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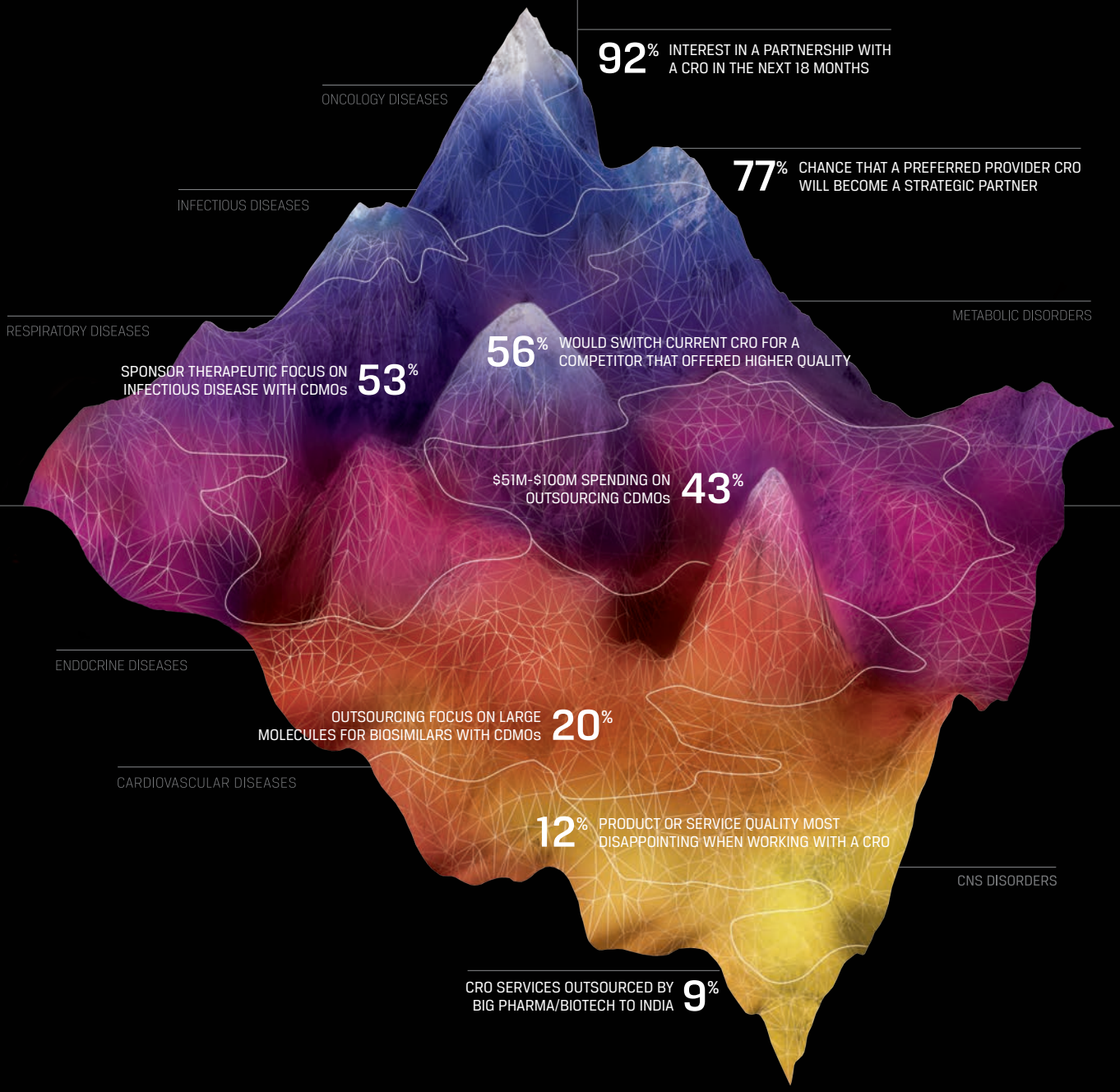
A NICE INSIGHT SUPPLEMENT

Q1 2016 EDITION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN LANDSCAPE

CLINICAL SERVICES, CONTRACT DEVELOPMENT & MANUFACTURING



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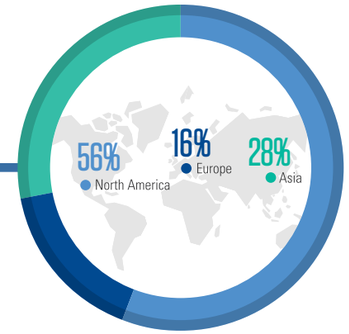

2016 NICE INSIGHT CDMO OUTSOURCING SURVEY FINDINGS

CDMOs

STRONG CMO/CDMO MARKET OUTLOOK FOR 2016, BUT BEWARE MODERATING FACTORS

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Nice Insight is the market research division of That's Nice LLC, the leading marketing agency serving life sciences.
We publish Pharma's Almanac, a special supplement that contains results from our annual industry surveys on buyer needs, supplier evaluation and selection criteria, and ratings for CROs, CDMOs, pharmaceutical excipients, and products/services for pharmaceutical equipment.

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STRATEGIC PARTNERS PREFERRED

→ BY STEVE KUEHN, EXECUTIVE CONTENT DIRECTOR

Outsourcing can help biopharmaceutical manufacturers leverage positive growth drivers and overcome or mitigate negative pressures. The strong growth of outsourcing to CROs, CDMOs, and CLOs should therefore be no surprise, given the numerous and varied forces working on the pharmaceutical industry today.

Not every service provider will automatically end up a winner, though. Clients are winnowing down their outsourcing partners to increase sourcing efficiencies. They are also moving from tactical suppliers to preferred and strategic partners that develop much more collaborative and long-term relationships. These partners typically offer development through commercial manufacturing and even lifecycle management support, eliminating the delays typically associated with technology transfer from one provider to another. They also have unique combinations of specialized capabilities designed to help their customers overcome formulating and manufacturing challenges and differentiate their products.

The greatest opportunities, therefore, are waiting to be captured by innovative and flexible outsourcing partners that can help their customers manage complexity, enhance efficiency and productivity, improve quality, and increase collaboration. Service providers with flexible operating strategies that can offer accelerated development services and proprietary and differentiating technologies, and reliably exceed project deliverables, will benefit the most from the growing demand for external research, development, and manufacturing support.

Pharma's Almanac was created as a platform for exploring the issues that impact the pharmaceutical outsourcing market. It brings together the insights of thought leaders involved in the contract research, development, and manufacturing of small-molecule and biologic APIs and formulated drug products, with the research results generated by Nice Insight, the research arm of That's Nice, to provide a unique perspective on effective solutions to the challenges and opportunities facing service providers today.

This issue includes articles from specialty outsource service providers focused on both chemical and biologic APIs and formulated drug products, as well as logistics and equipment. Each addresses different client needs and actions that service providers can take to provide unique and effective solutions. Other articles discuss the challenges of clinical trial material delivery and measuring and improving customer satisfaction. Nice Insight also provides the results of its 2016 CRO and CDMO Outsourcing Surveys.

We are excited to bring you this second edition of the Pharma's Almanac. While many of the articles may not directly relate to your specific area of expertise, we believe that each offers insightful commentary that can be applied to most outsourcing relationships, regardless of the nature of the API or the specific contracted service. Whether you agree or disagree, please share your feedback. P

SPECIALIZED EXPERTISE IS ESSENTIAL FOR PHARMACEUTICAL OUTSOURCING PARTNERS

→ BY **CYNTHIA A. CHALLENER PH.D.,** THAT'S NICE

While the pharmaceutical contract services market is growing at a healthy rate, CROs and CDMOs are competing head-to-head to earn the right to be preferred providers, while other contract and specialty service providers are excelling to be top providers. Only organizations with specialized capabilities ranging from the technical to the strategic will be successful.

In this edition of the Pharma Almanac, you will find 17 articles that discuss aspects of pharmaceutical outsourcing for both small- and large-molecule drug substances and drug products across the value chain: development, process optimization and scale-up, formulation, technology transfer, and manufacturing of clinical and commercial materials. The authors share valuable insights on their areas of expertise and how to improve both existing processes and outsourcing partnerships – all learned first-hand. Enjoy the read!

[1] Nigel Walker, founder of life sciences marketing agency **That's Nice LLC** and **Nice Insight**, the company's research arm, outlines the trends driving growth in the pharmaceutical outsourcing market in 2016. Despite fierce competition in the market, there are opportunities for innovative and flexible CROs and CDMOs that can help their customers manage complexity, enhance efficiency and productivity, improve quality, and increase collaboration.

[2] The new **2016 Nice Insight CDMO Outsourcing Survey** results suggest strong growth of the pharmaceutical contract manufacturing market, with more companies than ever spending over $50 million annually for outsourcing services.

[3] Rajesh Shenoy, Ph.D., VP of Global Chemical Development, and Christopher Conway, Senior VP of Discovery and Development Services, from **AMRI**, explores how the use of Good Laboratory Practices and thorough process development and optimization early on can fa-cilitate scale-up to commercial GMP manufacturing and speed time to market.

[4] Ash Stevens' President & CEO, Dr. Stephen A. Munk, discusses the significant role that CDMOs with integrated service offerings, particularly those with excellent process optimization capabilities, are playing in the continued success of the small-molecule pharmaceutical market.

[5] New manufacturing strategies are needed to enable accelerated API and drug product development and commercialization. Continuous processing is an effective approach to increasing efficiency and quality and will be a key component of the manufacturing capabilities offered by the most innovative CDMOs, assert **Hovione**'s VP of R&D Filipe Gaspar, General Manager (NJ, USA) Marco Gil, and Head of Continuous Manufacturing R&D Nuno Matos.

[6] Syed T. Husain, Chief Commercial Officer of **AAIPharma Services–Cambridge Major Laboratories**, discusses the benefits to pharma companies of access to analytical, development, manufacturing, and oral solid dose and parenteral manufacturing / packaging from CDMOs that offer API and drug product development and manufacturing services.

[7] Kevin Haehl, General Manager of **Unither Pharmaceuticals**, discusses the importance of convenient dosing formats for improving the medication adherence of elderly patients. Single-dose options help reduce medication errors and can be designed for easy access, and blow-fill-seal and stick-pack products provide elderly patients with a means for keeping track of their medications.

[8] Greg Flyte, Director of Contract Manufacturing Organization (CMO) Alliance & Program Management at **GlaxoSmithKline**, highlights the importance of the ability of biopharmaceutical CDMOs to provide customized platforms to address specific customer needs, solve technical challenges, and bring products to market in the shortest possible time.

[9] CMC Biologics President and CEO Gustavo Mahler discusses how growth of the biologics market is creating demand for biopharmaceutical CDMOs with state-of-the-art facilities, a broad array of expertise, and accelerated process and product development capabilities.

[10] The advantages of premixed parenteral delivery compared to other leading parenteral drug delivery options are outlined by Marga Viñes, Business Development Manager for Contract Manufacturing with **Grifols Partnership**. Specialized CDMOs with the right set of capabilities can help drug companies reap the benefits of manufacturing parenterals without assuming the majority of the risk when switching from in-vial admixtures to premixed IV bags.

DESPITE FIERCE COMPETITION IN THE MARKET, **THERE ARE OPPORTUNITIES FOR INNOVATIVE AND FLEXIBLE CROs AND CDMOs** THAT CAN HELP THEIR CUSTOMERS MANAGE COMPLEXITY, ENHANCE EFFICIENCY AND PRODUCTIVITY, IMPROVE QUALITY, AND INCREASE COLLABORATION.

[11] Guy Tiene, Director of Strategic Content and Robert Leeuwendal, Senior Consultant with **Nice Consulting** review alternative approaches that CDMOs can adopt for exceeding client expectations and improving the customer experience. Understanding customer expectations, aligning internal processes to support the desired customer experience, and demonstrating leadership are three key factors for success.

[12] Nice Insight discusses the top-line results of Nice Insight's new 2016 **CRO Outsourcing Survey**. The level of CRO engagement at every clinical phase has increased prominently, and outsourcing expenditures will continue to increase in the next five years.

[13] The development of innovative, specialized technologies is crucial if clinical logistics organizations (CLOs) and others involved in clinical trial design and management are to meet the increasingly complex needs of the sector while simultaneously increasing study efficiency and reducing cost. CEO Wes Wheeler and CCO Ariette van Strien of **Marken** explore the growing need for CLOs that employ state-of-the-art information, inventory, temperature control, and other technological systems to provide patient-focused delivery of clinical trial materials anywhere in the world.

[14] Trends driving the pharmaceutical equipment market as revealed by **Nice Insight's 2015 Pharmaceutical Equipment Annual Study** are discussed by Nice Insight. Equipment needs across the supply chain are changing, and suppliers are responding with innovative technologies.

[15] Matt Hicks, Chief Operating Officer, **Federal Equipment Company**, explains why managing surplus and idle equipment inventories without interrupting current development and manufacturing programs has become an increasingly complex task, and strategies to manage surplus equipment to reduce costs, eliminate redundant or idle manufacturing equipment and facilities and free valuable manufacturing space.

[16] The 2016 **CDMO and CRO Industry Leaders** results are in. Companies have been ranked according to CP score, a measurement of customer perception that averages six key drivers. These CDMOs/CROs are ranked to the nearest decimal, suggesting a competitive landscape in which consumers are attuned to individual service offerings and overall market trends.

[17] Aaron Mazze, Digital Director of That's Nice, outlines the **Power of "Inbound" for Digital Marketing and Sales Success.** As a complement to traditional "outbound" marketing, inbound techniques emphasize content development to pull customers towards a company's brand and value proposition, increasing both awareness and credibility. P

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Dr. Challener is an established industry editor and technical writing expert in the areas of chemistry and pharmaceuticals for various corporations and associations, as well as marketing agencies and research organizations, including That's Nice and Nice Insight.

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OPPORTUNITIES ABOUND FOR CONTRACT SERVICES IN 2016

→ BY **NIGEL WALKER,** THAT'S NICE LLC / NICE INSIGHT

Growth in demand for biopharmaceuticals will remain strong in 2016, further boosting both internal investments and outsourcing of drug discovery, development, and manufacturing activities.

Although the contract manufacturing and research markets will remain highly competitive, service providers with flexible operating strategies that can offer accelerated development services, proprietary and differentiating technologies, and a collaborative working environment with consistent high quality and on-time delivery will have tremendous opportunities for growth.

Both positive and negative forces continue to buffet the pharmaceutical industry in 2016. On the one hand, the global economy continues to strengthen and the growing middle classes in emerging markets are looking to take advantage of improving healthcare systems. Demand for medicines is expanding further as the global population continues to age and chronic diseases become increasingly widespread, even in emerging economies. The industry is also experiencing a significant return on its heightened investment in innovation over the last few years, with the strongest pipelines and largest numbers of drug approvals seen in many years. While these successes are leading to greater investment in internal production facilities and M&A activity by sponsor firms, including acquisitions to achieve vertical integration, they are also driving increased reliance on outsourcing, particularly to contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs) for drug substances that require specialized handling (e.g., highly potent compounds) or unique drug delivery solutions (i.e., poorly soluble drugs, unstable biologics, off-patent products), and contract research organizations (CROs) that can implement adaptive trial designs.

