffs needed to get a drug from development to commercialization and into the hands of patients. Avara brings a wealth of process and industry knowledge and expertise in supply chain management, process and formulation development, commercialization, product launch and technical transfer to bear on customer projects, facilitating the rapid, cost-effective development of advanced medicines. As a result, our customers receive significant benefits.

The foundation of Avara is accelerating the delivery of drugs to the marketplace while facilitating the changes that must happen in the industry. Those changes can only happen if there is a mutual understanding and participation by all in the market, including contract service providers and their customers. P

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MICROBIAL AND BIOLOGICAL DECONTAMINATION OF EQUIPMENT BRINGS PEACE OF MIND

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

A THREE-STEP DECONTAMINATION PROCESS WILL ENSURE THAT USED EQUIPMENT IS FREE FROM BETA-LACTAM ANTIBIOTICS **AS WELL AS DESTROY UP TO 99.9999% OF HARMFUL PATHOGENS AND CONTAMINATES.**

The ramifications of an adverse biological occurrence are higher in the pharmaceutical industry than in any other. Cross contamination has unintended consequences of product recalls, regulatory non-compliance, ruined brand reputation and, in extreme cases, even death.

To keep pace with an aging population, an increase in chronic and infectious diseases, and the ever-growing need to comply with various government regulations, the pharmaceutical industry is investing more heavily in processing equipment.[1] For many companies, purchasing used manufacturing equipment presents an excellent opportunity to implement necessary technology in a more cost-effective manner and with shorter lead times (it can sometimes take upwards of a year to manufacture new equipment).

Customers purchasing used equipment need complete assurance that the machinery presents no risk of cross contamination. Conducting microbial testing and biological decontamination of used equipment – before it is placed into service – offers peace of mind to customers who are worried about bringing an outside system into existing aseptic or controlled manufacturing conditions.

A VALUE-ADDED SERVICE

Microbial testing and equipment decontamination can be offered as a value-added service by an NIH-credentialed bio-decontamination company, providing value by saving manufacturers time and money. While some drug makers may have a decontamination program, the process of decontamination usually occurs in a dedicated area. It is often not practical to bring a used piece of machinery into that area, as it poses the risk of contamination. The decontamination company will perform microbial testing and biological decontamination prior to shipping the used equipment – along with all of the supporting validation documentation.

DECONTAMINATION IN THREE STEPS

While a company should have Good Manufacturing Practices (GMPs) unique to itself and/or dictated by FDA regulations or USP guidelines, manufacturers of biopharmaceutical and pharmaceutical finished products must demonstrate that harmful residues or organisms are properly removed to predetermined safety levels.[2] A three-step decontamination process will ensure that used equipment is free from beta-lactam antibiotics as well as destroy up to 99.9999% of harmful pathogens and contaminates.

1. β-lactam (beta-lactam) Antibiotic Testing

In pharmaceutical manufacturing, *β-lactam* and non- *β-lactam* production must be segregated due to the concern that a portion of the population is sensitive to broad-spectrum antibiotics like Penicillin G and Ampicillin, with serious health consequences if cross contamination occurs. It is important to note that a used equipment seller should not even accept pharmaceutical equipment into its facility without validation of what it had previously been used to manufacture. Any equipment that was used for *β-lactam* production should not be bought and resold unless the buyer is aware of the prior use and intends to use the equipment to manufacture the same product. *β-lactam* testing provides additional assurance to customers with heightened concerns of the machinery's prior use.

To confirm that critical *β-lactam* compounds are absent from product contact surfaces of the equipment, the following steps are taken:

+ **Swab equipment in several hard-to-reach areas.**
+ **Analyze swabs using mass spectrometry equipment.**
+ **Develop a report confirming the absence of Penicillin G and Ampicillin-lactam.**

2. Equipment Decontamination Exceeds Bioburden Standards

Bioburden standards are established in USP Chapter <1072> "Disinfectants and Antiseptics." There are several options that provide bioburden reduction ranging from Log^3 (99.9%) to Log^6 (99.9999%). Two of the most popular methods are standard and advanced.

+ **Standard Treatment:** Appropriate for most situations, this involves performing dry vapor fogging with pharmaceutical-grade equipment and EPA-registered peracetic acid/hydrogen peroxide cold sterilant.
+ **Advanced Treatment:** This can be used for challenging or high-risk applications, or for equipment with complex geometries. The process achieves sterilization results using chlorine dioxide gas with an EPA-registered chemical sterilant and treatment protocol. Gas is used because vapor may not be as effective for reaching all of the hard-to-reach areas.

CUSTOMERS PURCHASING USED EQUIPMENT NEED COMPLETE ASSURANCE THAT **THE MACHINERY PRESENTS NO RISK OF CROSS CONTAMINATION.**

The bio-decontamination company will assist the client in determining which process is most appropriate. The goal is to select the least expensive option that will achieve the desired consequence.

3. Validation Performance Compliance

Upon completion of the equipment decontamination process, and after receipt of the *β-lactam* lab analysis, an extensive report validating the mechanical, chemical and biological performance is issued to the pharmaceutical manufacturer. The validation should be placed in a file in the event of an internal or FDA audit.[3] The report is consistent with GMP compliance standards and follows the guidelines mandated by the associated decontamination equipment manufacturer.

+ **Biological Performance Validation:** Biological indicators inoculated with Log^6 *Geobacillus stearothermophilus* bacterial spores (ATCC 12980) are used to validate the efficacy of the decontamination treatment. The biological indicators contain some of the most difficult to kill microorganisms and far exceed USP pharmaceutical requirements. While decontamination can be performed in less than one day, biological validation requires that samples be incubated for up to seven days.
+ **Mechanical Process Validation:** All process steps are documented, including the proper chemical diffusion within the entire decontamination zone.
+ **Chemical Process Validation:** Specific chemical strength levels and airborne vapor levels as measured in parts per million are monitored and documented.
+ **Beta-lactam Validation:** Mass spectrometry analysis is conducted by an internationally renowned expert on beta-lactam contamination, identification and remediation.

ON-SITE DECONTAMINATION

In addition to decontaminating used equipment prior to shipping, a decontamination company can go to a customer's site to decontaminate equipment or complete facilities. This alleviates the customers' burden or expense of having to purchase decontamination equipment, maintain it and train people to use it. Instead, they can subcontract the process, saving both time and money.

Common Equipment Contaminants

- Bacterial spores
- Fungi, mold and biofilms
- Gram-positive bacteria
- Enveloped viruses
- Myco bacteria
- Non-enveloped viruses
- Gram-negative bacteria
- β-lactam (beta-lactam)

Decontamination services can be scheduled on a pre-determined or emergency basis. The frequency becomes more pronounced in the case of a Contract Development and Manufacturing Organization (CDMO) that works for multiple clients and makes multiple changes in what it produces. CDMOs have to ensure the item produced prior doesn't cross contaminate the next batch, which may be a different product altogether. In these cases, decontamination between batches of different products is essential.

THREE POINTS TO CONSIDER

1. World-class equipment and facility bio-decontamination services are a value-added service offered by a used equipment reseller like Federal Equipment Company.
2. Pharmaceutical manufacturers with potential cross contamination concerns can have them addressed by a certified bio-decontamination company and receive validated compliance reports.
3. Pharmaceutical manufacturers can save time and money by having a contractor decontaminate their used equipment purchase before it enters their facility. P

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Matt Hicks, Chief Operating Officer & Counsel at Federal Equipment Company, is a pharmaceutical industry veteran with more than 15 years of experience helping companies get the most value and utility out of their manufacturing and process equipment assets.

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INVESTING IN NEW TECHNOLOGIES FOR INNOVATIVE FUNCTIONAL SOLUTIONS

→ BY **SARATH CHANDAR**, SPI PHARMA

SPI PLANS TO WORK ON NPD INITIATIVES TO DEVELOP INNOVATIVE IDEAS AND TECHNOLOGIES TO EXPAND THE RANGE OF HIGHLY FUNCTIONAL EXCIPIENT SYSTEMS. THIS IS ACCOMPLISHED BY LEVERAGING THE SYNERGIES OF EXCIPIENT COMBINATIONS THROUGH VARIOUS COPROCESSING TECHNOLOGIES TO DELIVER COMPENDIAL MATERIALS (LOOKING FOR 1+1=3).

Associated British Foods (ABF) and its Ingredients division (ABFI) are committed to growing their global pharmaceutical footprint. Included in this initiative are significant investments in their pharma subsidiaries — one such subsidiary of ABFI is SPI Pharma (SPI), headquartered in the US. Following a reorganization and finalization of its new growth strategy, SPI is re-engaging in innovation. As a result, SPI has created a new team called the Applied Innovation Group (AIG). AIG is entrusted with developing innovative technologies and drug formulations that will create new opportunities for pharmaceutical and nutraceutical customers worldwide, while ultimately benefiting patients.

COMMITMENT TO GROWTH

In January 2017, ABFI brought Jeanne Thoma on board as President and CEO of SPI and immediately embarked on the development of a new strategic direction for our company. Based on external market data, voice of customers, and input from across the organization, two strategic business units (SBUs) were created with dedicated business teams, and our global technical resources were consolidated into one group – AIG.

The two business units are Antacids & Catalysts and Excipients & Drug Delivery Systems (EDDS). SPI is one of the largest suppliers of immediate relief antacids, offering aluminum-, magnesium- and calcium-based actives. Several major brands across the globe use SPI's antacid actives. The market drivers and innovation needs for antacids and catalysts are quite different from those of the products and services in the EDDS segment.

The EDDS business offers a broad array of products and technologies combined with customized drug formulation expertise. Products and technologies include excipients, microencapsulation technologies for taste masking and controlled-release applications, drug delivery platforms, fast-dissolve systems, effervescent products, vaccine adjuvants based on $Al_2(OH)_3$ chemistry, and a variety of other creative offerings focused on building patient-friendly dosage forms (PFDFs).

FOCUSING ON APPLIED INNOVATION

At SPI, applied innovation means market-relevant innovations that deliver solutions to enhance convenience, compliance, and efficacy to patients **(see Figure 1)**. To accomplish this, the AIG team is comprised of 3 distinct functions: R&D, strategic business development (BD), and technical business development. R&D works on material and drug development, while BD explores partnerships and licensing, and Technical Development Managers (TDM) interact directly with drug formulators in pharma companies. This new organization enables valuable cross-pollination and coordination amongst subject matter technical experts and customer-facing commercial folks. Market-relevant new ideas are discussed and prioritized, facilitating rapid product development.