On the flip side, the movement towards evidence-based medicine marches on, along with growing pressure from payers, governments, and patients for reduced drug prices. Generics, and now biosimilars, are growing as more blockbusters fall off the patent cliff, and demand is largely occurring in emerging regions where lower prices aren't optional. These trends are driving pharmaceutical/biopharmaceutical companies to improve efficiency and productivity, implement novel lifecycle management strategies, and seek technological solutions (single-use systems, continuous processing) that can aid both of these efforts. CROs, CMOs, and, increasingly, CDMOs with the right sets of capabilities are often part of the solution.

OPPORTUNITY NO. 1: MANAGING COMPLEXITY

The structures of large- and small-molecule drug substances are increasingly complex and potent, requiring vast and advanced development and formulation expertise, as well as specialized production and analytical capabilities and packaging/delivery solutions. For CROs and CMOs/CDMOs that offer integrated services across discovery, development, drug substance, and product manufacturing and lifecycle management phases, this complexity provides numerous opportunities to attract client projects. A few examples include:

+ Small-molecule drugs with complex scaffolds whose syntheses require the use of low-temperature or hazardous chemistries
+ Highly potent and cytotoxic compounds
+ Drug substances with poor solubility/bioavailability
+ Off-patent drug substances that require novel reformulation/delivery solutions
+ Unstable biologics that must be produced via perfusion and require rapid purification and analyses
+ Next-generation medicines (cell- and gene-based therapies, virus-like particles, etc.) that require state-of-the-art production techniques

Formulation to achieve high bioavailability, efficacy, and safety has become more challenging. The shift to specialized medicines, such as orphan drugs and therapies with breakthrough or fast track status, has required the development and commercialization of these complex products with highly accelerated timelines. Extension of product lifetimes through modification of delivery and/or packaging technologies has become crucial for achieving reasonable profitability levels, given heightened generics competition. Outsourcing to CMOs/CDMOs with state-of-the-art and often proprietary technologies is an efficient, cost-effective way to meet many of these rapidly changing industry needs.

GLOBAL TRIALS

The complexity of clinical trials has also increased dramatically in recent years, with global, multi-site studies, requiring larger numbers of patients and lasting much longer, which is increasingly common. The number of clinical trials has also risen dramatically. Sponsor companies now increasingly rely on CROs with advanced systems in place to collect, monitor, and manage the huge quantities of generated data, ensure that the data is accurate, and provide easily accessible, non-intrusive tools for both patients and investigators.

In fact, "Harnessing information technology and novel scientific tools in the service of medical product development has been a central priority for the FDA," wrote Dr. Leonard Sacks, when serving as Acting Director for the U.S. Food and Drug Administrations Office of Critical Path Programs. He continued, "These innovative tools provide a historic opportunity to move medical product development into the 21st century and to deal with the challenges of spiraling research and development costs in the face of diminishing returns."

OPPORTUNITY NO. 2: ENHANCING EFFICIENCY AND PRODUCTIVITY

The need for a more efficient drug development process attracted the bipartisan support of the U.S. Congress in 2015. The House of Representatives passed the 21st Century Cures Act, and the legislation is under review by the Senate Committee on Health, Education, Labor, and Pensions. The Act attempts to address the need to accelerate the discovery, development, and delivery of promising new medicines, with the need to streamline clinical trials.

Pharmaceutical companies, in response to continued downward pricing pressure on drug products, are also taking actions to reduce costs and increase efficiency and productivity. New technologies must, however, provide demonstrated benefits without impacting drug safety and efficacy. Early adopters of innovative approaches to development, manufacturing, analysis, and clinical studies therefore assume a high level of risk, but CROs/CMOs/CDMOs willing to take that risk have the potential to reap significant rewards.

THE COMPLEXITY OF CLINICAL TRIALS HAS ALSO INCREASED DRAMATICALLY IN RECENT YEARS, WITH **GLOBAL, MULTI-SITE STUDIES,** REQUIRING **LARGER NUMBERS OF PATIENTS** AND LASTING MUCH LONGER, WHICH IS INCREASINGLY COMMON.

[1] CROs/CMOs/CDMOs that employ automated processing and/or analytical solutions offer clients improved quality consistency, increased operating productivity and greater flexibility, creating overall manufacturing systems that are more cost-effective and efficient, and enabling more rapid development and commercialization of safer drugs.

[2] Continuous manufacturing leads to more consistent products and processes. CMOs/CDMOs can achieve reduced resource consumption and waste generation for lower operating costs. Smaller footprints and the elimination of storage capacity can result in lower capital costs. Scale-up is simpler and more rapid, leading to lower costs as well as accelerated development and commercialization timelines. For small-molecule API synthesis, flow chemistry also enables manufacturers to perform reactions not possible in traditional batch mode.

[3] Adoption by CMOs/CDMOs of single-use technologies for commercial production of biologic APIs can lead to decreased capital expenditures and operating costs due to the reduction of cleaning and sterilization steps and the need for validation. Processes based on single-use equipment are also more flexible, with shorter required set-up times and significantly reduced cross-contamination risks, enabling faster time to market and more robust and reliable production processes.

THAT'S NICE – A SCIENCE AGENCY

That's Nice is a science agency, which reflects our evolution and focus in markets over 20 years. We began with opportunities in fine chemicals and moved into specialty chemicals. Our significant growth into life sciences came with clients working in small-molecule APIs – a significant long-term market for us – and one we still serve today. We also subsequently moved into large-molecule biologics and then began to establish client relationships we have today with some of the world's leading drug innovators.

NICE INSIGHT

Nice Insight offers custom primary and secondary research products and services focused on a variety of marketing intelligence needs, and conducts the largest annual industry survey on various purchasing parameters in pharmaceutical contract services outsourcing.

[4] CMOs/CDMOs willing to utilize modular facilities can quickly deploy small, flexible, and pre-sterilized production sites to rapidly meet client and patient needs, even in locations where a traditional plant could not be built due to a lack of resources.

[5] CROs that employ electronic data capture technology benefit from efficient data monitoring, analysis and reporting, more reliable data, better tracking of drug suppliers, enhanced communication and collaboration, better budget forecasting, shorter study times, and significant cost savings.

OPPORTUNITY NO. 3: IMPROVING QUALITY

Quality is the top selection factor when sponsor companies are choosing contract manufacturing partners. It is also the top criterion on which existing partners are judged, the key source of dissatisfaction with service providers, and the main impetus for switching from one CRO/CMO/CDMO to another. Furthermore, the FDA has made the improvement of quality in the pharmaceutical industry a priority, opening its Office of Pharmaceutical Quality in 2015 in order to more effectively address quality management issues.

In this environment, CROs/CMOs/CDMOs with effective quality management systems in place and "right-first-time" strategies for designing processes that provide maximum product quality will be most successful. Key practices include:

+ Use of design of experiment (DoE) approaches to efficiently establish critical process parameters
+ Application of advanced modeling, quality-by-design (QbD) and process analytical technology (PAT) methodologies during development and commercialization to ensure that processes are both robust and optimal for easy scale-up and consistent performance
+ Focus on achieving enhanced process understanding for ongoing, continuous improvement
+ Implementation of quality assurance programs and quality controls over data to support trial requirements

OPPORTUNITY NO. 4: INCREASING FLEXIBILITY AND COLLABORATION

To address the development challenges presented by the creation of increasingly complex drugs in a more efficient manner, pharmaceutical companies are seeking outsourcing partners that emphasize collaboration within their own firms and with their clients. According to a recent report by the Tufts Center for the Study of Drug Development (CSDD), while seeking ways to better serve public and patient communities (reducing rising development costs, shortening cycle times, and delivering better innovations), many pharmaceutical firms are also implementing highly collaborative approaches to validating drug targets. These include integrating real-world data into the R&D process, employing flexible and adaptive clinical trials, and using green manufacturing techniques, including the sharing of pre-competitive information among government agencies, academia, patient groups, payers, and providers.

The accelerated development timelines so common in 2016 require effective cross-functional teams, open communication between the service provider and the client, and strong relationships with regulatory authorities. In fact, CDMOs with integrated capabilities across all stages of development and manufacturing, with advanced technologies and methodologies that are designed to speed development and reduce costs, are increasingly preferred over traditional CMOs.

This trend is, in fact, driving consolidation within the contract services industry. Patheon, Catalent, Capsugel, and AAIPharma – all leaders in the contract manufacturing sector – have been exceedingly active on the M&A front and in making internal investments in capacities and technical capabilities. Examples of recent CRO deals include LabCorp's $6.1 billion purchase of Covance, MPI Researchs' purchase of Jasper Clinical Research and Development, and Eurofins Scientific's acquisition of Viracor-IBT Laboratories. More of the same from these firms and many others can be expected in 2016.

ADDITIONAL OPPORTUNITIES: BIOLOGICS, EMERGING MARKETS' AND MORE

CROs/CMOs/CDMOs can find additional opportunities for expanding their client base by providing services that support branded biopharmaceutical and biosimilar development, formulation, and manufacturing. Outsourcing partners with flexible, small-scale manufacturing facilities, designed to provide safe, efficient/accelerated production of multiple materials, will be attractive to clients looking to produce niche therapies that target specific patient populations, including orphan drugs and drugs that receive breakthrough therapy and fast-track designations from the FDA. Providers of contract research, development, and manufacturing services with regulatory-agency-inspected facilities in emerging markets will be well positioned to serve clients interested in leveraging the stronger growth in demand in these regions.

MANY WINS IN 2016

The contract research and manufacturing markets are growing at very healthy rates, ranging from 6%-9%. There is stiffer competition though, with a limited number of larger, integrated CDMOs dominating the marketplace. Even so, both pharmaceutical and biopharmaceutical manufacturers have robust R&D portfolios of complex and highly promising drug candidates and will require the assistance of outsourcing partners to bring these molecules to the market. Contract research and manufacturing organizations that understand the changing needs of drug companies (for advanced technical solutions and flexible, collaborative support designed to ensure the rapid development of cost-effective, robust processes, yielding high-quality, safe, and efficacious medicines) will end up as winners in 2016. P

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

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STRENGTHENING CDMOS TO MEET INDUSTRY NEEDS FOR 2016 AND BEYOND

→ BY **SYED T. HUSAIN,**
AAIPHARMA SERVICES – CAMBRIDGE MAJOR LABORATORIES

Outsourcing companies pursuing an integrated services model aim to facilitate drug development and commercialization for drug sponsors by enabling them to work with a single partner for activities that often require multiple, specialized vendors.

With a single qualified partner, pharma companies can have simplified access to integrated analytical, development, manufacturing and packaging services, as well as a broad range of dose form manufacturing and similar services. Some contract development and manufacturing organizations (CDMOs) offer both API and drug product manufacture, while others offer formulation development and clinical supply manufacture to complement their commercial production operations. Regardless, the aim is to provide a seamless supply chain solution.

Along with integrated service offerings, CDMOs are increasingly motivated to offer an expanded array of enhanced drug-delivery technologies, giving their customers broader options for patient care. Delivery technologies can include various targeted and timed release/dissolution and formulation technologies.

This article discusses these industry trends and issues, focusing on the outsourcing model of consolidated companies offering development and manufacturing services, a broad range of delivery technologies, and why more drug sponsors are relying on full-service outsourcing partners to design and implement their programs. Included is an example of these trends: the consolidation of AAIPharma Services and Cambridge Major Laboratories, to form a full-service, global CDMO that supplies drug substance and drug product development, manufacturing, testing and packaging services.

CHANGE IS A CONSTANT

Looking at the state of the pharmaceutical-biotechnology industry in 2016, here are a few key trends:

+ The industry is facing issues such as continued demand to lower costs, improve productivity, build pipelines faster, streamline infrastructure, meet ever-more-rigorous regulatory requirements and shorten time to market.
+ Companies are increasingly relying on contract outsourcing partners to provide the services, expertise, infrastructure and technologies they need to compete successfully and get the necessary medicines to patients.
+ Just like their pharma and biotech partners, contract service providers are consolidating, forming alliances to strengthen their capabilities to satisfy current industry demands.
+ The global outsourcing industry has seen a rise in strategic alliances, acquisitions and joint ventures among contractors, intended to extend service offerings and meet demand.

According to Nice Insight's CDMO Outsourcing survey of over 500 outsourcing-facing pharmaceutical and biotechnology executives (2016), the percentage of respondents whose companies spend more than $50 million on outsourcing has remained fairly stable over the last three years (24% to 23%) 2013-2015.[1] The 2016 survey shows that 43% spend $51-100M annually on outsourcing. The percentage of respondents whose companies spend $10 million to $50 million on outsourcing decreased from 62% to 23%, and the percentage of participants whose companies spend less than $10 million also decreased (16% to 3%).[2]

In 2014 for example, Cambridge Major Laboratories, a full-service CDMO, combined with AAIPharma Services, to become a major global supplier of integrated chemistry, manufacturing and controls (CMC) services. With the merger complete, the whole has become greater than the sum of its parts. The combination offers proven expertise in API development, analytical chemistry, and finished dosage forms while significantly elevating their ability to support the market with expanded expertise and compliant infrastructure.

SOLID DOSE TECHNOLOGIES

Oral solid dose forms continue to play a major role in the contract manufacturing industry and this market is set for a new period of gradual expansion. Fixed-dose combinations, controlled-release dosage forms and other lifecycle management strategies will continue to have significance.[3]

Recently, AAIPharma Services–Cambridge Major Laboratories (AAI-CML) added additional capabilities and capacity for oral solid dose manufacturing, sterile manufacturing and packaging, as well as expanded development services. This expansion also included additional laboratory and headquarters space to support the increased demand for small and large molecule clinical and commercial products.

The new facilities and equipment complement the CDMO's dosage-form capabilities, which include minitabs, pediatric sprinkles, chewable products, sublingual tablets, orally disintegrating tablets, extrusion granules, and extrusion spheronization. Extrusion spheronization makes spheroids uniform with dense granules for controlled-release oral solid dosage forms with a minimum amount of excipients. AAI-CML also has the capability to manufacture highly potent API drugs, controlled substances and tough-to-manufacture moisture /oxygen-sensitive drugs.

PARENTERAL DRUG DELIVERY: MEETING ESCALATING CHALLENGES

According to Frost & Sullivan, sterile parenteral contract services make up about 82.8% of the total sterile outsourcing market. This includes small-volume parenterals (e.g., vials, ampoules, and syringes), which make up the majority of sterile CDMO services with 88.9% of market share, and large-volume parenterals (e.g., bags and bottles). The sterile parenteral manufacturing subsegment is expected to reach a market size of $6.5 billion by the end of 2016.[4] Outsourcing parenterals is anticipated to increase and continue to benefit established companies in this market.[5]

As individual companies and as partners, AAIPharma Services and Cambridge Major Laboratories have accomplished a significant amount of sterile parenteral fills in their aseptic manufacturing facilities processing small- and large-molecule parenteral products as well as lyophilized products, suspensions, emulsions, and terminally sterilized vials. The operational setup of the combined company allows for the seamless integration of services covering development, testing, and manufacturing from API to finished packaging.

PARENTALS OFFER CONSIDERABLE CHALLENGE

It's generally accepted that there are considerable challenges to success in the parenteral market, including quality concerns, stringent regulations and lack of funding. The aseptic processing of parenterals involves complexities such as protecting the sterility of a product as it moves through each phase of formulation, filtering, filling, and packaging.

THE PERCENTAGE OF RESPONDENTS WHOSE COMPANIES **SPEND $10 MILLION TO $50 MILLION** ON OUTSOURCING ALSO **INCREASED FROM 38 PERCENT TO 62 PERCENT.**

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Syed Husain serves as the commercial leader for AAIPharma Services – Cambridge Major Laboratories, leveraging in-depth experience in sales, business development, marketing, and operations for the custom development and manufacturing of small molecules, antibody drug conjugates (ADCs), peptides, biologics (mammalian- & microbial-based drug substances), and drug products. 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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Companies specializing in the aseptic processing of parenterals are compelled to implement advanced controls, optimize internal processes and packaging materials and techniques to ensure drug quality and ultimately, patient safety.

Many pharmaceutical companies do not have the resources necessary to manage the increasing complexity of producing and filling parenteral substances. To achieve optimal results, the development and manufacturing processes for parenterals require the high level of expertise and experience as well as the specially designed infrastructure and sophisticated instruments and technologies of a contractor that specializes in this area.

Stringent regulatory requirements must be followed, including maintaining compliance with US and international regulatory requirements, and current good manufacturing practices (cGMP) to protect product safety, identification, strength, purity and quality (SISPQ).

The parenteral drug pipeline has continued to shift from small molecules to complex biologics such as monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs). A significant percentage of new items in the product pipeline are biologics. The expansion of biological therapies provides additional challenges for parenteral drug delivery specialists seeking to develop ways of improving standard injections and patient safety of these products. Biologics and biotech drugs are typically not stable in solutions, which can lead to cold chain and storage hurdles.

PROCESS CHALLENGES MET

CMOs capable of developing and testing lyophilization cycles on a lab scale can prove to be cost effective. Lyophilization can be an important process in maximizing the stability of a product and manufacturing processes around aseptic compounding equipment utilization have also become increasingly complex and resource intensive with specific environmental monitoring and controls.

The rapid expansion of biopharmaceutical products has resulted in a growing trend by companies in the space to commission the contract manufacturing of mostly parental biologic drug products. Sponsor expectations from a CDMO include broader analytical test methods for the release and stability of increasingly complex drug products. The demand for analytic single-use systems has increased due to the need for multiple test methods to assess drug purity and stability.

For example, the fill-finish process of aseptically prepared drug products requires sophisticated equipment in a highly controlled cGMP environment. These elements are vital to ensure product quality and patient safety. Single-use fill-finish assemblies must meet stringent requirements to ensure flow path sterility and integrity as well as operational safety, and provide fill-volume accuracy.

Accuracy is a significant technical challenge on the filling line. Parenteral drug sponsors expect advanced filling lines that improve quality and save costs – such as fully automatic equipment to optimize yield. Many are also interested in the ability to rapidly identify and characterize particles to help with solubility and other issues. In addition, there is a high demand for flexible equipment and processes to handle new materials and injectable systems. These capabilities should be paired with highly proscribed processes and equipment to contain drugs where limited toxicity data exists or potency/toxicity is high.

Continuous investment in advanced technology, staff training, as well as constant monitoring of the market and industry environment are key behaviors every drug sponsor should look for. Similarly, proactively keeping up with new regulations pertaining to parenterals helps meet these challenges.

ON THE HORIZON

Looking ahead, pharmaceutical and biotech companies will likely continue the trend toward outsourcing solid-dose and parenteral development and manufacturing. At the same time, the complexity of active ingredients and production processes will grow. These changes will require strategic partnerships with highly competent, experienced CDMOs that have the expertise and thus the strength to meet new industry demands able to respond to current and future challenges through flexible operations and creative solutions to help their customers to handle increasingly complex supply chain relationships. It's obvious that it will continue to be critical for CDMOs to offer both individualized and integrated supply chain solutions to the marketplace if they are to be successful at helping their customers achieve the success they seek for their formulations and therapies. P

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PUTTING THE "D" IN CDMO WITH ADVANCED PROCESS DEVELOPMENT

BY **GREG FLYTE,** GLAXOSMITHKLINE BIOPHARMACEUTICALS

Biopharmaceutical companies are increasingly turning to service providers for all aspects of drug development. More often than not, they are looking to contract development and manufacturing organizations (CDMOs) with integrated service offerings across the entire pharmaceutical development cycle, from discovery to commercialization, for APIs and formulated drug products with lifecycle management that can help drug manufacturers meet aggressive development timelines for complex products while realizing greater efficiencies.

The most successful CDMOs have a tradition of innovation, cost-effective operational scale, and the ability to customize platforms to suit customer needs. These services are made possible by teams of scientific experts capable of highly efficient process and analytical development and that can solve technical challenges and bring products to market in the shortest possible time.

While the concept of the contract development and manufacturing organization (CDMO) has been discussed for some years, it has been fully realized in the last few. A flurry of acquisitions in the CMO space, including CMO-CMO and purchases of facilities from sponsor pharmaceutical companies, has occurred, largely with the intention of establishing integrated service capabilities. Some CMOs have sought to expand their global footprint in order to provide local service to their global clients. Others looked to achieve greater cost efficiencies by expanding their capacities. Many, however, participated in the M&A frenzy in order to expand into new service areas – particularly process / analytical development and / or final formulation – and gain access to highly differentiating, advanced technologies.

Effective process development is, in fact, essential for achieving cost-effective, robust biopharmaceutical manufacturing operations. In particular, processes designed with scale-up to commercial volumes in mind enable much smoother technology transfer, reduced manufacturing issues, higher product quality, lower processing costs, and faster time to market. It is therefore not surprising that as pressures from consumers, investors, insurance companies, regulators, and governments to drive down costs and improve product performance have increased, biologic drug manufacturers have turned to integrated CDMOs with advanced process development and scale-up technologies to realize measurable efficiencies and cost savings without compromising patient safety and product quality.

FROM EXPRESSION TO VALIDATION

Process development begins with the expression system and continues through to API release, covering all of the upstream and downstream unit operations that lie in between, plus analytical and cleaning method development and validation. True biopharmaceutical CDMOs can support their clients across the entire gamut of process development activities, including cell line development and banking, scale-down, process characterization utilizing design space mapping via design of experiment (DoE) approaches, process optimization, and viral clearance studies and toxicology lot manufacture – in addition to scale-up, tech transfer, GMP manufacture, and validation.

Strategies and procedures for effectively managing client projects from start to finish are also necessary. Many clients prefer to form strategic partnerships with CDMOs that have a culture and processes designed to encourage collaboration with client personnel and across functions (such as process development, manufacturing, and quality assurance) within the CDMO. Dedicated program and project managers that serve as the main points of contact and work closely with clients are often effective at facilitating this much-needed communication. A commitment to innovation and continuous improvement and a stable yet flexible and skilled workforce, including employees with demonstrated technology transfer/scale-up experience, are also invaluable.

GREATER UNDERSTANDING AND CONTROL

The increased emphasis of regulatory authorities on quality-by-design (QbD) for risk mitigation has created an even greater need for process development expertise. Meeting these requirements increases the level of work that must be completed during early process development phases, but the increased process understanding enables greater process control. The result is more robust processes with higher yields and productivities, and fewer impurities and process variations. In addition, troubleshooting and problem resolution generally can be achieved more rapidly with enhanced process knowledge.

The most successful CDMOs, therefore, have identified strategies for completing process development projects efficiently and effectively while incorporating DoE and QbD approaches that provide increased process understanding and lead to optimal processes.

SCALE-DOWN MODELS

Strong scale-down models are essential for successful process development, character-

ization and validation. Development of relevant scale-down models requires both process development experience and equipment representative of large-scale manufacture.

Scale-down models, which can mimic and predict large-scale operations, are instrumental for DoE characterization and validation studies, including media stability, generation of Cells at the Limit (CAL) of in vitro Cell Age (IVCA), resin lifetime, resin cleaning and disinfection, and viral clearance.

CDMOs with the ability to develop scale-down models that provide good predictions of large-volume process behavior in the lab, plus have the necessary skills for conducting and evaluating scale-down model runs, are in a position to more rapidly develop scalable processes and achieve seamless tech transfer for their clients.

HIGH-THROUGHPUT ADVANCES

Scale-down modeling allows for the use of less material, but is often still insufficient for speeding up the process development process given the larger number of runs that must be completed to acquire the desired level of process understanding. State-of-the-art process development laboratories at both CDMOs and sponsor companies have therefore pursued the use of high-throughput systems to increase productivity.

High-throughput development (HTPD) techniques require much smaller quantities of material and more rapidly provide information on a greater number of process parameters. As a result, it is possible to more quickly identify optimum process conditions for the development of more robust processes. HTPD techniques can now be applied to a number of bioprocesses, including clone selection, protein production, and downstream chromatography and viral clearance steps, among others.

Many high-throughput technologies incorporate automated systems for sample handling and data analysis and reporting, which further accelerates process development programs. The use of automation also has the benefit of reducing the opportunity for human error and providing more consistent results.

For upstream process development, the most widely used high-throughput systems are based on miniaturized parallel experimental technologies. High-throughput miniscreening systems have been applied for clone screening and selection, while micro- and miniature bioreactors (< 1 to 500mL), designed with the same mixing properties and control software as commercial-scale counterparts, are used for the rapid determination of critical process parameters (CPPs) and the determination of optimal cell-culture conditions. Slightly larger systems (up to 4L) that are designed to operate in parallel are also available for the investigation of process parameters that cannot be evaluated using the very small quantities in microreactors.

High-throughput systems for the development of downstream processes include micro-column and plate-based methods that, for instance, allow the determination of equilibrium constants and binding capacities for different chromatography resins under various elution conditions.

The use of process analytical technology (PAT) is also valuable for accelerating the process development process. The data that can be rapidly obtained using HTPD techniques combined with PAT provides much more information about processes than was ever possible before. Once the optimum process conditions are determined and a robust process is developed, PAT can then be used to monitor and control the commercial-scale process for enhanced process performance and product quality.

ANALYTICAL IMPROVEMENTS

CDMOs with such advanced process development capabilities also generally have advanced analytical capabilities, because state-of-the-art analytical systems are required to evaluate the results generated during high-throughput experimentation. In fact, advanced analytical procedures and state-of-the-art instrumentation are required for not only process characterization, but also raw material testing, product characterization, and impurity identification. CDMOs should also be aware of new rapid assays and next-generation sequencing technologies for the detection of known and unknown adventitious agents. Assay development, tech transfer, validation, and qualification capabilities are also essential.

DATA ANALYSIS AND PROCESS MODELING

Effectively evaluating all of the data that is generated when implementing a QbD approach and utilizing high-throughput development techniques can be a challenge. Advanced CDMOs have developed data analysis capabilities that enable them to realize the maximum value afforded by that data. For example, techniques such as multivariate data analysis (MVDA) can be used to map the behaviors of CPPs in order to develop process models that can then be used to further explore the process operating space without the need for additional practical experimentation. These models can also be employed as algorithms in combination with PAT to provide model-predictive control (MPC) of the process.

CONCLUSION

The preference of biologic drug manufacturers for CDMOs that offer integrated services across the entire pharmaceutical development cycle appears to have crystallized in the last few years. The most successful CDMOs are able to provide advanced process development services, including effective scale-down modeling, high-throughput techniques, state-of-the-art analytical capabilities, and effective data analysis and modeling. P

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CLINICAL LOGISTICS – MEETING THE 21ST CENTURY CURES CHALLENGE

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

Numerous changes in the pharmaceutical industry have affected the nature of clinical trials, which in turn have led to the evolution of systems used for the supply of clinical trial materials.

Today, both large biopharmaceutical companies and emerging pharma/biotech firms rely on clinical logistics organizations (CLOs) to ensure the seamless flow of shipments and information, and reduce waste and inefficiencies in the global supply chain. With the rise of evidence-based medicine and a patient-centric industry focus, however, improving efficiencies is no longer sufficient. Successful CLOs must employ state-of-the-art information, inventory, temperature control and other technological systems to provide patient-focused delivery of clinical trial materials to any location in the world, on time and within specifications.

INCREASE IN GLOBAL CLINICAL TRIALS

Efficient clinical trial supply has simultaneously become increasingly important and challenging in recent years. First, there are simply many more trials being conducted – according to the National Institutes of Health, the number has increased 33-fold since 2000.[1] The complexity of clinical trials has also increased dramatically. Most are now global, multi-site studies with locations in less- and poorly developed regions. In some cases the size is needed to achieve sufficient patient enrollment. In others – particularly for orphan drugs, which are a growing percentage of the pharma pipeline – there is a need to evaluate efficacy and safety in specific and very limited patient populations, and access to patients across the globe is necessary.

Clinical trials also often last much longer in order to demonstrate improved efficacy over existing therapies (a key performance metric in the age of evidence-based medicine) or demonstrate the long-term safety of treatments designed for chronic diseases.[2] Trial protocols tend to be more complicated as well, and many involve complex dosing schedules. The use of adaptive trial designs, in which trial parameters may change in response to early trials results, adds additional complexity. The percentage of candidates that are biologically derived has also increased significantly. Most biopharmaceuticals are temperature-sensitive and require shipment in insulated packaging designed to maintain them at low temperatures. In many cases, administration of such drugs is also complex.

These changes have not only led to dramatic increases in clinical trial costs, they have also posed many challenges with regard to effective clinical trial design, the management of massive quantities of generated data, and the timely supply of on-spec clinical trial materials. Most sponsor companies have responded by outsourcing the vast majority of their clinical trial activities to specialist providers that offer increased efficiencies and reduced costs. For the supply of clinical trial materials, clinical logistics organizations (CLOs) are relied upon to ensure the seamless flow of shipments and information and reduce waste and inefficiencies in the supply chain, despite increasing and varied customs regulations.

Until recently, the improved distribution models provided by CLOs have been sufficient to meet the needs of pharmaceutical clients. As the industry becomes more patient-centric, however, even these more advanced, centralized clinical trial supply chains must evolve.