R&D

The R&D group within AIG is responsible for new product/material development (NPD), applications development/technical support (ARTS), and drug development in patient-friendly dosage forms (Pharmasolutions).

Given the number of excipients and other materials approved for use in drug formulations is finite and limited, SPI plans to work on **NPD** initiatives to develop innovative ideas and technologies to expand the range of highly functional excipient systems. This is accomplished by leveraging the synergies of excipient combinations through various coprocessing technologies to deliver compendial materials (looking for 1+1=3). Co-processing (co-drying, co-granulating, co-congealing, etc.) has the potential to provide additional functional benefits that aren't realized when different excipients are simply dry-mixed together in a formulation. The NPD group also focuses on safely enhancing the performance of APIs through microencapsulation techniques to mask taste as well as adjust the release profile of the active using aqueous media instead of a solvent-based system.

All of the products in the SPI portfolio are characterized for functionality by **ARTS**. They focus on understanding the cause-effect relationship in excipient functionality. They also provide technical support to our customers that are using our excipients and platforms in their drug formulations.

Pharmasolutions covers dossier development for out-licensing as well as customized drug development service to meet customers' specific needs. Our customers benefit from the ability to market specialty drug products that are highly differentiated in the marketplace. Pediatric and geriatric formulations developed and tested by SPI support our customers' product lifecycle management, reducing risk

Figure 1

SPI's Applied Innovation

SPI's Applied Innovation will enable patient-centric formulations that provide the following benefits and lead to improved patient outcomes:

CONVENIENCE
- Innovative excipients and platforms that make drug dosage forms easy to manufacture, transport, and store. They can be made small, robust, orally fast-dispersing with or without water, and are easy to take.

COMPLIANCE
- Microencapsulation of APIs achieving taste-masking and extended release, when combined with innovative platforms, results in PFDFs that are palatable and easy to swallow, resulting in adherence to the dosage regimen.

EFFICACY
- Examples of SPI's excipient systems have led to faster/better absorption, resulting in lower quantity of active required to achieve similar therapeutic benefit, thus reducing unwanted side effects. eg, Zolpidem tartrate, ED Drug

of failure while achieving speed to market. The business model is structured on a milestone-based fee for service. Since the inception of this service, SPI has established a strong track record of helping customers successfully launch commercial drug products for treating migraine, Parkinson's, schizophrenia, nausea, allergy, erectile dysfunction, diarrhea, smoking cessation and others in patient-centric formulations. A partial list of such products with APIs and dosage forms is available on our website: **www.spipharma.com**. A fully equipped drug development laboratory in India, staffed with scientists from major pharma companies, supports the Pharmasolutions initiative.

TDM

The technical development managers are regionally focused and responsible for supporting pharma customers in the US, Latin America, Europe, Middle East/Africa, and Asia-Pacific regions. Each of these technical development experts provides technical support for existing projects as well as promoting innovative ideas developed by the AIG. They work closely with the commercial team, reaching out to senior formulators around the world to identify areas in which SPI's capabilities connect with our customers' drug product strategies. The AIG works closely with the SBUs to ensure alignment with the business plans. Once fully developed, the technologies and products, whether developed internally or in-licensed, are transferred to the SBU's commercial team.

STRATEGIC BUSINESS DEVELOPMENT

BD is responsible for partnerships and licensing (in- and out-). They explore partnerships with companies that offer unique/specialty ingredients/actives that, when combined with SPI's products and technologies as well as drug development knowledge, will enable the development of unique solutions for our customers.

The most recent example is the signing of a Letter of Intent in October 2017 with Noramco, one of the largest producers of opioid agonists and antagonists for the treatment of opiate addiction. The main focus of this agreement will be the development of unique products for treating opioid addiction by leveraging Noramco's experience with APIs and our expertise in functional excipient platforms and specialized drug development capabilities. In addition, Noramco and SPI will be developing drugs for the treatment of CNS conditions like migraines, epilepsy and pain management, using our drug delivery technologies and Noramco's patented synthetic cannabinoid APIs. These APIs are expected to provide the therapeutic benefits of cannabis without any of the problems or negative hallucinogenic side effects associated with consumption of tetrahydrocannabinol (THC) in cannabis.

INVESTING FOR THE FUTURE

SPI Pharma, backed by ABFI and ABF's strong commitment to investment and growth, is focused on the development of innovative technologies, products and services that deliver functional value to our customers. Following the changes made during 2017, SPI Pharma is well positioned to meet the complex challenges faced by our pharma customers. We are developing new products using a stage-gate process and actively exploring potential partnership opportunities. Our mission is to deliver tangible benefits to our customers, who have the same commitment to bringing value to the ultimate consumer: patients. These combined efforts will enable improved quality of life for patients and ease the burden of caregivers in terms of compliant administration and accurate dosage, while enabling the growth of SPI, our customers, and our partners. P

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SUPPORTING PARENTERAL DEVELOPMENT AND MANUFACTURING WITH END-TO-END SERVICES

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LEVERAGING END-TO-END SUPPORT

The manufacture of biologic drug products, particularly those that require aseptic processing, is quite complex and requires specialized expertise. Early and careful planning for the future can significantly contribute to the success of a development project. The involvement of an experienced solution provider with end-to-end capabilities contributes to the monetary value of drug substances and formulated products. These CDMOs can support drug candidates from the development phase through late development, market launch and subsequent commercial manufacturing, as well as lifecycle management activities, maximizing the value of the complete drug package.

Smaller and virtual biotech companies that lack the resources to focus on the complete drug package sometimes may fail to achieve optimized outcomes. Partnering with a trusted, full-service CDMO early in the process offers a greater likelihood of success. In addition, startups that pursue projects from the very start with the end goals (packaged final products) in mind often attract the financial assistance of large companies, relationships that can lead to out-licensing deals or even acquisitions.

For both small and large drug developers, using different outsourcing providers for different phases of the development and commercialization cycle can increase both cost and risk due to the need for technology transfer activities. In addition, with an end-to-end CDMO, knowledge gained during early development work is retained and can be applied during late-stage process development.

PILLARS OF SERVICE

Vetter has long-term experience offering services ranging from early development support including clinical manufacturing, to commercial supply and various packaging solutions – to small, midsize and large pharmaceutical and biotech companies. We specialize in the aseptic manufacturing of prefilled syringes, cartridges and vials and have experience with monoclonal antibodies, peptides, interferons, vaccines and other complex compounds. Our state-of-the-art technologies and innovative processes are able to improve product quality and maximize API yields.

Vetter Development Service partners with clients from preclinical development through Phase III, planning for commercial production from a product's earliest stages. Services include formulation support, process development, clinical trial manufacturing and analytical and regulatory support. We develop processes that mirror those at our commercial production facilities, enabling seamless product transfer to Vetter Commercial Manufacturing, which provides Phase III manufacturing through to a global market supply.

At this level, Vetter offers a full range of services to deliver quality across the supply chain, including fill & finish, analytical services, regulatory support and product lifecycle management activities. These efforts are backed by measures taken both downstream and upstream to strengthen security of supply, including regular quality reviews of all suppliers and cross-linked IT systems to monitor manufacturing processes.

For final packaging, Vetter Packaging Solutions matches client products with appropriate drug-delivery systems (primary packaging); and provides secondary packaging, such as cartoning or blister packing, and other packaging services, including pen-system assembly, printing and labeling, and serialization. Our capabilities include customized packaging development, specialized technologies, platform technologies, and packaging and logistics services.

Clinical manufacturing is performed at a dedicated facility in Chicago, USA and in Ravensburg, Germany, where Vetter also operates three commercial facilities, a secondary packaging facility and a center for visual inspection and logistics. P

An Example of Vetter Innovation

At their core, aseptic processes and technologies are designed to minimize any contact between a drug product and the outside environment, thereby minimizing any chance for contamination. Historically, cleanrooms have employed either isolators or restricted access barrier systems (RABS). Isolators are generally considered to provide the highest level of sterility, but RABS offer greater flexibility and thus are suitable for realizing numerous filling projects in a single cleanroom.

In response to changing market needs and to meet the competing demands for the highest levels of quality and flexibility in aseptic processing, Vetter has developed the Vetter CleanRoom Technology V-CRT®, an innovation that combines the advantages of isolators and RABS, bringing together the safety and quality standards of isolator performance with the flexibility offered by RABS. The company will implement this decontamination concept in all of its cleanrooms within the coming years.

DEATH TO CLEANROOMS IN BIOPHARMACEUTICAL MANUFACTURING

→ **MARC PELLETIER, Ph.D.**, CRB

For as long as most of us can remember, the manufacture and purification of biologic drug substances has mostly been performed in cleanrooms. Recently, advances in the design, form, function and operation of bioprocessing equipment has made it possible to close — or functionally close — biological active ingredient (API) manufacturing operations. As expressed in the most recent regulatory guidelines (PIC/S 2017, Annex II), closed bioprocessing can be moved into simpler, unclassified environments and even outdoors! This strong endorsement of closed processing provides enormous opportunity and cost benefits to drug manufacturers.

WHY CLEANROOMS ANYWAY?

At the inception of the biopharmaceutical industry, with the production of antibiotics via fermentation, bioreactors were often located outside, with plumbing inside in locations that experienced colder weather. Contamination of these processes was seldom an issue during fermentation, given that the cultures in question were of a short duration and the organisms used produced antibiotics that inhibited the potential invasion of other contaminating species. In addition, the analytical tools available at the time often could not detect traces of contaminating organisms or chemicals.

Things changed with the introduction of mammalian cell-culture-based processes in the 1980s. The longer duration of the cell culture (from 24 hours to 12-180 days) and the lack of natural antibiotics produced by mammalian cells resulted in a higher frequency of detected contamination rates of up to 50%. Detected contamination rates of less than 5% were often considered acceptable or even "ideal" given the limitations of the industry's capabilities for effective SIP, sanitary design and maintenance of an aseptic state. Today we know that the failures were largely due to the fact that the equipment was not appropriately designed for aseptic operations. The biopharmaceutical industry's response to this deficiency was to move bioprocesses into cleanrooms, where the levels of bioburden were lower, thus reducing the level of bioburden to which our process streams were exposed. This solution was successful at reducing the frequency of **detectable** contamination rates to 5%-10%, so the strategy of moving bioprocesses into cleanrooms was adopted. The irony is that **actual** contamination rates likely remained the same. Only by improving the integrity of the equipment used can one truly mitigate the risk of contaminating a bioprocess from environmental elements. Unless one works in a bioburden-free environment (Grade A/ISO 5), the risk of contamination of an open operation cannot be totally eradicated.