EXISTING SYSTEMS HAVE MANY ADVANTAGES

Supply chains managed by third- and fourth-party clinical logistics organizations that use interactive response technology (IRT) and other advanced IT systems are far more efficient. Specific quantities of needed doses are provided, rather than large quantities of all possible doses, and patient-specific labeling is no longer required. Both changes have significantly reduced medication waste, which has become increasingly important, as the costs of drugs have skyrocketed. Inventory is now stored in central, regional locations (depots) and shipped as needed in small quantities with general country labeling; sponsor companies need only supply the CLO.

For instance, in Europe, one depot with an EU Qualified Person can in some cases serve the entire region. There are, however, several countries in Europe with significant import challenges, such as Russia, Ukraine, and Belarus. Therefore, the use of one vs. several depots in Europe varies depending on the specific drug product (its value, stability/sensitivity), the comparator drug, the therapeutic indication, the number of patients/patient visits, and the trial phase. Regional depots are also effective for serving emerging clinical trial markets.

This approach has also helped overcome the challenges of burgeoning and evolving import regulations and requirements across the world. Customs and trade experts located at each hub are able to ensure compliance and allow the sponsor to avoid the need to obtain import licenses for every country. CLOs can advise clients on the value of the drug and estimate taxes and duties, plus offer study-specific 4PL services with reduced numbers of shipments to each investigator site, through consolidation of all of the different materials needed for clinical trials at that site.

THERE ARE SIMPLY **MANY MORE TRIALS BEING CONDUCTED** – ACCORDING TO THE NATIONAL INSTITUTES OF HEALTH, THE **NUMBER HAS INCREASED 33-FOLD** SINCE 2000.

As IT and communications technologies have advanced, CLOs have also been able to further increase the efficiency of their operations and increase their ability to track and manage supply chain data. This improved supply chain intelligence has, in turn, led to further improvements in CLO services, including increased optimization of material deliveries (quantities and timeliness) and greater reduction of costs. In some cases, they have also enabled more complex clinical trial protocols through the on-time delivery of sensitive clinical trial materials.

The latest Sentry technology from Marken, for instance, allows online GPS tracking, in addition to monitoring of temperature, vibration, light, and shock exposure. Automatic text messages can be sent to the final destination when the delivery is 10 miles away. This "Amazon-like" experience responds to the increasing expectations of both patients and sponsor companies. Importantly, all shipments must be fully compliant with the increasingly stringent regulations and guidelines of each country, while also providing these advanced tracking features.

AND PATIENTS ARE TAKING CENTER STAGE

With the advent of the Internet and social media, potential trial participants, including both patients and healthy volunteers, are far more educated about diseases and potential treatments, as well as the possible risks presented by clinical studies. They also share information and seek advice from advocacy groups through various online forums, websites, and blogs. Consequently, participants are in a position today to change current perspectives about clinical trials.[3]

Indeed, clinical studies are only successful if sufficient numbers of patients are enrolled, follow trial protocols, and remain active participants. The greater awareness of patient populations has led many pharmaceutical companies to realize that clinical trial participants should not be considered only as subjects, but as key collaborators in the clinical trial process.[4] The concept of patient-centric trials is, as a result, becoming a reality.

Considering patient preferences and needs during trial design can lead to the development of trial protocols that are easier and more convenient for patients to follow, which leads to greater patient adherence and retention, and thus more reliable trial results. Consideration of both patient and caregiver capabilities, schedules and locations, as well as patient comfort, is important.

The interest of many patients in the latest personal electronics technologies can also be leveraged to facilitate trial participation and better data collection. Smart watches, fitness trackers, and other wearable devices on the market today can be used to track and transmit real-time patient data, while also providing trial managers a means for communicating directly with patients on an ongoing basis. Smartphones, too, are easily accessible, non-intrusive tools that can make it easier for patients to regularly log data and increase the likelihood of participation throughout long-term trials.

WHY THAT MATTERS TO CLOs

One consequence of the move towards patient-centric trials is increased expectations for direct-to-patient delivery of trial materials, patient home treatment, and the capture of multiple clinical and biological data points at patient homes. Such an approach can actually lead to more successful patient recruitment and, significantly, increased patient retention, because people are more willing to participate in trials with this type of personalized service. In addition, direct-to-patient clinical trial material delivery increases protocol compliance and the likelihood of patient retention throughout the extent of the trial.

It can be challenging, however, as delivery to many different residences is often required. In addition, coordination with nurses or other caregivers may be necessary if special delivery systems, such as injection and infusion, must be used.

It is also worth noting that direct-to-patient clinical trial material delivery can be very effective for clinical

trials designed to evaluate orphan drugs, indications for patients that are dependent on a legal representative or family members (certain CNS and oncology indications) and pediatric trials. In many cases, because it is difficult to locate patients with rare diseases, orphan-drug programs often have long-term trials. Under these conditions, the line between clinical trials and prescribed-drug delivery to patients is somewhat blurred. Getting the clinical trial materials to these patients can be critical to the success of such programs.

NEXT-GENERATION MEDICINES ARE IMPORTANT TOO

The number of clinical trials for the evaluation of next-generation treatments includes cell and gene therapies, which is increasing rapidly. These clinical trials pose significant challenges with respect to delivery of clinical trial materials. First, gene- and cell-based bio-hazardous materials require special handling under cryogenic conditions (liquid nitrogen storage), which is not yet widely available on a global scale. Second, samples taken from patients must typically reach the manufacturing site within 28 hours of the patient visit. Once the drug is prepared, it must then be delivered back to the specific patient for treatment, also within a short period of time.

The development of innovative, specialized technologies is also crucial if CLOs and others involved in clinical trial design and management are to facilitate sample preparation; transport across country borders, delivery within short timeframes to the manufacturing site for patient-specific drug product preparation, and final delivery back to the patient for treatment is a complex undertaking. It is made more challenging by the fact that the regulations for handling such shipments can vary from country to country, and therefore specialized knowledge and skills are required. As these therapies move through the pipeline and approval process, it is even more important to design clinical supply chains with the needs of commercial products in mind; supply chains for marketed drugs will continue to be critical and increase in complexity.

Advanced technology is the solution to meet the increasingly complex needs of the sector while simultaneously increasing study efficiency and reducing cost. Indeed, many of the achievements in clinical logistics can be attributed to advances in information technology. Cloud-based systems for electronic data capture (EDC) are now employed for shipment tracking and clinical trial data collection, monitoring, and reporting. Such real-time data management tools allow ongoing data analysis and transparency into the supply chain, even with regards to the physical conditions of individual shipments.

While increasing the efficiency of the regulatory review process is recognized as a key requirement for accelerating drug development, such improvements will be slow in coming. More immediate solutions must also be taken in the meantime. Researchers in one study noted that the use of lower-cost facilities and in-home testing (which would be facilitated by direct-to-patient material delivery and home treatment) and increased use of mobile technologies and EDC.[2]

The FDA is, in fact, committed to the use of advanced technologies to address rising drug development costs. In 2010, then-Acting Director for the U.S. Food and Drug Administration's Office of Critical Path Programs, Dr. Leonard Sacks, noted that "Harnessing information technology and novel scientific tools in the service of medical product development has been a central priority for FDA. These innovative tools provide a historic opportunity to move medical product development into the 21st century and to deal with the challenges of spiraling research and development costs in the face of diminishing returns."[5]

The U.S. Congress is also focused on the need to accelerate the discovery, development, and delivery of promising new treatments and cures for patients. In June 2015, the U.S. House of Representatives passed the 21st Century Cures Act, a bipartisan piece of legislation targeting multiple areas for improvement.[6] Not surprisingly, one of the five key issues identified in the Act is the need to streamline clinical trials through greater adoption of adaptive clinical trial designs and the use of innovative technologies and statistical modeling. P

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GROWING DEMAND FOR SMALL-MOLECULE CDMO SERVICES

→ BY **DR. STEPHEN A. MUNK,** ASH STEVENS

Although many reports have focused on growth in the biopharmaceutical sector, small-molecule drugs continue to account for the vast bulk of drugs on the market and in development. New classes of increasingly potent small-molecule therapeutics are addressing more unmet medical needs with fewer side effects, often at a significant cost advantage compared to biologics.

In many cases, contract development and manufacturing organizations (CDMOs) play a critical role in facilitating the successful development of innovator small-molecule drug candidates, since these important development activities are often achieved through outsourcing partnerships with CDMOs. CDMOs can vary significantly with respect to the services they offer, from one-stop-shops offering a myriad of services to those with expertise focused exclusively on the development and manufacture of innovator Active Pharmaceutical Ingredients (APIs). Regardless of the breadth of CDMO services offered, CDMOs today are seeing increased demand for drug substance development and GMP manufacturing services for innovator small-molecule drug development projects. Some areas of increased demand for CDMO services are discussed herein.

DEMAND FOR SMALL-MOLECULE DRUGS REMAINS STRONG

Small-molecule drugs accounted for 84% of pharmaceutical industry revenues in 2014.[1] In addition, small-molecule drugs still account for approximately two-thirds of the candidates in the current robust pharmaceutical industry pipeline.[2] Contract manufacturers that focus on the development and production of small-molecule APIs are experiencing significant growth as a result. According to PharmSource, the revenues of publicly traded contract manufacturing organizations (CMOs) and CDMOs that are involved only in the development and production of small-molecule drugs increased by 15% in the first half of 2015, with some companies achieving revenue growth of greater than 20%.[2] Both biopharmaceutical and small-molecule approaches have established track records for providing valuable therapeutic benefits to patients. Both approaches also have their inherent advantages and disadvantages and will remain as complementary strategies for drug discovery for the foreseeable future.

GROWTH IN THE ONCOLOGY SEGMENT IS A STRONG DRIVER FOR SMALL-MOLECULE CDMO SERVICES

All indications are that demand for innovator API manufacturing services will likely remain strong for the next few years. It is difficult to accurately assess the size of the innovator API market that is accessible to CMOs/CDMOs, since this sector data is not easily broken out from broader analyses of the overall API markets. The current strong demand for CMO/CDMO services is driven by a number of factors, which include a robust industry pipeline, the ability to raise public and private financing, and successful market approvals.

For example, the growing oncology drug pipeline is largely the result of significant investment in R&D and innovation by the pharmaceutical industry over the last 10 years.[2]

GROWING DEMAND FOR CDMOS OFFERING HIGHLY POTENT API (HPAPI) MANUFACTURING SERVICES

Another area of strong demand for innovator small-molecule API manufacturing services is in the highly potent API (HPAPI) segment. HPAPIs make up one of the fastest-growing segments of the global API market. Grand View Research estimates the demand for HPAPIs will grow at an average annual rate of 14.4%, from $12 billion in 2014 to $25.86 billion in 2022.[3] This strong demand for HPAPI manufacturing services is having significant impact on the contract manufacturing market. Companies with existing HPAPI capabilities have been busy expanding their facilities, while many without have sought to acquire existing businesses or add HPAPI capacity. HPAPI manufacturing requires millions of dollars in investment over and above that of CDMOs/CMOs providing traditional API (non-HPAPI) manufacturing services. Furthermore, CDMOs/CMOs providing contract HPAPI manufacturing services must be prepared to adopt, improve, and/or implement new protocols, equipment, training, and technologies to meet the ever-rising bar for risk reduction and regulatory compliance in HPAPI manufacturing. Continuous improvement is essential to sustaining safe operations, mitigating risk, and attracting client opportunities.

APIs with occupational exposure limits (OELs) of 10 μg/m³ or less are generally classified as HPAPIs. Increasingly, APIs of small-molecule therapeutics in development today, particularly in the oncology therapeutic area, are falling into the HPAPI category. The growth of potent new targeted therapies in oncology (e.g., kinase inhibitors) is helping to fuel the growth of this segment, with the future trending towards even more potent drugs. HPAPIs, however, present a special challenge for API manufacturers requiring appropriately designed facilities, with the necessary engineering and containment controls in place to handle these potent compounds as well as requiring highly trained and experienced staff to ensure safe and contained operations.

Key to Life Science companies looking to outsource HPAPI manufacturing is finding a CMO/CDMO partner with clearly demonstrated experience and expertise for both safely and effectively managing projects involving highly potent compounds. Many Life Science companies developing potent small-molecule drugs prefer to use a HPAPI manufacturer in the U.S. or Europe that has a sustained and exemplary track record for safety, regulatory compliance, and a successful audit history when working with HPAPIs. The ability to support both the development and commercial manufacture of highly potent compounds in order to avoid any need for process transfers is also often preferred by many Life Science companies that outsource HPAPI projects. The demanding nature of HPAPI manufacturing requires careful scrutiny of the potential CMO/CDMO partner's chemical hygiene and environmental, health, and safety (EH&S) programs as well as an understanding of their commitment to HPAPI manufacturing, and continuous improvement. When it comes to HPAPI manufacturing, there is no middle ground – it is "all in" or nothing.

GROWING DEMAND FOR PROCESS DEVELOPMENT CDMO SERVICES

A growing number of small and midsized Life Science companies developing innovator small-molecule therapeutics are driving demand for more contract chemical process development capacity. These companies many times lack in-house laboratory infrastructure, expertise, and/or chemistry personnel to transition a laboratory synthesis of a development candidate to a chemical process suitable to cGMP manufacture and scale-up. Since these companies typically either license in their small-molecule assets from Universities or other research laboratories or, alternatively, use in-house or CRO Med. Chem. resources to develop their small-molecule assets, the chemical synthesis of these assets is many times not readily amenable to cGMP manufacturing without further process improvement.

Initial laboratory syntheses are focused on making enough of the compound as fast as possible for preclinical testing, whereas process development focuses on multiple aspects for process improvement, such as improving process yields, reducing the number of steps and operations, reducing reaction volumes and the quantities of solvents and reagents, improving safety and robustness, mitigating negative environmental impacts, increasing scalability, and eliminating time-consuming steps such as chromatographic purifications. Consequently there exists a growing gap in the API development pathway going from laboratory syntheses to cGMP processes.

CDMOs are best suited to address this gap since, by definition, they provide development services, which generally include process development support. Effective process development and optimization is most efficient when integrated with scale-up and cGMP manufacturing operations. CDMOs with integrated capabilities from early-stage drug substance development through commercial manufacturing can potentially effect a smoother transition from the laboratory to commercial manufacturing, streamlining the process, reducing complexity, and building process knowledge. This is particularly true when key stake holders, such as process chemists and engineers working on the project, transition with the process through the various stages of scale-up to ensure the tech-transfer proceeds seamlessly.

Drugs with Fast-Track or Breakthrough status place even more pressure on CDMOs to rapidly scale the process to meet the deliverables of a significantly accelerated timeline on schedule, and expedite a potentially promising new therapy to patients with serious medical conditions. Here especially, a well-integrated team of engineers and process chemists are essential to bringing the process online in time to meet the accelerated timelines of the project.

SMALL-MOLECULE DRUGS ACCOUNTED FOR 84% OF PHARMACEUTICAL INDUSTRY REVENUES IN 2014.

GROWING DEMAND FOR QUALITY BY DESIGN (QBD) SERVICES

The growing demand for ever-higher quality pharmaceuticals by regulatory authorities and consumers is in turn driving more demand for Quality by Design (QbD) services from CDMOs. More Life Science companies developing drugs today are looking to apply the principles of Quality by Design to their manufacturing processes, to better comply with current regulatory guidelines for QbD, and with the anticipation that QbD will become a requirement at some point in the future. QbD is a statistical method employed to gain an enhanced understanding of process control and safety for a manufacturing process, ensuring consistent and robust quality.

Most CDMOs have been using elements of QbD for quite some time, such as "design of experiments" and understanding critical failure points. The FDA guidelines, however, provide a more structured framework anchored in statistical methods to provide accurate understanding and control of a pharmaceutical manufacturing process. Implementing QbD services can be expensive for CDMOs, requiring new equipment, statistical support, and the training and/or hiring of personnel. Not every CDMO, therefore, offers QbD services, but for those that do, it can be a draw for potential clients. In addition, since QbD remains a guideline at this point in time and not a requirement by regulatory authorities, it is not unexpected that drug developers have elected to pursue a variety of QbD strategies ranging from none at all to comprehensive QbD fillings consistent with regulatory guidelines. Nonetheless, the momentum is in the direction of more QbD work for CDMOs as drug developers try to get out ahead of the regulatory curve. P

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CONTINUOUS PROCESSING: MEETING THE NEED FOR NEW MANUFACTURING STRATEGIES

BY **FILIPE GASPAR, MARCO GIL** AND **NUNO MATOS,** HOVIONE

A number of trends in the pharmaceutical industry are placing pressure on drug manufacturers to reduce both development times and costs.

Clinical trials have been typically on the critical path, and the CMC section had less time pressure and moved forward according to clinical trial results; new regulatory avenues have changed this. New manufacturing strategies are needed to overcome these issues. Continuous processing of both drug substances and formulated drug products is championed by the U.S. Food and Drug Administration (FDA) as an effective approach to addressing the need for increased efficiency and quality, and some may be better suited to changing paradigms.

A confluence of factors is driving the need for a paradigm shift in pharmaceutical manufacturing strategies. Movement towards evidence-based medicine, rising generics competition, dramatically higher clinical trial costs and timelines, the shift away from blockbusters to niche products, and the growing number of candidates with accelerated development designations (Fast Track, Breakthrough Therapy, Orphan Drug) are all placing pressure on drug manufacturers to eliminate inefficiencies and increase productivity in order to reduce development costs and get new therapies to the market more rapidly.

Continuous processing, which has been utilized in numerous industries for many decades, is attracting significant attention as a plausible solution. Even the FDA reviewed the use of continuous processes as a way to improve efficiency and quality, and now a handful of technology and market leaders are taking the lead. Not surprisingly, given the conservative nature of the pharmaceutical industry, the transition to continuous manufacturing is occurring slowly.

We at Hovione are convinced, however, that as more branded drug companies and contract manufacturers begin to recognize the value provided by continuous processing, and any remaining questions about regulatory compliance and quality assurance are addressed, this manufacturing approach will be more widely adopted.

FLOWING IN THE RIGHT DIRECTION

There are a host of benefits associated with the use of flow chemistry for the production of active pharmaceutical ingredients (APIs); reduced operating costs, smaller manufacturing footprints, lower capital expenditures and operating costs, and improved process efficiencies, control, and product quality are at the top of the list. Additional advantages include increased development speeds, greater process safety when employing hazardous chemistries, and the opportunity to perform reactions that cannot be run under batch methods.

In general, reactions conducted in flow reactors are more selective, providing higher yields of the desired products and fewer impurities. As a result, purification processes are often much simpler and may even be eliminated in some cases. Solvent use can often be significantly reduced compared to that needed for batch reactions, and energy consumption is reduced, given the smaller reaction volumes. As a result, flow chemistry often enables greener chemistry with reduced raw material and resource consumption combined with shorter production times.

Scale-up with flow chemistry is also typically much simpler, leading to much shorter commercialization times. In some cases, commercial-scale production is achieved in the same reactor used for development work by performing longer runs. In others, additional reactors are used in parallel – "numbering up" – which also requires no further development work. Even if flow reactors must be scaled up, there are often few difficulties given the design characteristics of these systems.

Many of these benefits can be attributed to the fact that continuous processes are operated at a steady state. Processes at steady state conditions are easier to maintain than processes in which an end point needs to be achieved through a transient state. Process conditions are also more consistent, and therefore product quality is more consistent. The batch-to-batch variability observed in traditional manufacturing processes is eliminated. In addition, continuous processes are much more homogeneous as the result of improved mixing, so the "hot spots" and variability observed during a single batch run are also largely avoided.

Equipment for flow chemistry has advanced significantly in recent years as well. For instance, where initially it was impossible to conduct flow chemistry with solid reactants or products, many of the reactors available today are designed to allow these more complex transformations without plugging. Solutions of continuous solids handling during downstream purification and separation processes – filtration and, particularly, crystallization – are also under development, with significant accomplishments being made by groups such as the Center for Continuous Manufacturing and Crystallization (CMAC) and the Novartis-MIT Center for Continuous Manufacturing, both partnerships between industry and academia.

TOWARDS CONTINUOUS DRUG PRODUCT MANUFACTURING

Continuous manufacturing has also been demonstrated to be advantageous for the manufacture of final drug products. Here again, the key advantages are reduced development times due to simpler scale-up (often using the same equipment for development and commercial-scale production) and more consistent and higher product quality. For small-molecule drugs, continuous tableting is in fact increasingly common for the production of oral solid dosage forms, and we believe at Hovione that in the future, continuous processing of tableted products will become a growing trend.

Equipment manufacturers have invested significantly in the development of effective systems for continuous tableting operations, from feeders to tableting machines to coaters. Advances in process analytical technology (PAT) have also increased confidence in the ability to adequately monitor and control continuous operations. Access to these reliable and high-performing equipment and analytical tools is contributing to the adoption of continuous processing for tablet production. Pharmaceutical companies are also realizing how such continuous processes can help them improve productivity and flexibility to meet changing market needs.

Monitoring and control are, indeed, at the heart of successful continuous manufacturing operations. Continuous processing is not possible without PAT; immediate and ongoing feedback of critical process parameters is vital if optimum processing conditions are to be maintained. Advances in PAT have been significant in recent years, and today there is a wide range of tools applicable for the real-time monitoring of manufacturing processes for both drug substances and drug products.

Ultimately continuous process is ready to succeed because of the maturing of a combination of advanced technologies: improved equipment, precise monitoring, automation, and software.

REGULATORY BACKING

Another impetus for increasing adoption of continuous manufacturing strategies has come from FDA. The agency has encouraged the adoption of continuous manufacturing since 2004, and has been increasingly more vocal about the issue, speaking at various conferences and workshops.[1,2] Congress also supports this innovation; the 21st Century Cures Act, proposed in 2015, would require FDA to support the development and implementation of continuous manufacturing for drugs and biologicals as one of several approaches to speeding up drug development and commercialization.[3]

Industry should take the lead and propose solutions for the new regulatory environment that will need to address this field.

WE ARE NOW RESPONDING TO THEIR NEEDS FOR **MORE INTEGRATED MANUFACTURING SUPPORT,** INCLUDING THE PRODUCTION OF **FINAL PRODUCTS USING STATE-OF-THE-ART TECHNOLOGIES.**

Industry is the common denominator to all the regulators; therefore, if we want clear, harmonized guidelines, it is up to us to take a greater role in the standard-setting process and to present constructive solutions to real problems.

ADDING VALUE

As with any new technology, deployment of continuous processing must bring value. For API synthesis, continuous manufacturing is most likely to add value when it enables the use of process chemistry that cannot be performed under batch manufacturing conditions, or performs better continuously. Criteria to argue for a continuous process typically include: safety, yield, purity, and waste, as well as investment for the installed capacity for large volumes.

Continuous manufacturing of tablets has been the object of more innovation across many dimensions. Advances in processing equipment are overcoming many of the challenges posed by ingredients with physical properties that can cause difficulties with handling and processing. As a result, the percentage of APIs that can be reliably and consistently processed into high-quality tablets using continuous manufacturing equipment is expanding.

Continuous tableting can be a game changer when development time is highly compressed. When FDA grants Breakthrough Therapy designation, the CMC section becomes immediately critical to project success, and compliance. In these situations FDA may approve the NDA based on Phase II data alone; however, FDA has

been crystal clear that they will not compromise on the sponsor being able to demonstrate complete understanding and control over the manufacturing process.

Continuous tableting may be a preferred route in this case, as minimal amounts of API will suffice to define and validate a single-scale production; that can work continuously for a few hours to prepare clinical trial materials and generate validation data. The same production solution is then operated for 1,000 hours to deliver commercial quantities. In breakthrough therapies there may not be time to scale up drug product multiple times as the API may simply not be available in the given time frame. When an API costs ten thousand to tens of thousands of dollars per kilogram, there may well be considerable savings in API costs by opting for continuous dosage form manufacture.

A NATURAL EVOLUTION

Hovione has been producing small-molecule APIs for decades. In response to customer needs for assistance with overcoming formulation challenges posed by increasingly complex drug substances, we developed expertise in particle engineering. We are now responding to their needs for more integrated manufacturing support, including the production of final products using state-of-the-art technologies.

IMPLEMENTING PAT AT A CDMO

Hovione is committed to supporting an increased number of NDA programs, providing integrated solutions to CMC challenges and delivering a robust process for "right-first-time" commercial launch of much-needed medicines. Understanding the needs of fast-moving clinical candidates, we have as an organization decided to develop know-how and installed capabilities for continuous manufacturing for the production of both APIs and solid dosage drug products, particularly tableting. Throughout its history, Hovione has been a pioneer in technologies, and an early adopter. As early as 1982, patents were issued for Hovione claiming higher chiral purity when reactions were performed below -45°C; for example, a commercial process was inspected by FDA where liquid nitrogen was introduced into the jacket of a 2,000-liter vessel that same year.

Indeed, Hovione has, since 1997, made all new reactor capacity fully automated with distributed control systems (DCS) approaches, and all control strategies have been designed in-house and applied in a standardized way at all sites. PAT was implemented in 2005 with extensive expertise in its use for productivity and quality improvement. In other examples, Hovione has multiple installations in industrial processes (described in FDA filings) in drying operations, in controlling completion of reactions, and in the control of particle formation – in some cases in large-scale commercial continuous processes.

We also have been deploying advanced PAT solutions in our development and analytical labs. This experience makes Hovione ideally positioned to face the challenges of continuous manufacturing and be a CDMO that enables our clients to realize the maximum benefits of this revolution. To do so, we focus on utilizing continuous processes where they add value for the company, for our customers, and for our patients.

A CONTINUOUS FUTURE

The pharmaceutical industry is in a period of rapid change and innovation. Those companies – both brand manufacturers and contract service providers – that are able to adopt new technologies into their operations that result in better understanding, better control, and lower cost will come out winners during the turbulent times ahead. New manufacturing strategies will be essential, and we at Hovione believe that continuous manufacturing capabilities are part of the kit of the best partner CDMO for tomorrow's innovators. Many large pharmaceutical companies have, or are already investing in, continuous manufacturing systems for both small-molecule and biologic APIs as well as drug products.[4] Most have at least created internal groups focused on evaluating its potential. A few leading contract development and manufacturing organizations, such as Hovione, have also focused on the development and implementation of capabilities for continuous processing.

Adopting continuous manufacturing is a challenge in an industry that is risk averse and where for over 100 years everything has been done in batch production. This requires a change in mind-set, a whole reeducation of our scientists, and a re-kitting of our facilities at every scale – a big ask in a world of tightened budgets.

Hovione is convinced that our industry requires CDMOs that believe in this new paradigm and are prepared to invest, hire, and develop the right talent, and take on projects that have this extra dimension of risk. When a CDMO offers services in the area of continuous process, a wider range of pharmaceutical manufacturers will be able to discover the benefits of continuous processing without having to make significant up-front investments.

It is an exciting time for our industry; never has there been an environment where regulatory and manufacturing innovation combined to find ways for new drugs to go forward to approval in shorter time frames. We expect continuous processing to serve as fertile ground for further innovation. P

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GAINING OPTIMAL ROI FOR SURPLUS LABORATORY AND MANUFACTURING ASSETS

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

Major trends in the pharmaceutical and biotechnology manufacturing industries are driving significant shifts in the management of laboratory and processing equipment inventory. Product pipeline changes, mergers and acquisitions, price pressures, and the increased reliance on contract research, manufacturing, and packaging service providers are a few of the trends impacting manufacturers' equipment needs. At the same time, manufacturers and contract service providers are striving to keep costs down, manage their floor space, and ensure supply of products to the market.

As a result of these trends, manufacturers are looking for cost-effective, efficient solutions to manage surplus and idle equipment inventories without interrupting current development and manufacturing programs. This aspect of manufacturing equipment inventory management has become far more complex and challenging than in the past. Past strategies included storing idled equipment or, in many cases, leaving it in place on the manufacturing floor. That investment in capital equipment then leads to storage costs or consumption of valuable manufacturing space. In order to keep up with the major trends, these pharmaceutical manufacturers must make an effort to find effective ways to dispose of surplus equipment to reduce costs and make effective use of their resources.

IMPACTING MANUFACTURERS' EQUIPMENT SURPLUS

With the rising pace of mergers and acquisitions, companies are aiming to reduce costs through synergies, access to new therapeutic classes, and the consolidation of infrastructure and equipment. For larger companies, this has resulted in redundant manufacturing facilities and idled equipment. As these facilities are closed or consolidated, there is the issue of what to do with complete manufacturing plants full of equipment.

New products and processes require different types of equipment. Accelerated growth of specialty drugs, biopharmaceuticals, and biosimilars, and the increased market for generic drugs have led many companies to change their manufacturing mix, which requires a different mix of equipment. Every pharmaceutical manufacturing company has a process for scoping, purchasing, installing, and commissioning new manufacturing equipment. Those capital projects rarely spend time on what happens to the equipment already in that space.

Pharmaceutical manufacturing space is expensive. The costs and time associated with building good manufacturing practice (GMP)-compliant manufacturing space has grown significantly. In many cases, the price to build GMP space is much more than the price of the arriving equipment. With GMP space at a premium, manufacturers cannot afford to have idled or surplus equipment stack up in those spaces. Additionally, raw material and finished goods warehouse space is usually not the best place to store idled equipment.

The used-equipment market has experienced strong growth due to the increased awareness in the marketplace of the viability and quality of used equipment. There are a variety of strategies and disposal methods, as well as a host of service providers (including brokers, dealers, auctioneers, and demolition companies) who all claim to have the best solution for surplus and idle industrial equipment.

As a result of these trends, managing manufacturing equipment inventory for a pharmaceutical company can be a daunting process. There are several strategies to start the process.