CLEANROOMS WILL NEVER BE CLEAN ENOUGH

The observed contamination rates were achieved because existing analytical capabilities were limited, and therefore could not detect the lower levels of bioburden. As analytical detection limits continued to improve, it became possible to detect even minute levels of contamination in bioprocess fluids.

Equipment, raw materials, airborne particles, clothing, packaging, etc., are all sources of contamination of the environment. However, personnel represent the greatest source of contamination in cleanroom environments. Unless humans are removed from the bioprocessing environment, cleanrooms will always represent a risk of contamination to an open bioprocess. Because of personnel and the bioprocess itself, the level and type of environmental contamination in a cleanroom is ever-changing and thus impossible to control. As a result, cleanrooms will never be more than moderately effective in mitigating the risk of contamination of an open system except by reducing the **level** of contamination.

THE KEY TO SUCCESSFUL IMPLEMENTATION OF CLOSED OR FUNCTIONALLY CLOSED SYSTEMS IS GOOD DESIGN.

The only real solution to prevent contamination is through the use of closed equipment. Closed equipment is equipment or systems designed to be cleaned and/or sanitized to a point where the risk of contamination from environmental sources during product contact is fully mitigated. This includes single-use equipment and equipment designed to be CIP'd and SIP'd between operations. With such an approach, a process will only fail if there is an unusual event or malfunction of the equipment. An effectively closed process cannot be contaminated because of common human failures such as a torn glove, insufficient or inappropriate gowning, a cleanroom suite door that was improperly (or untimely) opened or closed, or because too many personnel were present in the suite during critical operations. If good science and process analytical technology are implemented, equipment can be appropriately closed by CIP and/or SIP and verified as closed. Personnel errors in gowning or transitions from one cleanroom zone to another will have little impact on the quality of the drug when manufactured in a closed system. Our regulatory agencies have recognized this, and for this reason, they are now inviting the manufacturers of biological APIs to perform these functions in unclassified environments (or "outdoors" as stated in the 2017 PIC/S regulations[1]).

CLOSED AND FUNCTIONALLY CLOSED EQUIPMENT

The solution of removing bioprocesses from classified cleanrooms can be achieved with closed or functionally closed equipment as defined in the International Society of Pharmaceutical Engineers (ISPE) Baseline Guideline.[2] A closed system is validated to show that there are sufficient layers of protection to mitigate the risk of contamination from the environment. Importantly, the environment housing the system is not a critical aspect of the process, because the product is never exposed to the outside environment. Thus the risk of contamination in a closed system cannot be mitigated by housing the process in a bioburden-free environment, so why put it there?

A functionally closed system is a system that is routinely opened, but then returned to a closed state via cleaning, sanitization or sterilization prior to product contact. The process, when run in a closed manner, does not expose the raw materials, in-process materials or bioprocessing fluid to the operators or environment. The cleaning and/or sanitization/sterilization process must be validated to confirm the return of the system to a functionally closed state.

The American Society of Mechanical Engineers (ASME) Bioprocessing Equipment Standards Committee (BPE) is charged with developing a standard covering the design, materials, construction, inspection and testing of bioprocessing equipment such as vessels, piping and related accessories, such as pumps, valves and fittings, for use in the biopharmaceutical industry. The ASME BPE standard[3] establishes requirements for the design of bioprocessing equipment and addresses the design features required for effective cleaning and sanitization of that equipment. The BPE is working to establish design standards for equipment for all biopharmaceutical unit operations that are single use or can be cleaned and sterilized/

sanitized for the purpose of effectively closing the system in which this equipment is used. With current technology available, it is possible to eliminate the environment as a factor for the contamination or adulteration of virtually all bioprocesses.

Unfortunately, some unit operations that have always traditionally been performed in open systems continue to be performed in this manner. Today, most – if not all – of these processes can be performed in closed or functionally closed systems. If the goal of 100% closed processing can be achieved, the need for cleanrooms can be eliminated completely. Doing so is not only safer for the operators, the manufacturing process and ultimately for the patient, it can also significantly reduce the cost of a unit operation from both OPEX and CAPEX perspectives. A cleanroom typically carries a capital cost of approximately $2000-$3000 per square foot, compared to $200-$400 per square foot for a high-quality unclassified environment suitable for housing a closed operation.

Closed processing can be achieved either by designing closed equipment or placing the open process inside a closed system such as an isolator. Whether using traditional stainless-steel tanks that are functionally closed by CIP and SIP or using single-use (SU) systems that are closed by gamma irradiation or by housing a process within a properly conditioned isolator, these options all represent a more cost-effective strategy that represents much lower risk to the patient.

RISK ASSESSMENT AND VALIDATION OF DESIGN

The key to successful implementation of closed or functionally closed systems is good overall design. Good design includes the use of connectors that are designed, installed and used correctly, effective sterilization/sanitization procedures, appropriate validation, effective monitoring and compliant documentation. Until all of these criteria are met, a system should not be considered closed.

CRB has developed a risk-assessment tool that helps its clients assess the potential for ingress of environmental contaminants into their processes. We have also created methodologies to mitigate these risks. As part of the ASME BPE, we are actively involved in the design of functionally closed solutions for existing open processes that can be readily cleaned and sanitized.

SOCIETIES/STANDARDS/GUIDELINES/TECHNICAL REPORTS AND THE REGULATORY AGENCIES

Among the challenges facing biopharmaceutical manufacturers are the numerous regulations, standards and guidelines applicable to bioprocessing. In addition to the ISPE Baseline Guidelines and the ASME BPE standard, the Parenteral Drug Association (PDA) has issued a series of technical reports with guidance on how to clean, sanitize and sterilize systems. And a consortium of biopharmaceutical manufacturers called the BioPhorum Operations Group is testing and challenging some of the former legacy paradigms and approaches (many of which have become folklore) and presenting new concepts to be considered in a series of white papers. Current good manufacturing practices issued by the USFDA (laid out in the Code of Federal Regulations, CFR) and the European Medicines Agency (EMA, laid out in the Eudralex in Annex I for drug products and Annex II for drug substances), as well as similar regulations in Japan, China and many other countries, must be complied with by producers of biologic APIs and formulated products.

The Pharmaceutical Inspection Convention (PIC) is working to address this issue through the development of harmonized regulations. The PIC consists of 52 participating authorities from all over the world. The group has created a new series of guidelines based on the European regulations but updated in more user-friendly language. Together with the societies stated above, the regulators are helping paint a clearer picture of what the real standards should be for the manufacture of biopharmaceuticals.

DEATH TO CLEANROOMS

Biologics manufacturers should be investing in process closure in lieu of investing in outdated, heavily customized, non-sustainable cleanrooms. The transition of our biopharmaceutical industry from open processing in cleanrooms and into closed processing is encouraged by regulators as well as other organizations responsible for publishing key bioprocessing guidelines. This strong endorsement of closed processing provides enormous opportunity and cost benefits to drug manufacturers. Simplifying the design and construction of a biopharmaceutical facility and the operation of an unclassified manufacturing environment results in huge capital and operational cost savings, and therefore fewer deviations and failures. The use of closed integral equipment also results in lower risks to the patient. May the next five years lead to improvements in equipment design, and ultimately to the death of cleanrooms in "Back to the Future Facilities™" for biopharmaceutical manufacturing. P

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Marc Pelletier, Ph.D.
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Marc Pelletier, Ph.D., is an internationally recognized biopharmaceutical process specialist. An industry leader in the area of fermentation and cell-culture-based bioprocesses, Marc has helped to revolutionize closed bioprocessing in the biopharmaceutical industry. He was main contributor for the ISPE Baseline Guideline on Biopharmaceutical Manufacturing Facilities. He also continues to serve on the ASME BPE Standards Committee after two decades. While his primary expertise is in upstream and downstream unit operations, Marc also has extensive experience in the area of plasma fractionation.

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MEET CHEMO CMO: PREFERRED PARTNER FOR INJECTABLES MANUFACTURING

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Started in 1977 as an API trading business focused on supplying high-quality drug substances to the pharmaceutical market, Insud Pharma (including Chemo, Exeltis and mAbxience) is today a global enterprise manufacturing generic APIs and Finished Dosage Forms – and offering comprehensive contract services for drug products manufacturing. Chemo CMO recently expanded its capabilities with the addition of state-of-the art sterile injectable manufacturing facilities.

TURNKEY SOLUTIONS FOR THE FULL PHARMACEUTICAL VALUE CHAIN

Chemo is part of the Spanish multinational, Insud Pharma, a large, diversified pharmaceutical company with an entrepreneurial spirit and commitment to continued investment in infrastructure and expertise to support its ever-widening activities. Chemo CMO is the latest division to be added to the group.

Chemo produces over 100 molecules (steroids, hormones, prostaglandins, prazols and antibiotics) and 50 formulated products in a variety of dosage forms (tablets, capsules, granules, inhalers, topicals, injectables and suspensions) covering all major therapeutic areas. Chemo also manufactures OTC and animal health products.

Our comprehensive integrated quality and safety management system ensures manufacturing in accordance with cGMP requirements and international pharmaceutical industry standards across our entire manufacturing network, which comprises eight state-of-the-art manufacturing facilities and eight R&D centers that are inspected regularly by FDA, EMA and local regulatory authorities.

Innovation and technology is the driving force of our business and is the backbone of our operations. We regularly invest in R&D to develop complex dosage forms, optimize manufacturing processes, and ensure a dynamic and useful portfolio of capabilities. Chemo's strong commitment to continual growth is reflected by the recent construction of two new manufacturing facilities in León, Spain dedicated to sterile hormonal products and in Madrid for sterile injectable manufacturing using state-of-the-art technology and the highest quality standards.

Chemo CMO's manufacturing expertise and flexible capacity provide a fast path to client drug approvals, making us the preferred CMO partner across all major dosage forms.

PREFERRED PARTNER FOR INJECTABLES MANUFACTURING

The newest dosage form for Chemo CMO is sterile injectables. There is growing demand for these products, but quality and capacity remain significant issues. Drug developers looking for CMO partners with sterile injectable capabilities are, for that reason, willing to look outside North America for manufacturing partners with state-of-the-art facilities and the assurance of high reliability and quality.

Chemo Industrial CMO is one of those partners. Our Universal Farma (Madrid area) and Farmalan (León) sites are new production facilities focused on sterile injectable manufacturing, with the Farmalan facility dedicated to hormonal products. Aqueous solutions, oily formulations, suspensions and lyophilized products can be produced at these plants in single- and multi-dose vials and prefilled syringes. Aseptic filling and freeze-drying services are provided at both facilities. Universal Farma also has capabilities in terminal sterilization, and unique and much-needed capability for API sterilization.

API sterilization is, in fact, a unique capability, and particularly important for products formulated as suspensions. This capability is offered both to clients that come to Chemo CMO with fill/finish projects that require sterile APIs and as a standalone service. API sterilization is obtained using aseptic filtration, with two possibilities – either micronization for particle size reduction or bead milling to create suspension dispersion. This area is segregated from the rest of the plant and serviced by a dedicated CIP/SIP system.

The new facilities are state-of-the-art and designed to be flexible. They were constructed so that the unique requirements of each sterile injectable manufacturing project can be accommodated. Vial and syringe filling line work under grade A (in RABS), and grade B and grade C formulation and filling areas are present at both sites.

As a dynamic company with a truly entrepreneurial spirit, yet with long-standing expertise in pharmaceutical development and manufacturing, we are eager to expand into new activities and have much to offer our customers. Clients can benefit from co-development opportunities and the greater freedom for creativity at Chemo CMO. P

FULLY SUPPORTING CUSTOMER NEEDS FOR BIOLOGICS DEVELOPMENT AND MANUFACTURING

→ BY **JAMES PARK**, SAMSUNG BIOLOGICS

Over the past seven years, Samsung BioLogics has constructed three state-of-the-art production facilities offering end-to-end integrated services to support the rapidly expanding clinical and commercial needs of customers. Building on successful FDA, EMA, and PDMA approvals in Plants 1 and 2, Samsung BioLogics increased capacity with Plant 3 (12 x 15,000 L bioreactors) and offered expansion of developmental capabilities, including Analytical Testing Lab, Process and Product Development, and Cell-Line Development Laboratory services to further support a growing customer base.

The biopharmaceutical market continues to grow at a healthy pace, though intensive capital and expertise requirements often pose barriers to development. At Samsung BioLogics, we believe that a quality-driven contract development and manufacturing organization (CDMO) that is designed to be flexible and multi-product focused can operate more efficiently and cost-effectively than internal biopharmaceutical manufacturing organizations. Given the unified focus of a CDMO, Samsung BioLogics can maintain a high level of quality and compliance, while reducing the cost of new biologic drugs and accelerating their development and commercialization.

INTEGRATED DEVELOPMENT SERVICES – CLINICAL TO COMMERCIAL

Given the dramatic success achieved in commercial-scale biologics manufacturing in just six years, Samsung has expanded services to include the production of non-clinical and clinical trial materials.

Customers can receive support for cell-line development, upstream/downstream process development and optimization, and analytical development. Leveraging new 50 L and 200 L bioreactors in the development lab and 2 x 1000 L bioreactors for clinical manufacturing, every step is geared toward developing a fully compliant and efficiently scaled-up manufacturing process to 15,000 L bioreactors. Samsung BioLogics' experts use scientifically sound techniques and statistically meaningful analysis methods to reach optimal titer values and improved yields to fully support production of drug substances for use in clinical studies.

The development services complement existing capabilities in cGMP mammalian cell-culture manufacturing and downstream processing (centrifugation, depth filtration, chromatography, virus removal and ultrafiltration/diafiltration). Drug product services include aseptic fill and finish (lyophilization development, aseptic vial filling for liquid or lyophilized products) and full visual inspection and warehousing. Since Samsung BioLogics can produce both high-quality bulk drug substances and drug products in multi-product facilities located in Incheon, South Korea, customers receive truly integrated services while minimizing unnecessary costs.

Analytical capabilities include analytical method development, qualification/validation, comparability studies, release testing, and stability testing. For clients looking only for analytical support, Samsung BioLogics provides Standalone Analytical Testing services. Regulatory experts also provide support to clients throughout a project, including assistance with the filing of biologics license applications (BLAs).

WORLD-CLASS CAPABILITY IN QUALITY AND PRODUCTION SCALE

In just seven years, Samsung developed world-leading single-site production capacity with the construction of three plants. Plant #1 began production in May 2011 with a capacity of 30,000 liters, followed by Plant #2 in September 2013, which added an additional 152,000 liters. Plant 2 was cGMP-ready for drug substance production as of February 2016. FDA and EMA approvals for production of its first monoclonal antibody were received in October and December 2017, respectively.

Groundbreaking for Plant #3, adding an additional 180,000-liter capacity, was held in November 2015. Construction of this facility – one of the world's largest biological drug production facilities – was completed at the end of 2017. When this plant is cGMP ready in Q4 of 2018, Samsung BioLogics will have a total production capacity of 362,000 liters and will be the world's largest biopharmaceutical CDMO.

With the completion of the third biomanufacturing facility, Samsung BioLogics has the ability to reliably supply large volumes of biologic APIs and formulated products to the global biopharmaceutical market at the most competitive cost. In six years, Samsung BioLogics has received 11 manufacturing approvals from regulatory authorities (US, Europe, Japan, and Korea) and won over 16 product manufacturing orders.

Samsung has earned a reputation for reliable, high-quality services. In 2017, the organization was recognized by *Life Science Leader Magazine* as a CMO Leadership Award winner for the fourth consecutive year, winning awards in all of the six core categories: overall quality, reliability, capabilities, expertise, compatibility, and development. Samsung BioLogics also received recognition at the Asia-Pacific Bioprocessing Excellence Awards 2017 in Singapore (in quality and manufacturing speed), and Best CMO in Korea Award 2017 and in 2018 "Best CMO to Watch Out For in 2018" by Korea & Company.

Samsung has rapidly built a strong track record in the biologic manufacturing industry on the foundation of world-class quality and compliance. At its core is a highly talented and committed workforce dedicated to client satisfaction and integrity. In its DNA is an insatiable focus on operational excellence in every aspect from process development, to tech transfer, to manufacturing execution. Ultimately, Samsung BioLogics understands that on the other side of every product it produces is a patient who is depending on the quality and efficacy of that product. At Samsung, we never lose sight of our responsibility to deliver for our clients and their patients. P

Development Services

DEVELOPMENT

- Cell Line Development
- Upstream/Downstream Process Development
- Scale-up Studies
- Process Characterization
- Analytical Method Development
- Bioassay Development
- Lyophilization Development and Optimization

cGMP CONTRACT MANUFACTURING

- Mammalian Cell Culture (Clinical & Commercial)
- Fill & Finish (Liquid/Lyophilization)

SUPPORT SERVICES

- Project Management
- Technology Transfer
- QA/QC — Analytics
- Stability Testing
- Regulatory Support
- Raw Material Management
- Product Release Testing

ABOUT THE AUTHOR

James Park
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James Park is the Senior Vice President responsible for the Business Development Center of the Samsung BioLogics. Prior to joining SBL in 2015, Mr. Park held technical and operational positions in biopharmaceutical companies in the US. From 2004-2015, Mr. Park participated, led, and directed CMC due diligence on assets ranging from pre-clinical to commercial products and managed BD activities including Licensing, Outsourcing and M&A at Bristol-Myers Squibb. Mr. Park holds a BS in Chemical Engineering from University of California, Davis and an MS in Industrial Engineering & Operations Research from Columbia University.

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MEETING THE NEED FOR SMALL-VOLUME API MANUFACTURING

BY **JIM SCANDURA**, AVARA PHARMACEUTICAL SERVICES

As the pharmaceutical industry shifts its focus from blockbusters to targeted therapies and advances rapidly expanding numbers of increasingly complex molecules into clinical trials, the demand for active pharmaceutical ingredient (API) manufacturing capabilities at the kilogram scale is increasing. CDMOs with broad chemistry capabilities, extensive experience, a track record of performance and the flexibility to offer both non-GMP and GMP services at the large-laboratory/small-volume production scale are ideally positioned to meet the needs of the marketplace.

FLEXIBLE GMP SMALL-VOLUME API MANUFACTURING

Innovation in the pharmaceutical industry has never been greater. The numbers of novel therapies entering all stages of clinical trials are increasing at a dramatic rate. On ClinicalTrials.gov, the number of studies listed based on the first submitted date has increased from 5,627 on January 1, 2001, to 263,689 on January 1, 2018. In just over one month, the latter number rose to 265,793 (February 11, 2018).[1]

Many of these candidates – approximately two-thirds – are based on small-molecule active pharmaceutical ingredients (APIs).[2] In 2017, 33 of 46 novel drugs approved by the FDA's Center for Drug Evaluation and Research (CDER) were formulated using small-molecule APIs.[3] Efficient and economic synthetic routes must be developed for the production of APIs that will ultimately be formulated into clinical trial materials. Contract development and manufacturing organizations (CDMOs) that have extensive experience and capabilities in both API process development and optimization, and GMP manufacturing at the kilogram-scale can accelerate development timelines and help their customers more rapidly get into the clinic.

INTEGRATED OFFERING: AVARA PHARMACEUTICAL SERVICES

At Avara, our API services are provided by sites in Avlon, UK and Shannon, Ireland. Both sites have a proven track record and vast experience in developing optimized routes to complex molecules, including hazardous processes. We have strong technology transfer records and cGMP manufacturing environments supported by the latest processing and finishing technologies and excellent FDA and MHRA inspection records.

Shannon adds value with different milling and blending technologies, while Avlon is a top-tier Control of Major Accident Hazards (COMAH) site. For kilogram-scale manufacturing, the capabilities of the two sites are complementary and support preclinical through Phase III projects. Together these two sites leverage their capacities and experience to serve as key components of our strategic global manufacturing model.

FLEXIBLE SMALL-SCALE MANUFACTURING CAPABILITIES

The Shannon multipurpose, flexible GMP-approved kilo plant has two reactors (65 and 70 L glass-lined and stainless-steel) and advanced isolation/purification equipment (Hastelloy centrifuge and inline Cunoi filter). A Jet Pharma MC-150 is available for pilot-scale milling. The kilo plant is supported by fully equipped cGMP analytical laboratories, a material staging area and waste-management capabilities. Hydrogenations can be performed in the facility, as can reactions at -30°C to 160°C.