STRATEGIES FOR MANAGING EQUIPMENT SURPLUS

Manufacturers and service providers can manage surplus equipment through different strategies. Broadly, these strategies are:

+ Case-by-Case, Project-by-Project
+ A Dedicated Investment or Resource Recovery Team
+ Outsourced Services

CASE-BY-CASE, PROJECT-BY-PROJECT

Many companies elect to evaluate surplus equipment strategies on a case-by-case basis with an individual, such as a project manager or a project team. This is the most common approach and can be very effective with a large project, such as a plant shutdown. This strategy usually revolves around the size of the project, the project type, and the method of sale.

If the project is large enough, there is usually a team of individuals from various functions within the organization, such as manufacturing operations, engineering, and purchasing. Generally someone identifies the equipment available for sale and creates a list. The list is then used as part of a bidding or request for quote process. If the project involves demolition contractors, they will include a dollar amount for the equipment as either a stand-alone equipment credit or as part of their scrap credit. If the equipment is being bid separately, there may be several different sale methods proposed.

This can be anything from auctions and liquidations to piece-by-piece offers. This largely depends on whether there has been a method of sale pre-determined or whether the owner is willing to evaluate piece-by-piece offers.

ACCELERATED GROWTH OF SPECIALTY DRUGS, BIOPHARMACEUTICALS, AND BIOSIMILARS, AND THE INCREASED MARKET FOR GENERIC DRUGS **HAVE LED MANY COMPANIES TO CHANGE THEIR MANUFACTURING MIX.**

COMPANY HIGHLIGHTS

FEDERAL EQUIPMENT COMPANY

For more than 50 years, Federal Equipment Company has been a trusted name in the pharmaceutical, chemical, and plastics industries. With **thousands of pieces of inventory in stock**, Federal Equipment is dedicated to providing customers with quality **used equipment available immediately** 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.

A case-by-case approach with individual projects will usually result in single machines or production lines being either left in place, if nothing is moving into that space, or removed to "bone-yards." The project manager's focus is to either decommission the equipment or remove it and get new equipment installed and qualified. There is rarely room in the project for serious consideration of the sale proposition for existing equipment. If the equipment is removed, bone-yards can be expensive to maintain in an off-site warehouse, and may become an eyesore if left on site, accumulating behind the building or in storage trailers. Any bone-yard or other out-of-sight-out-of-mind storage can result in significant, rapid decreases in value over time. Also, in many cases, valuable equipment is not stored at all. It is scrapped or trashed to make way for new equipment, which can create additional costs.

A DEDICATED INVESTMENT RECOVERY TEAM

Many companies have adopted programs to minimize waste, including zero landfill policies. Dedicated investment recovery or resource recovery groups are usually key parts of these efforts and are used to sell goods in secondary markets whenever possible. The team is usually well-versed in investment recovery strategies and takes on this role for many different types of goods, including raw materials, waste materials, scrap metals, and other goods – in addition to equipment. This option requires investment in office space, staff, and systems required to track all of the information and goods available for sale. There are additional overhead costs, because everything must be stored until sold, and the team requires the usual support from other business functions, including IT, Legal, HR, and Finance.

OUTSOURCED INVESTMENT RECOVERY SERVICES

Many firms use an approach combining case-by-case and an investment recovery team, along with outsourced services. The investment recovery approach is managed by a smaller in-house team with major service components, such as inventorying, evaluating, sales, and outsourcing marketing to firms experienced in the asset class. Often the in-house team is not dedicated to investment recovery, nor is it even their primary responsibility. When process and packaging equipment at pharmaceutical plants fall within this strategy, the client (equipment seller) establishes a relationship with an experienced equipment dealer that specializes in the pharmaceutical/biotechnology industry.

This strategy can manage the ongoing process and provide services for large projects, like facility shutdowns, as well as bone-yard liquidations and single machine cases. A reputable dealer can act as a trusted advisor to accurately and quickly appraise the equipment, evaluate removal costs, and recommend the best sales method, which will bring about the best financial return within the clients' time frame. Additionally, the dealer can leverage its network to find the best partners for each case or project, from mechanical and rigging contractors to remove the equipment, to partnering with the appropriate auctioneer for the job.

An experienced dealer brings industry experience, equipment expertise, and a network of equipment buyers, which the client can use to make timely and informed decisions about the best approach for each case of idle or surplus equipment. Some dealers will even help re-market the equipment for the clients' internal use; for example, redeployment to an in-network manufacturing site, or to another facility where that equipment can best serve the needs of the company.

LOOKING AHEAD

Pharmaceutical manufacturers must be aware of the outlets for their surplus and idled equipment so that they do not lose opportunities to redeploy that equipment to another area of the business or sell it for cash. The pharmaceutical merger and acquisition pace show no signs of slowing. Idle equipment will not be allowed to sit on such valuable real estate, but the best place for that equipment may not be the scrap hopper or trash bin; excess equipment may be best utilized as cash-in-hand, or in a different area of your company's network, where it can be used to generate income. P

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Matt Hicks, Chief Operating Officer 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 its manufacturing and process equipment assets.

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STRONG CMO/CDMO MARKET OUTLOOK FOR 2016, BUT BEWARE MODERATING FACTORS

2016 NICE INSIGHT CDMO OUTSOURCING SURVEY FINDINGS

Increasing consumption of medicines around the world; a more robust pipeline of drug candidates and an increasing rate of FDA NDA/BLA approvals; the growing number of biologic drugs in development, many by traditional pharma companies that lack biotech expertise; the entrance of numerous small, virtual startups into the market that have no manufacturing capacity; the rise in patent expiries and increasing generics competition, which is driving a greater need for cost efficiencies and access to novel, proprietary technologies for achieving product differentiation; and the increasing complexity of both small- and large-molecule drugs such as antibody-drug conjugates and highly potent compounds will all continue to drive growth in the contract manufacturing market in 2016.

SPENDING IS UP

Visiongain (February 2015) estimates that the global contract pharmaceutical manufacturing market will grow at an average annual rate of 7.5% from $54.54 billion in 2013 to $79.24 billion in 2019.[1] This strong growth is supported by the results of Nice Insight's annual survey of professionals in the pharmaceutical and biopharmaceutical industries; participants have indicated that their companies have dramatically increased year-over-year spending on outsourcing for the last four years. Most notably, while the percentage of respondents whose companies spent more than $50 million on outsourcing remained fairly stable at 24%-24% from 2013-2015, the number of respondents nearly tripled to 71% in the new 2016 Nice Insight CDMO Outsourcing survey of nearly 600 pharmaceutical and biotechnology executives seeking outsourcing. Likewise, manufacturing equipment needs are shifting; as seen in the Nice Insight 2015 Pharmaceutical Equipment Annual Study, 54% of respondents (n=560) indicated that their companies spend over $100 million on equipment per year.

Importantly, 75% of respondents to the new CDMO survey expect that their companies will increase expenditures on contract services (research and manufacturing) over the next five years. Another 18% expect their level of outsourcing to remain the same, while just 4% predict a decrease. Furthermore, while three-quarters of respondents currently use 0-10 CDMOs and/or CMOs, 7% use 11-20, and 5% use 21-30; 69% of participants in the CDMO survey expect to increase the use of contract development and manufacturing organizations (CDMOs) and contract manufacturing organizations (CMOs) going forward, with 29% expecting the number of manufacturing partners to remain the same, and only 1% anticipating a decrease in the number of partners. All of these numbers clearly indicate that strong growth in the pharmaceutical and biopharmaceutical contract manufacturing sectors can be expected for some time to come.

SURVEY PROFILE INFORMATION

By Region

56% North America

16% Europe

28% Asia

By Annual Outsourcing Expenditure

43% $51M to $100M

- 28% More than $100M
- 23% $10M - $50M
- 3% Less than $10M

NEW NICE INSIGHT SURVEY FOCUSES ON

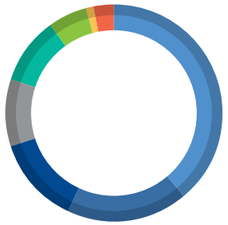
CDMOs

A comprehensive study of 123 CDMOs for strategic use by both buyers and sellers of contracted services

For the first time since we began gathering data on the pharmaceutical and biopharmaceutical contract services markets, That's Nice Insight survey in 2016 focused on contract development and manufacturing organizations in recognition of the key trend in this sector toward companies that provide integrated offerings. The new 2016 Nice Insight CDMO Outsourcing survey includes responses of 587 outsourcing-facing pharmaceutical and biotechnology executives.

Importantly, the majority (39%) of survey participants are key decision-makers (executive / management positions) in their organizations. Professionals with positions in R&D, formulation and analytical (18%), development, production, and manufacturing (13%), and operations and engineering (10%) functions are also well represented. As a result, the survey is quite balanced, representing the opinions of both company leaders and those in the trenches. The new CDMO survey is also truly global in nature, with 56% of respondents from North America, 28% from Asia, and 16% from Europe. It also includes input from representatives of biopharmaceutical and pharmaceutical companies of all sizes: large (>$5 billion in annual sales), medium ($500 million to $5 billion), small ($100 million to $500 million), and emerging (<$100 million), with 36%, 43%, 12%, and 9% share, respectively.

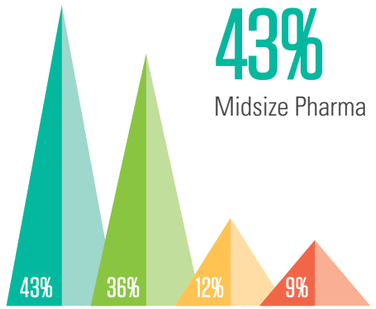
By Department



39% Corporate Management

- 18% R&D / Formulation / Analytical
- 13% Drug Development / Production / Manufacturing
- 10% Operations / Engineering
- 10% Quality Assurance / Quality Control
- 6% Contracting / Sourcing / Purchasing
- 1% Regulatory Affairs
- 3% Other

By Buyer Group



43% Midsize Pharma

- 36% Big Pharma
- 12% Small Pharma
- 9% Emerging Pharma

% Of Respondents Who Will Attend The Following Industry Events

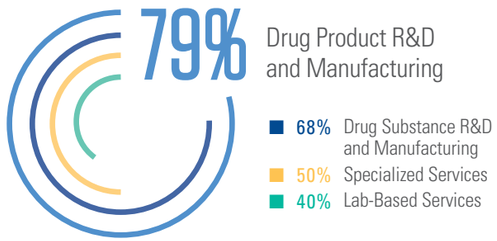
BIO International	DCAT	AAPS	BIO Europe	Contract Pharma	BPI
41%	36%	33%	33%	32%	32%

DIA	CRS	ChemOutsourcing	Informex	Interphex	CPhI Europe
28%	27%	27%	26%	22%	22%

Interestingly, while the last set of data appears to contradict the notion that sponsors are whittling down their manufacturing partners to a select few (vide infra), these numbers may in fact reflect the strong growth in the number of drug candidates and an overall greater need for support. In fact, 56% of respondents to the 2016 Nice Insight CDMO Outsourcing survey indicated that an expanding R&D portfolio is driving their increasing use of CDMOs and CMOs. Companies also seem to be increasing their use of outsourcing as part of the manufacturing strategies (60%), perhaps because they have had positive experiences with outsourcing to CDMOs and CMOs in the past (59%).

23% RESPOND THEY'LL BE SPENDING **BETWEEN $10M-$50M** ON OUTSOURCING ANNUALLY

% of Respondents Who Outsourced Each Service Category



CONSOLIDATION CONCERN?

Service providers should be cognizant, however, of the investment activities underway at both sponsor companies and their competitor CMOs. In addition to many large, even mega, deals at the sponsor level (e.g., Pfizer's recently announced $160 billion acquisition of Allergan), the pharma-biotechs are investing significantly in internal manufacturing capabilities, through the expansion of existing or additional new manufacturing facilities and/or the acquisition of production capability. This is the case with Shire's pending acquisition of Baxalta and its pipeline and manufacturing capacity. This in-house expansion activity is largely due to pipelines that are much more robust than have been seen for many years. Some sponsor companies are also acquiring CMOs in order to achieve greater vertical integration. Again, look to Pfizer and its acquisition of Hospira and their One2One CMO.

It is also worth noting that many sponsor firms are looking to simplify their CMO networks by working with CDMOs that can support their projects from the development phase through clinical trials and on to commercial API production, as well as drug product formulation, manufacturing, and packaging. The pharma-biotechs are establishing more collaborative relationships with a smaller set of carefully selected, preferred suppliers. Such an approach, unlike the use of a large number of tactical suppliers, leads to simplification of the supply chain for increased management, and reduced costs and development timelines. CDMOs with fully integrated capabilities and cultures, systems, and processes that support these types of collaborative relationships are an important component of this type of outsourcing strategy.

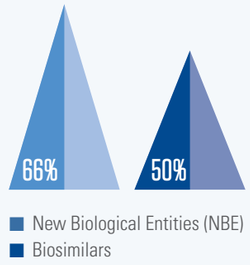
THE RISE OF THE "CDMO"

This trend is in turn leading to heightened M&A activity amongst CMOs as they attempt to transform themselves into CDMOs. A few recent notable examples include Merck KGaA's acquisition of Sigma Aldrich, Pfizer's purchase of Hospira, the merger of Patheon and DSM and the acquisition of Gallus Biopharmaceuticals by the newly formed DPX Holdings, the merger of Cambridge Major Laboratories with AAIPharma, and the acquisitions of Bend Research and Xcelience by Capsugel.

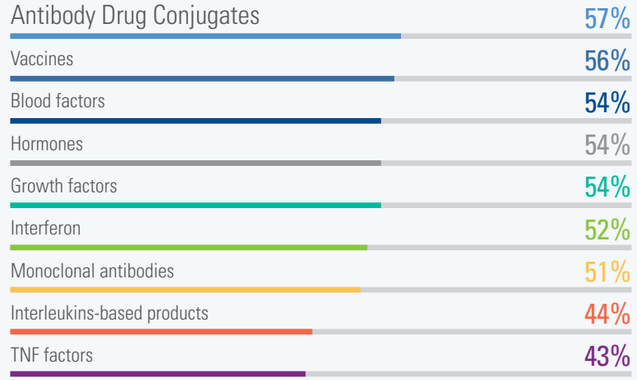
Also worth mentioning are the activities of AMRI (Albany Molecular Research Inc.), and the launch of Avara Pharmaceutical Services, a private, wholly owned subsidiary of American Industrial Acquisition Corporation (AIAC). AIAC, which was founded in 1995, consists of 60 manufacturing sites and more than 8,500 employees in 15 countries, generating $1.2 billion in revenues, providing contract manufacturing and technical services to the biopharmaceutical market. There are too many others to list, as is also the case with internal investments by CMOs and CDMOs. Leading the pack in that area is Catalent, which also recently acquired several companies (Pharmapak Technologies, Redwood Bioscience, and Micron Technologies). Both Catalent and Patheon have also announced initial public offerings to raise capital for further expansions.