Avlon is in the process of reopening an existing GMP small-scale manufacturing facility suitable for the production of APIs and intermediates on the kilogram-scale. The systems and equipment are being modernized to facilitate many types of complex chemistries and include six reactors (20-100 L) and various equipment for the isolation (vacuum Nutsche filters, Buchi rotary evaporator, vacuum/pressure filter, centrifuge) and drying (oven tray dryers) of solid compounds under GMP conditions.

To increase capabilities, the GMP small-scale manufacturing facility was designed as a flexible asset with the ability to accommodate additional specialized equipment as needed by individual processes. The reactors are designed to handle flammable solvents and have varying temperature capabilities ranging from -80°C to 200°C. Automation software provides temperature and agitation control, process monitoring and data recording.

EXPERIENCE WITH GMP MANUFACTURING

The Avara Process Development Groups have a proven track record of developing API processes from Phase I/II to Phase III/commercial scale, as well as in process scale-up and optimization, process validation and technical transfer, and analytical method development/validation. Experts at both Shannon and Avlon have developed processes and analytical methods for new chemical entities from lab to commercial scale and demonstrated their technology transfer capabilities. In one example, significant cost savings were achieved introducing novel hydrogenation enantiomeric resolution and salt exchange steps; and re-engineering the crystallization process using Optimax modeling software and FBRM particle size analysis technology. In another example, process step improvements were made, and overall yield was increased through numerous enhancements, including modification of the crystallization process, which allowed for elimination of a micronization step. Commercial processes were also developed involving a patented alternative o-methylation process that replaced a process requiring a phase-transfer catalyst and pyrophoric BuLi, which also suffered from high levels of impurities.

Avlon also implemented a program of improvements that drove down manufacturing costs by 38% and improved the yield from 70% to 95% through reduction of the use of expensive starting materials. Manufacturing productivity increased plant output 6-fold with the same assets and staffing through application of Lean Principles.

Operational efficiency projects, chemistry improvements and process safety improvements were achieved over several years. Processes have been simplified, variability significantly reduced, and many manual interventions removed. For instance, process concentrations were increased through the application of Factorial Experimental Design. In addition, many process steps were optimized in the plant through lab development work, including the improvement of temperature ranges, optimization of reaction times and drying and wash cycles, and enhancement of automated controls for reduction of wait times in the plant.

ON-TIME, IN-FULL DELIVERY

All Avara sites are committed to delivering reliably, to the highest-quality standards, while using our skills and experience to reduce costs and manage supply chain issues. Shannon and Avlon exemplify this approach as both sites have established impressive records. In 2017, each site had an OTIF KPI greater than 99%.

As a testament to this, Avara has won a 2018 CMO Leadership Award from Life Science Leader magazine, receiving recognition for our performance in all six Core Award Categories: Capabilities, Compatibility, Expertise, Quality, Reliability and Service. This award reflects the success we have achieved by making a total commitment to our customers and delivering on our promises for scope, schedule, quality/regulatory compliance and price. P

ALL AVARA SITES ARE COMMITTED TO DELIVERING RELIABLY, TO THE HIGHEST-QUALITY STANDARDS, **WHILE USING OUR SKILLS AND EXPERIENCE TO REDUCE COSTS AND MANAGE SUPPLY CHAIN ISSUES.**

Special Thanks to **Gary Butler,** Vice President & Avlon Site Director and **Werner Kunz,** Vice President & Shannon Site Director for their contribution to this article.

Selected Capabilities

Small-volume GMP manufacturing capabilities at Avara encompass a broad array of chemistries and technologies. In addition to performing all traditional reactions, we are particularly adept at hazardous chemistry, such as nitrations, hydrogenations and organometallic transformations. We can conduct cryogenic chemistry, milling and crystallization at the lab to kilogram-scale. We have expertise in chiral chemistry and both chemo- and biocatalysis, too. Avara also has the necessary licenses and permits for the manufacture of scheduled drugs (controlled substances).

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Jim Scandura
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Jim Scandura has a wealth of pharmaceutical industry experience through projects with i-Solutions — a Life Sciences specialty consulting company. He has managed three major pharmaceutical manufacturing network change programs, three consent decree recovery efforts, over 30 manufacturing-site audit and operational improvement efforts, integration of a large R&D center, and the direct management and integration of several manufacturing sites. Mr. Scandura has experience working for Bristol-Myers Squibb, GSK, Roche, Valeant, Patheon, Aptuit and many other pharmaceutical companies. Previously, he was Senior Vice President at Johnson Controls Inc. and, prior to that, served in the US Navy Nuclear Submarine Service.

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FOCUSED ON FERMENTATION

→ BY **ELISE MOUS** AND **THOMAS DE MARIA**, CAPUA BIOSERVICES

Microbial fermentation continues to be an important upstream bioprocess for the production of conventional and next-generation biologics. Capua BioServices continues to invest in the latest laboratory and process-scale equipment and analytical capabilities to support modern fermentation.

WHY FERMENTATION?

Biologic drug substances can be produced using cell-culture or microbial fermentation processes. For many larger biomolecules, cell culture is the method of choice. Microbial expression using bacteria, yeast or fungi is generally preferred for smaller biologics. The microbes used in pharmaceutical manufacturing are genetically engineered to produce large quantities of biologically active substances, including peptides, proteins, cytokines, growth factors, plasmid DNA, single-domain antibodies, peptibodies and antibody fragments. For these compounds, microbial fermentation offers several advantages over cell culture. The processes are typically much shorter, less complex and generally more economically attractive. Media components applied are often free from animal-derived components, and associated costs are much lower as compared to cell culture.

FERMENTATION FOCUS

Capua BioServices (formerly known as Patheon Capua and DSM BioSolutions) is an independent, global provider of microbial custom development and manufacturing services. Located in Capua, near Naples, Italy, we began operating as Capua BioServices in July 2015. We have more than 50 years of experience applying bacterial, yeast and fungal systems for the production of proteins, enzymes and small molecules at the lab, pilot and commercial scales.

We have an extensive track record of developing and optimizing robust, cost-effective, high-quality microbial fermentation processes for the pharmaceutical and food markets, as well other specialty applications. Some of the microbes with which we have expertise include *Escherichia coli* and *Bacillus* spp, *Saccharomyces* spp, *Klyveromyces lactis, Pichia pastoris* and *Aspergillus* spp. We also have the requisite permits and capability to work with GMO strains.

LABORATORY INVESTMENTS

Recently, Capua opened a new laboratory facility that further strengthens our ability to conduct lab and pilot-scale activities. The investment is intended to better support the onboarding of new projects and facilitate the development of processes from the start that will be practical for sustainable, large-scale manufacturing. The addition of the new lab increases Capua's flexibility and enables us to provide a more complete on-site offering and support seamless technology transfer. The new facility includes upstream, downstream and basic in-process control areas. Upstream equipment includes shaker-incubators, autoclave, biohazard hood, several autoclavable (2L) and in situ sterilizable (15L) fermenters with control system, while downstream includes large-capacity bench centrifuge, high-pressure homogenizer, multiple configurable automatic skids for microfiltration and ultrafiltration, GE AKTA pure chromatography system up to 150 mL/min with 16 to 100 mm diameter columns, and several process vessels and pumps. Basic in-process control is present directly inside the facility with UV-VIS, HPLC, pH, conductivity, refractometry, multiple scales, etc. The lab is served by HVAC, filtered industrial steam, deionized water, brine and oil-free compressed air.

MICROBIAL EXPRESSION USING BACTERIA, YEAST OR FUNGI IS GENERALLY PREFERRED FOR SMALLER BIOLOGICS.

EXPANDED SPRAY DRYING FACILITY

In 2017, Capua BioServices opened a new spray drying facility to provide our customers with a technical and economically attractive alternative to lyophilization, crystallization and micronization. Spray drying allows the production of stable formulations of dry powder proteins, peptides, monoclonal antibodies and vaccines and can often enhance the bioavailability of poorly soluble compounds. It also enables precise engineering of particle size and the embedding of microencapsulation technology. The facility includes pilot-scale equipment and a cGMP spray drying suite with evaporation capacities of approximately 3-5kg and 100kg of water/hour, respectively. Our spray drying services include excipient and solvent screening, process parameter optimization, scale-up and cGMP spray drying, stability testing and QA release.

CAPACITY AND FLEXIBILITY

In order to best support our customers, Capua BioServices has designed its facility to be very flexible and developed expertise in a broad diversity of process types and processing technologies that can be applied at development to commercial scale. Our site in Capua contains dedicated manufacturing areas for pharmaceutical products and is regularly audited by the US FDA, EMA and specific European country authorities. With a total fermentation capacity of about 1400 m^3 spread over two separate fermentation areas, it is one of the largest independent beta-lactam-free microbial contract manufacturing facilities in Western Europe. The site also houses comprehensive downstream processing, formulation and final product filling and packaging areas. Capua's seven (soon to be eight) distinct recovery/purification plants include a large diversity of unit operations, which are designed to handle multiple projects in parallel from lab scale to pilot scale to commercial scale. Our development, optimization and commercial production activities are supported by an on-site GMP-qualified QC laboratory where biological and chemical assays are performed for raw material, in-process control and final product release testing.

UNIQUE POSITION

Product development, applications and regulations in the pharmaceutical and food industries are getting closer and closer. More often, it may be unclear whether a particular product is a medicinal product, food product/supplement, cosmetic, medical device or biocide. With quality systems and certifications in place to manufacture medicinal products as well as food-grade products, we are perfectly experienced and set up to support clients navigating through the landscape of these so-called "borderline products." Capua BioServices is GMP FDA approved since 1970 and FSSC 22.000 certified since 2016. P

ABOUT THE AUTHORS

Elise Mous
Director Sales & Marketing / Business Development, Capua BioServices

Elise Mous joined Capua BioServices in 2015 as Director Sales & Marketing / Business Development to further strengthen and develop Capua BioServices' positioning as a microbial CDMO. She started her career at DSM in 2004, followed by Patheon in 2014, and during the past 8 years built up her international business development experience in the field of custom research, development and manufacturing services. Mrs. Mous holds an MSc degree in managerial sciences next to a BSc degree in chemistry/biotechnology.