All of this activity certainly suggests that the CDMO concept has been fully realized in the contract manufacturing marketplace. Today, just 30 CMOs/CDMOs account for more than half of the industry's revenues,

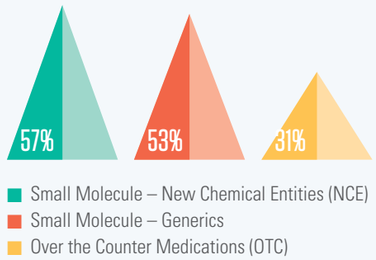
% of Respondents Whose Business Is Engaged In The Development Of Biologics



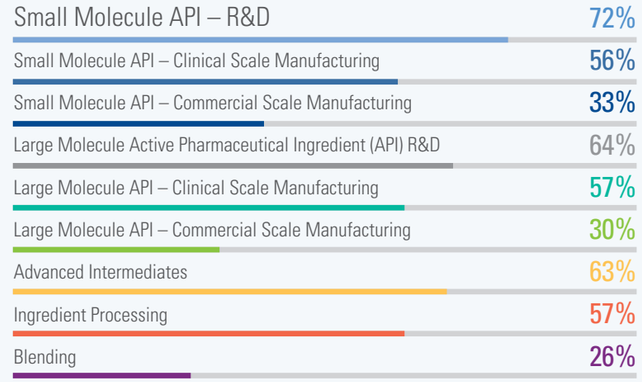
Types of Biologics Included in Respondents' Product Pipeline



% of Respondents Whose Business Is Engaged In The Development Of Small Molecules



% of Respondents Who Outsourced Drug Substance Services



according to PharmSource.[2] These combined firms have developed a global footprint, with large-scale capabilities for greater cost efficiencies, service offerings (including development and final formulation/drug delivery), and access to advanced technologies, and are positioned to be competitive with in-house sponsor capabilities.

DELIVER BIG OR GO HOME

A key implication of this trend, however, is increased demand for those CDMOs that can provide measurable added value that sponsor organizations cannot realize on their own. This will create more challenges for traditional CMOs and less competitive CDMOs. It will be interesting to see which CDMOs rise to the top in this highly competitive landscape. At a minimum, a contract service provider must have a track record of success, financial stability, and an industry reputation for doing quality work. In fact, quality has also supplanted cost savings as the key criterion when sponsor companies are seeking contract service partners, while poor product and service quality remains the top source of dissatisfaction, according to the 2016 Nice Insight survey results.

CDMOs that are willing and able to collaboratively develop operating procedures, use dedicated project managers, demonstrate a clear willingness to make long-term commitments, and customize protocols for different projects will also have an edge, according to survey participants. Specialized technical capabilities

are also increasingly important, particularly those that ensure high bioavailability, efficacy, and safety, even for the most complex and challenging-to-formulate APIs. Those CDMOs that can provide such differentiating solutions cost effectively, and under the accelerated timeframes required for drug substances that are granted orphan drug, breakthrough therapy, and/or fast track designations from the FDA, stand out even more.

97% OF RESPONDENTS OUTSIDE OF THE U.S. INDICATED INTEREST OR VERY STRONG INTEREST IN A STRATEGIC PARTNERSHIP.

GET YOURSELF "PREFERRED"

Outsourcing for such complex products serves as an efficient and cost-effective way for sponsor companies to gain access to the most advanced technical solutions, and CDMOs that can offer novel, proprietary technologies have the greatest chance of attracting their attention. As sponsor firms continue to pare down their vendor numbers and establish preferred/strategic partnerships with fewer, integrated suppliers, technological capabilities will equate directly to completive advantage. Indeed, the introduction of innovative new technologies to the lab, manufacturing plant, and supply chain is helping service providers attract projects from sponsors looking to be first to market with differentiated products, according to participants in the Nice Insight survey. In fact, the preference for "Preferred Suppliers" rose to 43% from 35% last year, while the preference for tactical suppliers dropped from 35% to 31%. Use caution, however: over 50% of survey respondents also indicated that they would switch CDMOs for poor quality and lack of on-time delivery.

So where will the opportunities lie for CDMOs in 2016? Companies with truly integrated offerings and unique technical capabilities will enter into collaborative capacity management and long-term, multi-project relationships. Emerging markets, value-added generics (so-called supergenerics), and biosimilars will provide other potential opportunities for growth to contract manufacturers with the global reach and technical capabilities necessary to capitalize on them. Those that are positioned to leverage these opportunities and survive the more competitive contract manufacturing marketplace are likely to benefit from improved pricing and increased margins.

% of Projects Contracted to Each Type of Outsourcing Relationship

43% Preferred Provider

- 31% Tactical Service Provider
- 26% Strategic Partnership

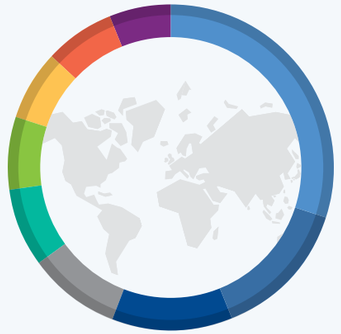
Respondents Who Do Not Consider Emerging Market Providers Mentioned the Following Concerns

Regulatory compliance concerns	49%
Quality is too risky	44%
Intellectual property concerns	41%
Communication concerns / challenges	41%
Logistics are too complicated	37%
Simply have not considered it	28%

Factors That Would Prompt Respondents to Switch From Their Current CDMOs/CMOs

Better quality at competing CDMO/CMO	50%
Operational expertise offered by competing CDMO/CMO	41%
Better timelines promised by competing CDMO/CMO	41%
Better price offered by competing CDMO/CMO	40%
Improved logistics	37%
Therapeutic expertise offered by a competing CDMO/CMO	34%
Geographic convenience of the competing CDMO/CMO	32%
Low error rate compared to current CDMO/CMO	32%
Poor regulatory compliance of current CDMO/CMO	24%

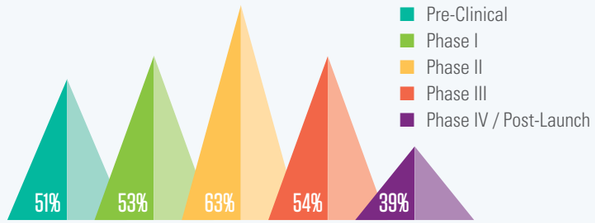
% of Outsourced Projects Assigned to Each Region (Among Respondents Who Engage Emerging Market Providers)



30% U.S. & Canada

- 14% Western Europe
- 12% India
- 9% China
- 8% Singapore & South East Asia
- 7% Japan & Korea
- 7% Argentina & Brazil
- 7% Eastern Europe & Turkey
- 6% Middle East

Phases Of Development During Which Outsourcing Partners Are Engaged



71% of Emerging Pharma/Biotech Outsources during Phase I and 70% of Midsize Pharma/Biotech Outsources during Phase II.

Therapeutic Areas Of Focus

Metabolic Disorders	53%
Infectious Diseases	53%
Cardiovascular Diseases	50%
Respiratory Diseases	48%
Endocrine Diseases	45%
Oncology Diseases	44%
CNS Disorders	43%

OH, WE'RE GLOBAL NOW

These statistics clearly suggest that the results of the new 2016 Nice Insight CDMO Outsourcing survey should be highly indicative of the conditions in the global CDMO marketplace. Initial analysis of the data indicates that survey participants utilize contract manufacturing services in all key pharmaceutical and biopharmaceutical markets around the world. Most projects are outsourced in the U.S./Canada (30%), Europe (14%), and India (12%), but a reasonable amount of activity is also taking place in China (9%), Singapore/Southeast Asia (8%), Japan and Korea (7%), Argentina and Brazil (7%), Eastern Europe and Turkey (7%), and the Middle East (6%).

The obvious, #1 reason respondents give for outsourcing to both traditional CMOs and CDMOs is to improve quality. Other important drivers include the desire to improve time to market, increase efficiency, reduce cost, and leverage contractor regulatory expertise. Participants of the 2016 Nice Insight CDMO Outsourcing are also looking to gain competitive advantage and access to specialized technical and operational expertise by outsourcing to CMOs and CDMOs.

And they are doing so for projects at all development phases, although the largest percentage of respondents indicated that they are outsourcing Phase II projects to CDMOs and CMOs. A similar number of respondents are using manufacturing services for Phase III (54%), Phase I (53%) and Pre-Clinical (including discovery phase) (51%) projects. This strong distribution reflects the recent industry investment in innovation and the currently robust drug pipeline, with drugs steadily moving toward commercialization. Phase IV/Post-Launch projects are outsourced by 39% of survey respondents; the lower percentage reflects the attrition that occurs as safety and efficacy are evaluated. However, the fact that Phase II projects are most often outsourced and the high percentage of participants outsourcing Phase IV projects may indicate that new programs that are designed to eliminate unlikely candidates are achieving the desired results. P

→ REFERENCES

1. Visiongain, Pharmaceutical Contract Manufacturing World Market To Reach $79.24bn In 2019. Press Release, February 10, 2015.

2. PharmSource, Contract Dose Manufacturing Industry by the Numbers, 2015 Edition, July 2015.

CDMO INDUSTRY LEADERS

Nice Insight's Top Companies lists are comprised of the highest scoring companies, as rated by buyers of outsourced services, with respect to customer perception within each category. Customer perception describes how a current buyer or prospect rates a company based on the information they have been exposed to — from marketing materials to word-of-mouth influence, as well as experience with the company. Nice Insight uses six key drivers of outsourcing — quality, reliability, productivity, affordability, innovation and regulatory history — to measure customer perception; the number listed is the average of the six individual scores, down to the decimal point.

587 SURVEY RESPONDENTS

123 CDMOS IN THE SURVEY

6 KEY DRIVERS OF OUTSOURCING

Quality, Reliability, Productivity, Affordability, Innovation & Regulatory

CP CUSTOMER PERCEPTION SCORE

Average of six individual key driver scores

Drug Substance
Specialized Services

High Potency Compounds

1 Cambrex — 89.17% CP Score Mean

2	Sandoz	88.33%
3	Aesica	88.17%
3	BioVectra	88.17%
5	Lonza	88.00%
6	Pierre Fabre	87.50%
7	Almac	87.00%
7	Dishman Pharmaceuticals	87.00%
7	Johnson Matthey Pharma Services	87.00%
10	Dottikon Exclusive Synthesis	86.50%
10	Corden Pharma	86.50%

Drug Substance
Specialized Services

Cytotoxic Compounds

1 AMPAC Fine Chemicals — 92.00% CP Score Mean

2	Corden Pharma	91.33%
3	Dishman Pharmaceuticals	89.33%
4	Sanofi CEPiA	89.17%
5	Aesica	89.00%
6	Albany Molecular Research Inc. (AMRI)	88.00%
7	Cambrex	87.50%
7	Lonza	87.50%
7	Coldstream Laboratories	87.50%
10	Almac	86.67%

Drug Substance
Biomanufacturing

Mammalian Biopharmaceuticals

1 Samsung Biologics — 94.33% CP Score Mean

2	GSK Contract Manufacturing	90.67%
3	Pfizer CentreSource	90.33%
4	Sanofi CEPiA	89.00%
5	Boehringer Ingelheim	88.67%
6	AbbVie Contract Manufacturing	88.50%
6	Kemwell	88.50%
8	Cytovance Biologics	88.33%
8	WuXi	88.33%
10	Cobra Biologics	88.00%

Drug Substance
Clinical Scale Manufacturing

Small Molecule API

1 Aesica | Fareva — 89.83% CP Score Mean

3	Corden Pharma	89.17%
4	BASF	89.00%
5	Cambrex	88.33%
6	Pfizer CentreSource	88.00%
7	Solvias	87.33%
7	Arevipharma GmbH	87.33%
9	Siegfried	87.17%
10	Halo Pharma	86.83%

Drug Substance
Clinical Scale Manufacturing

Large Molecule API

1 Samsung BioLogics — 92.00% CP Score Mean

2	Pfizer CentreSource	89.00%
3	Cook Pharma	88.50%
4	Dishman Pharmaceuticals	87.83%
5	Cytovance Biologics	87.67%
6	AbbVie Contract Manufacturing	87.17%
7	Corden Pharma	87.00%
7	Hisun Pharmaceuticals USA	87.00%
9	Fareva	86.83%
9	Paragon Bioservices	86.83%

Drug Product
Specialized Services

High Potency Compounds

1 Pfizer CentreSource — 89.33% CP Score Mean

2	GSK Contract Manufacturing	88.67%
3	Patheon	88.17%
4	Catalent	87.83%
4	Metrics Inc.	87.83%
6	Recipharm AB	87.67%
6	Siegfried	87.67%
8	Capsugel	87.50%
9	PCI Pharma Services	87.00%
9	Pii	87.00%

Drug Product
Specialized Services

Cytotoxic Compounds

1 Capsugel — 92.17% CP Score Mean

2	CMIC	90.33%
2	Delpharm	90.33%
2	BioVectra	90.33%
5	AbbVie Contract Manufacturing	90.17%
6	Dr. Reddys CPS	89.17%
7	Catalent	88.33%
7	Pfizer CentreSource	88.33%
7	Pii	88.33%
10	AAI Pharma - Cambridge Major Laboratories	88.17%
10	Pharmatek	88.17%

Drug Product
Clinical Scale Manufacturing

Solid Dosage Form

1 Pfizer CentreSource — 90.17% CP Score Mean

2	PharmaZell	90.00%
2	Xcelience	90.00%
4	Synerlab	89.67%
5	Capsugel	89.33%
6	Metrics Contract Services	89.17%
6	Siegfried	89.17%
8	Halo Pharma	88.50%
9	Aesica	88.33%
9	GSK Contract Manufacturing	88.33%
9	AbbVie Contract Manufacturing	88.33%
9	Albany Molecular Research Inc. (AMRI)	88.33%

Drug Product

Fill / Finish

1 Pfizer CentreSource — 94.00% CP Score Mean

2	Richter-Helm	91.83%
3	Samsung BioLogics	91.67%
4	Aenova	91.33%
5	Alkermes	90.33%
6	Coldstream Laboratories	89.83%
7	Dishman Pharmaceuticals	89.67%
8	WellSpring Pharma Services	89.33%
9	IDT Biologika	89.00%
9	Recipharm AB	89.00%

Drug Product
Commercial Scale Manufacturing

Solid Dosage Form

1 PharmaZell — 91.00% CP Score Mean

2	Catalent	90.33%
3	Siegfried	89.83%
4	Xcelience	89.50%
5	GSK Contract Manufacturing	89.33%
5	Patheon	89.33%
7	Synerlab	89.17%
8	Capsugel	89.00%
8	Aesica	89.00%
8	Metrics Contract Services	89.00%

Where scores are equal, all companies are listed.