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Thomas De Maria
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Thomas De Maria joined Capua BioServices in 2017 as Business Development Manager to further Capua BioService's market development in North America. Prior to Capua BioServices, Mr. De Maria was the founder of Avventura Consulting, supporting start-up life science companies seeking to develop business and market opportunities for their inventions. Prior to consulting, he worked for Saltigo GmbH, a small molecule CMO. Mr. De Maria has completed MBA studies at University of Washington and holds a B.S. in biology.

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LEVERAGING LYOPHILIZATION DEVELOPMENT EXPERTISE FOR CLINICAL MANUFACTURING

Jeff Schwegman, Ph.D.
Founder & CEO, AB BioTechnologies, Inc

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Email jjschwegman@ab-biotech.com

Founded as a teaching and consulting firm in 2008, AB BioTechnologies, Inc. has steadily expanded its services to include pre-formulation, formulation, analytical and process development capabilities, as well as cGLP production of small-molecule and biologic parenteral and diagnostics products, with particular expertise in lyophilization (freeze-drying). By late 2018, the company will be providing cGMP manufacturing of Phase I-III clinical trial material and small-volume commercial products.

EXPANDING LYOPHILIZATION SERVICES MARKET

Therapeutic proteins, antibodies and other biologics formulated in solution typically require refrigeration or freezing to retain stability. Maintaining the cold-chain for these drugs can be challenging in many parts of the world. Lyophilization enables the preparation of stable formulations of drug substances that are unstable in aqueous solutions or suspensions; sensitive to heat, oxygen and/or humidity, or formulated at very low or high concentrations, making exact dosing difficult.[1] The generated lyophilized powders are shelf-stable and do not require low temperatures for shipping and storage.

While both small- and large-molecule drugs are lyophilized, lyophilization has increased as the number of biologic candidates and approved products has increased. The percentage of new injectable or infusible drugs that were lyophilized grew from just under 12% in 1998 to approximately 50% in 2015.[2]

Lyophilization is highly complicated, however, involving complex heat and mass transfer processes.[3] Customized lyophilization cycles must be developed for each drug and the associated container closure system used. The drug formulation and lyophilization equipment both impact freeze-drying performance, which can also contribute to scale-up difficulties.

Biopharmaceutical companies are, therefore, increasingly relying on contract service providers with specialized lyophilization expertise and equipment. Roots Analysis expects the lyophilization services market for biopharmaceuticals to grow at an annualized growth rate of 9.5% between 2017 and 2027.[1] Many contract manufacturers offer lyophilization services, but only a limited number specialize in this technology.

LYOPHILIZATION EXPERTISE

Bloomington, Indiana–based AB BioTechnologies, is one. Our foundation lies in our industry-recognized subject matter expertise in lyophilization and formulation development for chemical APIs, pharmaceuticals, biologics, devices, and tissue-derived products. Formulations and optimized lyophilization cycles are developed at the bench to client specifications, then scaled-up to manufacturing levels. Thermal characterization and analytical development are available as stand-alone projects or integrated into larger projects.

AB BioTechnologies also offers Good Laboratory Practice (GLP) manufacturing services. We can perform your early-stage development work and produce material for your pre-clinical/toxicity studies at one facility, streamlining the path to the clinic.

FROM DEVELOPMENT TO MANUFACTURING

We are taking another step to further streamline the path to the clinic by adding small-volume production capabilities in compliance with current Good Manufacturing Practice (cGMPs). With this $12 million expansion, AB BioTechnologies is eliminating the need for tech-transfer projects outside of our facility. We will have the ability to produce cGMP material for Phase I, II, and III clinical trials and small-scale commercial sale.

The new, state-of-the-art, 23,000-square-foot pharmaceutical manufacturing facility includes a manufacturing area for formulating, filling, lyophilizing and packaging drugs. Our current warehouse and development laboratory are being relocated there. Once the plant is completed, AB BioTechnologies will be able to help our clients advance their drugs from concept to clinic under one roof.

NIMBLE AND FLEXIBLE

AB BioTechnologies is a nimble, flexible company with the express ability to facilitate the development and small-scale manufacturing of parenteral drug products. We can accommodate most types of injectable formulations and welcome projects that require production of 500 to 25,000 vials. Our goal is to help clients get their parenteral medicines into the clinic as quickly as possible, while maintaining exceptional quality. P

REFERENCES

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2. M. Arduini. *"Freeze Drying Market Analysis,"* Presentation at IMA Aseptic Processing Symposium, Amherst, NY, September 2016.
3. Agnes Shanley. "Modernizing Lyophilization." *BioPharm International* 30 .12 (2017). Web.

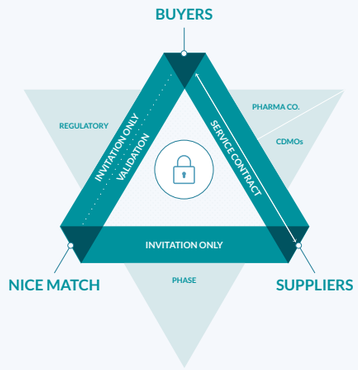
Matching Buyers & Suppliers
Bridging Capacity & Demand

Nice Match is Launching at DCAT
Nice Match introduces opportunities from buyers to the relevant member of an exclusive group of contract service suppliers known to have the right technology, expertise and available capacity. After an 18-month beta test, Nice Match will be launching at DCAT 2018. Visit **www.NiceMatch.com** to learn more about this exciting new offering.

How it Works
Nice Match leverages an exclusive network fostered through a combination of Nice Insight market intelligence and organic, long-established industry relationships to match pharmaceutical buyers with relevant outsourcing partners. Opportunities are brought into Nice Match through this network, qualified using Nice Insight market data, then presented to a supplier with the complementary capabilities to complete the project.

If you are struggling with your supply chain, you may be a perfect match.

Connecting the Pharma Community
Nice Match is an invitation-only service that matches the specialty needs of innovator and generics companies with contract service providers that have the right technology, expertise, equipment and capacity to meet the requirements of a given project. Designed primarily for the CDMO/CMO market, Nice Match addresses the industry-wide need to match up pharmaceutical supply and demand to accelerate development timelines, create reliable supply chains and free up business leaders to fully focus on getting much needed drugs to market — instead of searching for capable suppliers.



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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
- +1 910 254 7000
- 2320 Scientific Park Drive
  Wilmington, NC 28405

AB BioTechnologies, Inc is a contract service provider located in Bloomington, Indiana with a small dedicated staff of full-time employees with an analytical contractor.
The lab is full of various types of instrumentation and analytical equipment for the formulation and process development of injectable drug products, diagnostics, and tissue products. The eventual goal, as part of the next phase of expansion, is to have facilities, staff, and licenses from the FDA to manufacture injectable drugs for human and animal toxicology and Phase I clinical trials.

- www.ab-biotech.com
- +1 812 287 8493
- 3701 W. Jonathan Dr.
  Bloomington, IN 47404

Capua BioServices is a global provider of high-quality services in the field of custom microbial process development and manufacturing. We offer dedicated solutions for proteins, (high-value) small molecules and microorganisms for applications in pharma, food, feed and other bio-industrial markets.

We are one of the largest independent microbial contract manufacturing facilities located in Western Europe, with a total fermentation capacity of about 1400 m3. Our company is headquartered in Capua (Italy) with approximately 190 employees. Over the past 50 years, we have built a track record based on our extensive experience in working with a variety of bacterial, yeast and fungal systems.

- www.capuabioservices.com
- +39 0823 628111
- Strada Statale Appia 46/48 | 81043
  Capua (Caserta), Italy

Insud Pharma integrates our three areas of business and well-known brands: Chemo Industrial, Exeltis and mAbxience. Chemo is the Group's pharmaceutical division, and a leader in research, development and the manufacture of value-added finished dosage forms and active pharmaceutical ingredients for the main therapeutic areas. Exeltis is engaged in the areas of sales and marketing, with a strong portfolio of brand-name generic drugs, in particular for women's health and dermatology. mAbxience is our international biotechnical company, specializing in the development, manufacturing and global marketing of biosimilars for the treatment and prevention of diseases in various therapeutic areas.

- www.insudpharma.com
- + 34 93 330 62 12
- Gran Vía Carlos III, 98 7ª planta
  08028 Barcelona, Spain

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.

- www.crbusa.com
- +1 816 880 9800
- 1251 NW Briarcliff Parkway, Suite 500
  Kansas City, MO 64116

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
- +1 734 282 3370
- 101 Merritt 7
  Norwalk, CT 06851

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

CapsCanada is a leading innovator of empty hard capsules and capsule technologies for the pharmaceutical and nutraceutical markets. With 30 years of experience manufacturing high-quality capsules for medicines and supplements, CapsCanada serves global markets from facilities in Windsor, Ontario, Canada and Barranquilla, Colombia. CapsCanada's K-CAPS® vegetarian HPMC capsules are preferred among pharmaceutical and supplement makers in over 60 countries, and its vertically-integrated gelatin supply chain guarantees the integrity of its gelatin from sourcing to distribution.

- www.capscanada.com
- +1 866 788 2888
- 456 Silver Creek Industrial Drive,
  Windsor, ON N8N 4Y3, Canada

For more than 50 years, **Federal Equipment Company** has been a trusted equipment supplier to the pharmaceutical, chemical and plastics industries. With thousands of pieces of inventory in stock, Federal Equipment is dedicated to providing customers with immediate access to quality used equipment at competitive prices. Additionally, Federal Equipment offers a complete array of investment recovery and asset disposition services, including appraisals, auctions and liquidations, equipment purchase and removal, as well as consignment sales to dispose of idle and surplus equipment.

- www.fedequip.com
- +1 800 652 2466
- 8200 Bessemer Avenue
  Cleveland, OH 44127

Grifols is a global healthcare company with a legacy of improving people's health and well-being through the development of life-saving plasma medicines, hospital pharmacy products and diagnostic technology for clinical use. The company is present in more than 100 countries worldwide, with headquarters in Barcelona, Spain. Grifols Partnership is a business-to-business contract development and manufacturing platform for sterile solutions and lipid emulsions with over 75 years' experience in producing intravenous solutions for the pharmaceutical industry.

- www.grifols.com
- +1 34 93 05712200
- Avinguda de la Generalitat, 152
  Parc empresarial Can Sant Joan
  08174 Sant Cugat del Vallès,
  Barcelona, Spain

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
- +1 800 627 5361
- 4307 Emperor Boulevard, Suite 210
  Durham, NC 27703

SAMSUNG BIOLOGICS

Samsung BioLogics is a full-service CDMO focused on the development and manufacture of biologics for the improvement of global healthcare. Established in 2011, Samsung BioLogics offers a full range of solutions for the biopharmaceutical industry, including cell line process and analytical method development, analytical services, and bulk cGMP manufacturing of drug substance and drug product from clinical to commercial scale. Based in Incheon, South Korea, Samsung BioLogics' three manufacturing facilities are optimized for the production of monoclonal and recombinant drug substance and drug product.

www.samsungbiologics.com
+82 2 3782 7862
300 Songdo Bio Way (Daero)
Yeonsu-gu, Incheon 21987, Korea

SERVIER CDMO

Servier CDMO provides fully integrated manufacturing and supply chain services for small molecules & drug product, from development and clinical supply up to commercial launch. Servier CDMO includes a worldwide footprint with eleven 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

SPI Pharma

An ABF Ingredients Company

SPI Pharma serves over 55 countries with formulation innovation, technical assistance and troubleshooting support. SPI Pharma's products include antacid actives, excipients, taste-masking technology, drug delivery systems for tablets, fast-dissolve technologies and a variety of other creative offers for patient-friendly dosage formats. They focus solely on the pharmaceutical market, ensuring their best-in-class products provide exceptional quality by meeting or exceeding global regulatory requirements.

www.spipharma.com
+1 800 789 9755
503 Carr Road, Suite 210
Wilmington, DE 19809

UPM Pharmaceuticals

Formulating Your Future™

UPM Pharmaceuticals is a Bristol, Tennessee–based, independent drug-development and contract manufacturer serving the pharmaceutical and biotechnology industries. The company provides pharmaceutical drug development services — including formulation development, cGMP manufacturing, analytical methods development and stability testing — from concept to commercialization. UPM's focus is on drug development for dosages with oral routes of administration, in solid dosage forms such as capsules and tablets, and semisolid creams and ointments.

www.upm-inc.com
+1 423 989 8000
501 5th St.
Bristol, TN 37620

VETTER

Vetter is a global contract development and manufacturing organization (CDMO) headquartered in Ravensburg, Germany, with production facilities in Germany and the United States. The company has long-term experience offering services ranging from early development support including clinical manufacturing, to commercial supply and various packaging solutions for vials, syringes and cartridges. Vetter's customers range from small and midsize to the world's top 20 pharmaceutical and biotech companies. As a leading solution provider, the CDMO recognizes its responsibility in supporting the needs of its customers in developing devices that contribute to increased patient safety, convenience, and enhanced compliance.

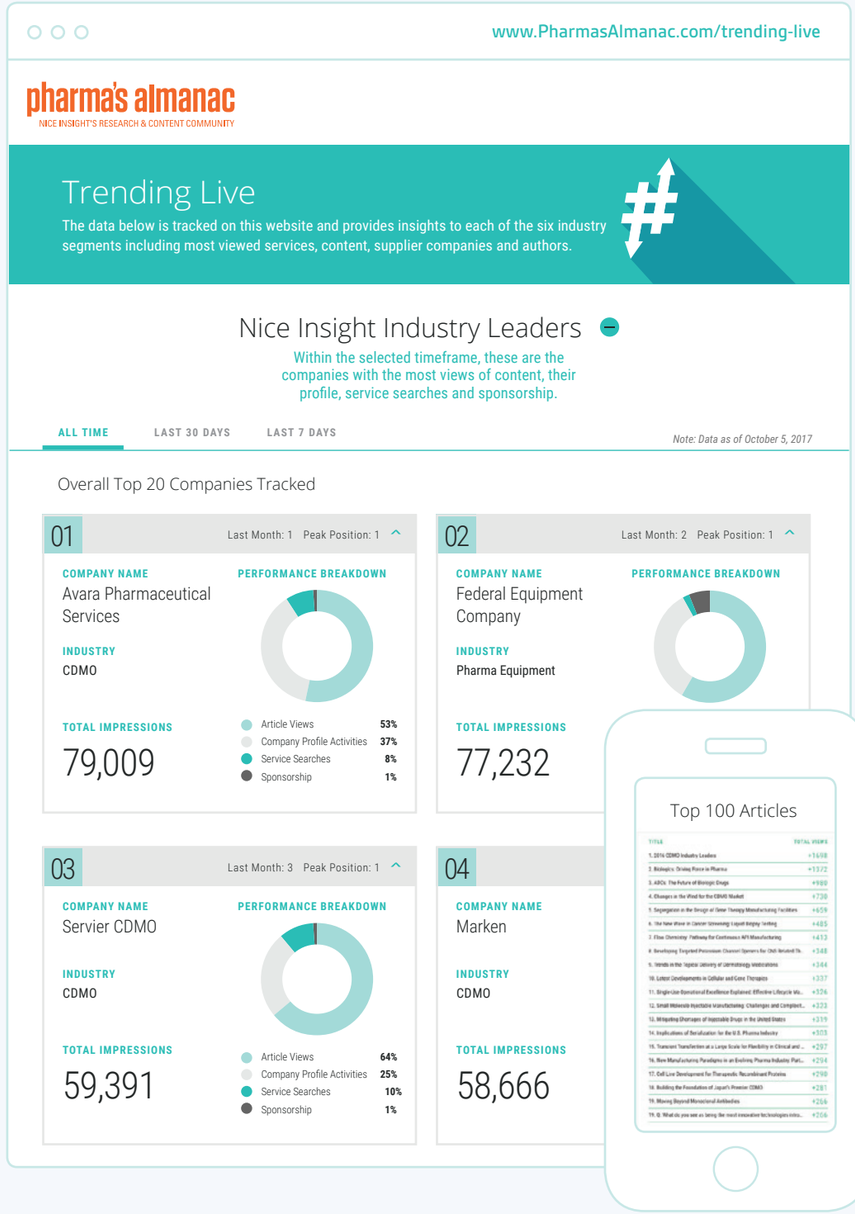
www.vetter-pharma.com
+49 (0)751 3700 0
Eywiesenstrasse 5
88212 Ravensburg, Germany

药明康德 WuXi AppTec

WuXi AppTec is a leading global pharmaceutical, biopharmaceutical, and medical device open-access capability and technology platform company with global operations. With its industry-leading capabilities such as small molecule R&D and manufacturing, cell therapy and gene therapy R&D and manufacturing, and medical device testing, the WuXi platform is enabling over 3,000 innovative collaborators from more than 30 countries to bring innovative healthcare products to patients, and to fulfill WuXi's dream that "every drug can be made and every disease can be treated."

www.wuxiapptec.com
+1 609 799 2295
107 Morgan Lane
Plainsboro, NJ 08536

Trending Live: Real-Time Data with Full Transparency



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Market Segments
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Nice Insight Live Data
Trending Live is a continuous data feed pulling from our Nice Insight research database and Pharma's Almanac content platform to provide near-instant insight on what the industry is seeking in contract service providers, as well as the thought leadership content in which they are most interested.

Research & Content Enterprise
Nice Insight has been providing decision-supporting market research and analysis for the past eight years, accumulating this information to form what has become the industry's most robust information repository and content platform.

Make Informed Decisions
Trending Live was conceptualized as a way to provide this information immediately and transparently, empowering key personnel with the means to make informed, strategic decisions to benefit their business.

MERGERS & ACQUISITIONS

What Role has M&A Played in your Company's Growth?

M&A has been a significant part of our growth strategy for a number of years. As an organization, we believe that growth is an integral part of being an industry leader. M&A provides us the opportunity to be more relevant to our customers — we don't grow for the sake of growth, or to move into areas we don't understand; we grow to strategically improve our portfolio. **We've acquired more than 35 companies over the past 15 years, including six in the past three years alone.** Each of those acquisitions has been the result of extensive due diligence, both into the companies we look at acquiring, and into our own to determine what areas make the most sense to grow.

William D. Barbo
Corporate Executive Vice President & Chief Commercial Officer, Charles River Laboratories

For Catalent, acquisitions have been transformative for the growth and diversification of the company's technologies and services offering, and in the last fifteen months alone **Catalent has made three significant acquisitions in distinct parts of its business, to address different strategic business needs.**

The most recent acquisition of Cook Pharmica, completed in October 2017 for 950 million dollars, strengthened Catalent's growing presence in biologic-based drug development. When integrated, Catalent's offering in biologics will cover development and analytical services, manufacturing and finished product supply, and of course its manufacturing capabilities and technology portfolio of GPEx® cell-line expression at its Madison, Wisconsin facility and SMARTag® antibody-drug conjugate development in Emeryville, California.

Early in 2017, Catalent acquired Accucaps, bolstering its OTC and prescription pharmaceutical softgel capabilities and manufacturing capacity in North America. This increased Catalent's portfolio of products supplied to pharmaceutical companies as well as adding two state-of-the-art facilities offering integrated softgel development, manufacturing and packaging into its global network.

The addition of Pharmatek Laboratories in 2016 expanded Catalent's early-phase drug development capabilities and added spray drying technology to the company's portfolio of drug formulation and delivery technologies aimed at overcoming solubility and bioavailability issues. Additionally, the San Diego facility gives Catalent a geographical presence on the US West Coast.

Mike Grippo
Vice President of Corporate Development, Catalent Pharma Solutions

Between 1993 and 2015, drug companies spent an estimated $1.7 trillion on M&A activity, with 74% of this activity attributed to only 20 companies. 2014 alone saw 185 deals, of which 22 were valued at more than $1 billion. This trend continues today with nearly $34 billion being spent on M&A in the first quarter of 2017, and is likely to continue and perhaps even escalate. In particular, the political climate in the USA, advocating lower corporate tax rates and supporting repatriation of overseas revenue, may provide pharmaceutical companies even more incentive to pursue acquisitions to augment their growth. This trend in M&A has been primarily driven by a need to compensate for reductions in growth as a result of investment in early phase pipeline development, aptly demonstrated by the very recent, $11.9 billion acquisition of Kite Pharmaceuticals by Gilead.

Interestingly, the CRO/CMO service industry has also undergone a similar trend with increasing M&A activity. For example, the estimated global deal value in 2015 is estimated at $12 billion. A major driver for this comes from increased competition as a result of active outsourcing partner consolidation by the pharmaceutical industry, to ensure better efficiency and consistency, particularly following acquisition. Larger service providers such as SGS have been able to take advantage of such strategy by providing a full range of analytical services across the globe. M&A in the CRO/CMO sector has been sought primarily to improve the global footprint, acquire higher levels of technology and provide a broader portfolio of services. There seems to be little evidence that M&A in the pharmaceutical industry has resulted in any significant loss of business, particularly for the larger CRO/CMO providers, but rather has been grounds for scope change and perhaps some downsizing. Despite the magnitude of the M&A activities, the fundamental and primary demands on the pharmaceutical industries' outsourcing partners for quality and on-time delivery will continue to dominate, regardless of the size or activity of the pharmaceutical business.

Mark Rogers
Global Technical Director, SGS Life Sciences

Almac Sciences, a business unit within the Almac Group, has grown organically since 2004 with a very respectable growth of more than 20% per year over 10 successive years.

Recently, Almac Sciences has made some well-targeted acquisitions, with the first being completed in November 2015 of Arran Chemical Company located in Athlone, Ireland. This focused on combining our strength, scale and technology. The impact on our business has been tremendous; the perfect combination of large-scale intermediates manufacture (Arran asset) and biocatalysis (Almac technology platform) has successfully given us the right route-to-market for many of our clients' development projects.

The second acquisition, again in Athlone, Ireland, was completed on November 1st, 2017 and builds on our complementarity and extended resource services. Though too early to discuss impacts on long-term business, we can already say that this is broadening our service offerings and addressing our global clients' growing demands for high-quality, integrated, efficient offerings.

Mike Cannarsa, Ph.D.
US Business Development Director, Almac Sciences

Recipharm has a clear merger and acquisition (M&A) strategy which is focused on expanding our capabilities as a full service CDMO, as well as our geographic presence.

In recent years we have established a strategic presence in both the emerging Indian market and the innovative US market. Our geographic footprint is now unique in the CDMO industry, and allows us to offer a local-level service to our customers. In addition, by bolstering our development and manufacturing expertise through our M&A activity, we are able to handle complexity for our customers, helping to simplify the supply chain by taking products from proof of concept to commercial reality.

Mark Quick
Executive Vice President, Corporate Development, Recipharm

OPERATIONAL EXCELLENCE

How do you Address Operational Excellence as an Institution?

At every step, we strive to optimize resources and maximize efficiency by implementing lean methods throughout the organization.

This means we can offer first-rate services that provide good value for money. As we continue to grow as an organization, with decentralized operations and relatively small central functions, we are highly dependent on talented people at key posts throughout the organization. Through attracting, developing and retaining talented people, we are able to drive operational excellence across our organization. The key to making this approach work, however, is shared learning, and we focus our efforts on ensuring that the good things which are being done in, say, Portugal, can be transferred effectively to, say, Germany.

Mark Quick
Executive Vice President,
Corporate Development, Recipharm

Operational excellence is a strategic priority across Intertek Group and plays a key role in our '5x5' differentiated strategy for growth with focus on continuous improvement to drive productivity and best-in-class management. Examples include the adoption at each Intertek facility of operational excellence tools such as Kaizen and structured simplification. Each laboratory has a Kaizen champion and team empowered by local management to drive and deliver change to processes to improve efficiency whilst improving the quality and timeliness of delivery to our clients.

Ben Cliff
Laboratory Director,
Intertek Pharmaceutical Services

As a large, global organization, we have two overarching priorities: to provide an exceptional experience to our customers and to make Charles River an engaging, rewarding workplace for our employees.

On the customer side, we want them to reap the benefits of working with an end-to-end provider throughout the preclinical drug discovery process, without ever feeling like our process is too slow or cumbersome. We highly value responsiveness and flexibility within our organization, and use those pillars for both training and recognition. For employees, we realize that providing growth opportunities, recognizing employee contributions, supporting our local communities, and allowing fun and flexibility in the workplace is critically important to operational excellence. Our employees are the backbone of our organization, and our success depends on their commitment.

William D. Barbo
Corporate Executive Vice President & Chief Commercial Officer, Charles River Laboratories

For almost fifty years, **the Almac Group** has established CDMO relationships to extend our range of services to the top pharmaceutical/ biotech companies. With over twelve facilities, sixty service depots, and close to five thousand employees around the world, we adhere to a strict ethical statement and have crafted a unique culture of accountability and integrity to be delivered in every product/service offering as a result of implementing and enforcing effective operational systems and controls.

Almac's commitment to the following five values is unparalleled and equips the company to ensure operational excellence is unsurpassed, ensuring our mission to partner to advance human health is fulfilled:

Outstanding Quality
We ensure exceptional and reliable quality in all aspects of our work and recognize that quality determines the extent of our success.

Exceptional Innovation
We promote an environment where extending the boundaries of knowledge, technology and creativity is encouraged.

Superlative Customer Focus
We are committed to understanding and exceeding our customers' needs and build relationships based on integrity, responsiveness and excellent communication.

Inspirational People
People are Almac's core asset. Individually and collectively, people are critical to the success of our vision.

Financial Performance
We will drive excellent, sustainable financial performance.

Mike Cannarsa, Ph.D.
US Business Development Director,
Almac Sciences

Continuous Improvement (CI) is best described as a journey toward excellence. Fundamentally, it starts with the leaders setting the right tone for the organization, and embedding excellence in the company's values. At every level, it is important to:

- Set clear expectations
- Align ALL activities or actions to company's vision and business strategies
- Define the measure of success — using simple language that is consistent and standardized across the company
- Engage and empower every employee
- Expect that leaders create an environment to succeed
- Drive accountability and responsibility where it resides

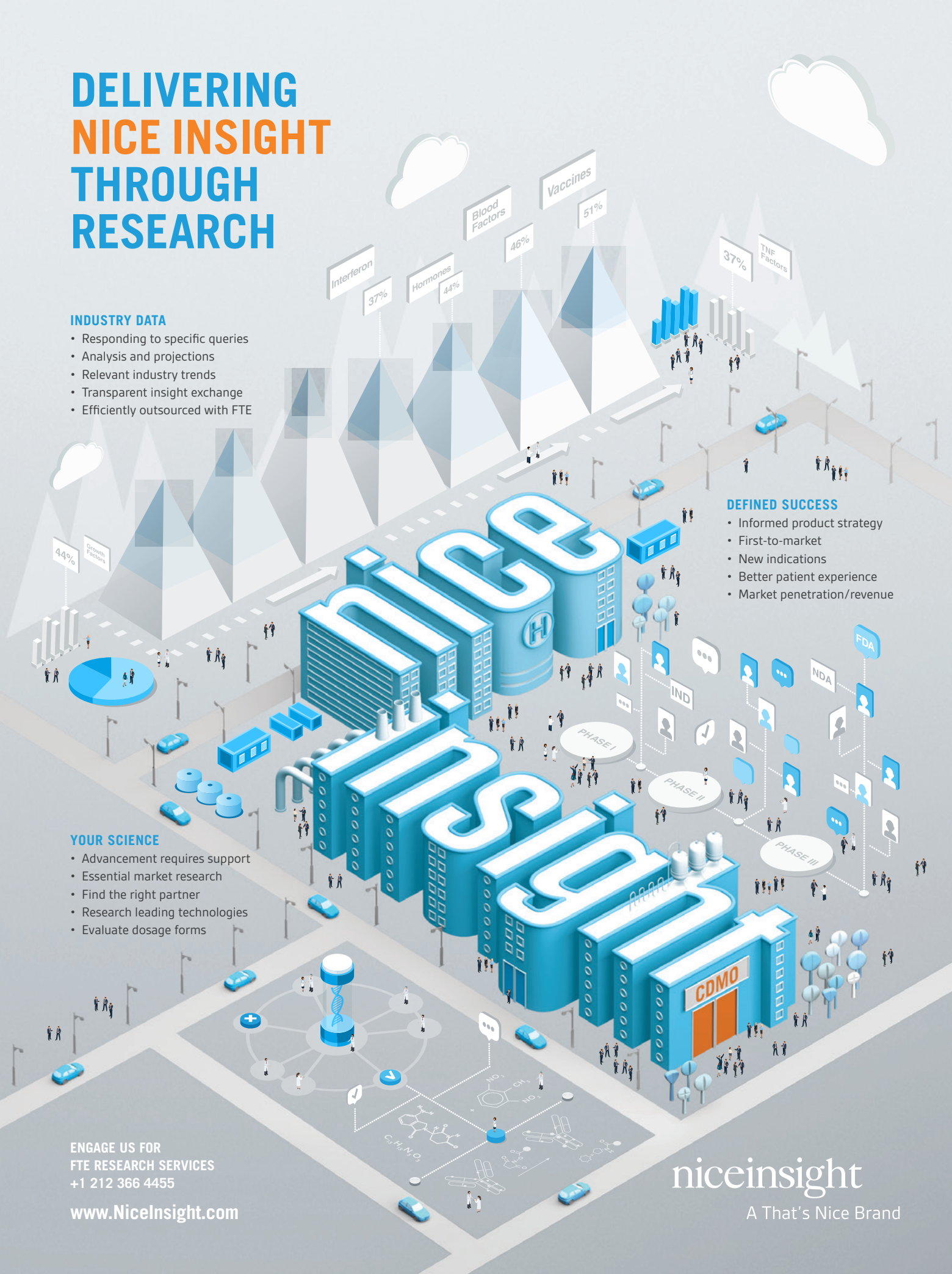
The single most critical factor is "focused execution," working on just 2 or 3 things at any given time and NOT trying to solve everything at once!

Building a strong CI culture, which focuses people on process improvements and automation, will ensure sustainable and predictable results.

World-class companies have frequent business processes/operating mechanisms in place to support and monitor the progress of transformation towards excellence. The positive impact felt by patients and customers cannot be achieved without a culture of the organization and employees to be better every 30 days!

Sridhar Krishnan
VP of Business
Analytics & Excellence,
Catalent Pharma Solutions

DELIVERING NICE INSIGHT THROUGH RESEARCH



INDUSTRY DATA

- Responding to specific queries
- Analysis and projections
- Relevant industry trends
- Transparent insight exchange
- Efficiently outsourced with FTE

DEFINED SUCCESS

- Informed product strategy
- First-to-market
- New indications
- Better patient experience
- Market penetration/revenue

YOUR SCIENCE

- Advancement requires support
- Essential market research
- Find the right partner
- Research leading technologies
- Evaluate dosage forms

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