ANOTHER EXCITING YEAR FOR CLINICAL RESEARCH OUTSOURCING

2016 NICE INSIGHT CRO OUTSOURCING SURVEY FINDINGS

In the 2016 Nice Insight CRO Outsourcing Survey, a few new and exciting trends emerged in sponsors' outsourcing practices. Pharma-biotech companies, regardless of size or type, demand a broad spectrum of services in preclinical and clinical phases for their research and development needs. An increased level of focus on many therapeutic areas was observed. This trend suggests that expanding product portfolios to multiple areas has become a commonly adopted pipeline development strategy by the industry. Meanwhile, the level of CRO engagement at every clinical phase has increased prominently. Along with the robust growth of the global pharmaceutical outsourcing market, buyers' outsourcing expenditures will continue to increase in the next five years as well as the number of service providers they will work with. In terms of CRO selection, quality continues to be the ultimate decision driver and the fundamental reason for dissatisfaction and/or causing of a current CRO. Finally, despite the growing importance of the emerging markets, the industry is still quite cautious about engaging CROs there.

The Nice Insight Survey represents the well-balanced perspectives of 586 buyer respondents from four different sectors of the industry: 39% from Big Pharma/Big Biotech, 41% from Midsized Pharma/Biotech, 14% from Small Pharma/Biotech, and 6% from Emerging Pharma/Biotech. Alternatively, the composition of the respondents can be initially broken into two primary sectors followed secondarily by size: 63% of the respondents are from the Pharma sector (Big: 24%; Midsized: 27%; Small: 9%; Emerging 4% †) and 37% from the Biotech sector (Big: 15%; Midsized: 14%; Small: 5%; Emerging: 3%). The 2016 survey also better provides a regional representation since respondents from Asia increased to 20% from previous year's level of 1%, an indication for the growing importance of Asia in the category of contracted services. Nevertheless, the majority (80%) of the buyers are still from North America (61%) and Europe (19%).

With respect to buyers' job functions, as with the previous study, the respondents work in a variety of departments. In comparison to the 2015 survey, proportionally, there are more respondents from Corporate Management, up by 20% to 37%; Clinical Trials Operations/Management up by 6% to 14%; and R&D/Formulation/Analytical up by 2% to 15%; Quality Assurance/Quality Control was down by 6% to 10%; Regulatory Affairs was down by 1% to 4%; and Contracting/Sourcing/Purchasing was down by 1% to 6% †. Ninety percent of the respondents hold management positions: C-Level Executive – 36%, Manager/Senior Manager – 25%, Director/Senior Director/Scientist – 23%, and Vice President/Senior Vice President – 6%. All of them have job duties closely tied up with contract research organizations (CROs), either being part of the decision-making unit that selects CROs (67%), or being part of the team that establishes criteria/makes recommendations on the selection of CROs (20%), or supervising or coordinating with CROs (13%).

SURVEY PROFILE INFORMATION

By Region

61% North America

19% Europe

20% Asia

By Annual Outsourcing Expenditure

38% $51M to $100M

- 18% More than $100M
- 32% $10M-$50M
- 10% Less than $10M

The Most Popular Methods Used To Select An Outsourcing Partner

Industry Research	59%
Referrals / Colleagues	53%
Consultants	50%
Web Searches	43%
Trade Shows / Events	42%
Online Directories	40%
Periodicals / Publications	38%

Industry Research was the most popular method cited for selecting an outsource partner, above word of mouth and consultants. This indicates that customers are more likely to conduct their own inquiry prior to choosing CRO.

Average Number of Methods Used To Select An Outsourcing Partner

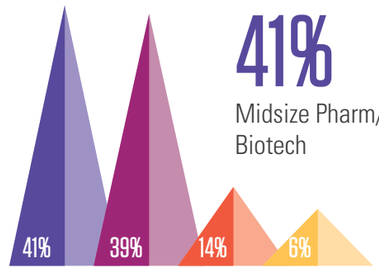
3.2 To ensure quality, sponsors are using more methods to identify new partners

By Department

37% Corporate Management

- 15% R&D / Formulation / Analytical
- 14% Clinical Trials Operations / Management
- 10% Quality Assurance / Quality Control
- 4% Regulatory Affairs
- 7% Preclinical Operations
- 6% Contracting / Sourcing / Purchasing
- 7% Other

By Buyer Group



41% Midsize Pharm/Biotech

- 39% Big Pharma / Biotech
- 14% Small Pharma / Biotech
- 6% Emerging Pharma / Biotech

% Of Respondents Who Will Attend The Following Industry Events

BIO International	BIO Europe	AAPS	Contract Pharma	DIA	DCAT
43%	35%	33%	33%	32%	32%

BPI	ChemOutsourcing	CRS	Informex	CPhI Europe	Interphex
29%	25%	25%	23%	22%	21%

† The 1%-2% discrepancy between the total percentages and the sum of individual percentages is due to number rounding.

THE LEVEL OF FOCUS HAS INCREASED IN MANY THERAPEUTIC AREAS, WITH METABOLIC AND CARDIOVASCULAR DISEASES RECEIVING THE MOST SCRUTINY

In the 2016 survey, Nice Insight observed a dramatic increase in the degree of focus on 6 out of 7 surveyed therapeutic areas. Infectious Diseases is the only area that received the same level of focus from 2015 to 2016. Further, it is no longer the most focused therapeutic area falling behind Metabolic Disorders (53%), Cardiovascular Diseases (52%), and Respiratory Diseases (50%). A smaller portion of respondents focus on Endocrine Diseases (46%), Oncology (44%), and CNS Disorders (33%). In addition, with the consideration of their current and future product pipelines, the respondents focused more on New Chemical Entities (NCEs) (60%), Generics (60%), and New Biological Entities (NBEs) (59%). A fair number of respondents (48%) focused their efforts on Biosimilars. Over-the-Counter medications (OTC) received the least attention, but are still strong at 27%. As the competition among drug makers intensifies, pharma/biotech companies expand and diversify their product pipeline portfolio, for example, focusing on multiple therapeutic areas and/or drug molecules, to counter the risk and uncertainty of drug development and maximize their chance of success.

PHARMA/BIOTECH COMPANIES REQUIRE A BROAD SPECTRUM OF CONTRACT SERVICES, AND BUYERS ARE ENGAGING MORE WITH OUTSOURCING PARTNERS FOR CLINICAL TRIALS

The 2016 Nice Insight industry-wide outsourcing survey took a deep look at buyers' demands for contracted service through all development phases as well as their current outsourcing practices based on drug type and development stage. The data indicate that pharma/biotech companies, regardless of size or type, acquire or plan to acquire a broad spectrum of services for their research and development needs. A strong demand for Preclinical Trial Services (80%) and Clinical Trial Services (76%) was observed. The demand for Clinical Trial Services is much more evident among Big Pharma/Biotech and Midsized Pharma/Biotech sectors (79% respectively) than Small Pharma/Biotech and Emerging Pharma/Biotech sectors (66% respectively).

Among a cluster of 13 Preclinical Trial Services, Bio-analytical Testing (53%), Analytical Testing (49%), Chemistry and Stability Testing (48%), and Biostatistics and General Toxicology (45%, respectively) are the top 5 most needed services. As for Clinical Trial Services, Clinical Trial Design (54%), Clinical Trial Phase I/IIa and Clinical Trial Phase II/III (51%, respectively), Clinical Trial Data Management (50%), and Clinical Trial Recruiting (48%) have made the top 5 list out of 13 services. Besides Preclinical and Clinical Trial Services, buyers also demand Specialized Services including Environmental Testing (55%), Regulatory Services (53%), Research Models (Animal Models) (50%), Process Chemistry/Scale-up (47%), Surgical Services (Animal Models) (45%), and In Vitro Assays (42%).

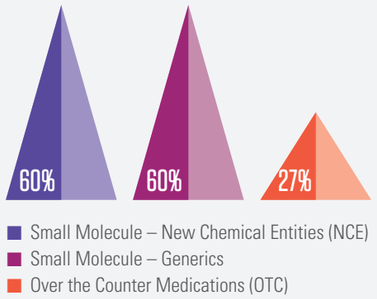
To fulfill their research and development needs, currently 75% of the respondents outsource services or operations to CROs (36%) or to both CROs and Contract Development & Manufacturing Organizations (CDMOs/CMOs) (39%). Big and mid-sized Pharma/Biotech companies tend to use a combination of CROs and CDMOs/CMOs (45% and 40%, respectively, within their sector) while Small and Emerging Pharma/Biotech companies rely more on CROs (45% and 55%, respectively, within their sector). Additionally, only 16% of the Emerging Pharma/Biotech respondents do not currently outsource research services or operations, which is the smallest fraction out of all sectors (Big Pharma/Biotech: 25%; Midsized Pharma/Biotech: 25%; Small Pharma/Biotech: 35%). Given Emerging Pharma/Biotech companies' limited resources and capital, it is not surprising that they are more inclined to utilize the outsourcing strategy to achieve their research and development goals.

Based on the types of drug molecule, on average, 24% of the contracted services are outsourced for NCEs, 22% for Generics, 21% for NBEs, 18% for Biosimilars, and 15% for OTCs. With respect to buyers outsourcing practices based on the development stage, an exciting new pattern was observed: a higher proportion of respondents were engaging CROs during clinical phases than before. In comparison to 2015 findings, buyers engagement with CROs has increased in every clinical phase in the 2016 survey: 58% in Phase I (up by 2%), 63% in Phase II (up by 21%), 51% in Phase III (up by 22%), and 39% in Phase IV/Post-Launch (up by 17%).

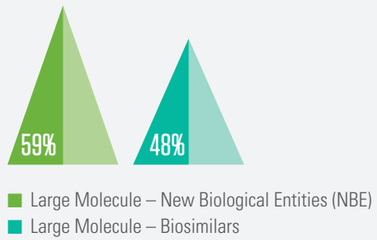
In addition, Phase II is now the phase with the highest CRO engagement rate, replacing last year's Pre-Clinical Phase. The increased engagement in clinical stages may be an indication of the pipeline drug candidates successfully advancing to the new development stages, or an indicator of buyers' enhanced willingness to engage CROs for their clinical development needs,

Therapeutic Areas Of Focus

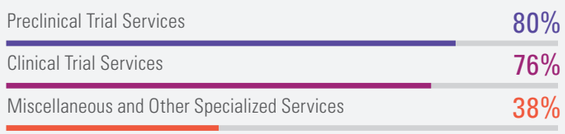
% Of Respondents Whose Business Is Engaged In The Development Of Small Molecules



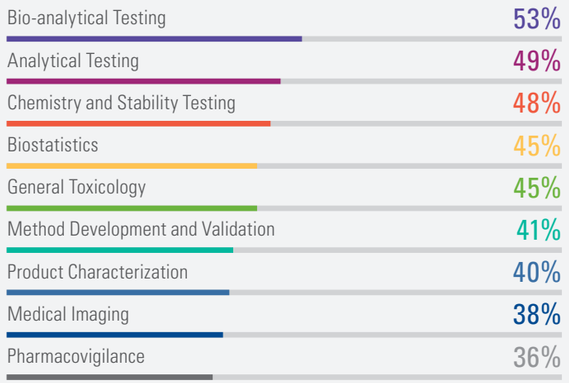
% Of Respondents Whose Business Is Engaged In The Development Of Biologics



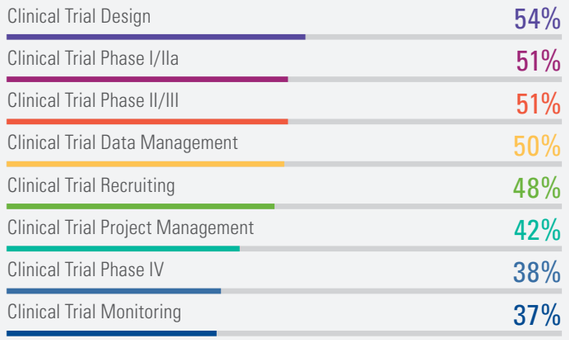
Respondents Who Outsourced Each Service Category



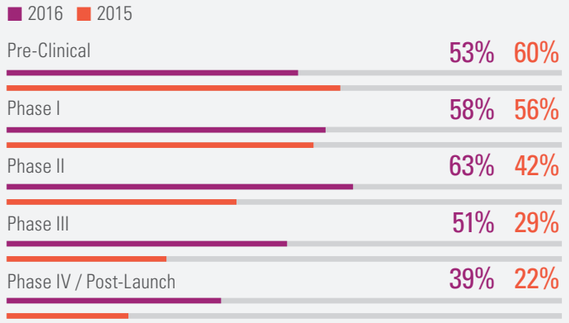
% Of Respondents Who Outsourced Preclinical Trial Services



% Of Respondents Who Outsourced Clinical Trial Services



Phases Of Development During Which Outsourcing Partners Are Engaged



PHASE II IS NOW THE PHASE WITH THE **HIGHEST CRO ENGAGEMENT RATE** REPLACING LAST YEAR'S PRE-CLINICAL PHASE.

especially during mid to late stage. Also, in the survey, Emerging Pharma/Biotech companies showed a much lower CRO engagement rate in Phase III (32%) and Phase IV (21%), which may be due to their lack of products in the late stage, or due to mergers and acquisitions. Generally, small and/or emerging companies will be acquired by larger companies once their products progress to late clinical stages, which in turn, can lead to fewer-than-expected CRO engagements at later clinical stages.

QUALITY CONTINUES TO BE THE #1 DECISION DRIVER IN CRO SELECTION

As the pharma/biotech industry is leaning more on outsourcing to meet their research and development needs, identifying and engaging with the right CROs and/or CDMOs/CMOs is an increasingly important business decision to make. From a buyers perspective, the desire to Improve Quality is the most important strategic reason for outsourcing. Other top-ranked strategic reasons include Improve Time-to-Market, Reduce Cost, Process Improvement, and Access to Specialized Technologies. Among the 6 decision drivers behind CRO selection, Quality remains to be the most important driver, followed by Reliability, Innovation, Productivity, Regulatory Track Record, and Affordability. Along with the decision drivers, a variety of attributes also factor into CRO selection. The top-rated attributes are: Regulatory Compliance (85%), CRO Understands the Customer's Requirements, CRO Industry Reputation (83%, respectively), Financial Stability and Experience (Operational, Methodological, Therapeutic), and Cost (82%, respectively), as well as Risk Adherence (81%).

77% OF RESPONDENTS FELT IT WAS HIGHLY LIKELY THAT A **PREFERRED PROVIDER WOULD BECOME A STRATEGIC PARTNER**, WHILE 75% AGREED THAT A CRO THAT STARTED OFF AS A TACTICAL SERVICE PROVIDER WOULD BECOME A PREFERRED PROVIDER.

In terms of buyers' satisfaction level with their current CROs, 82% of the respondents expressed satisfaction (43% Satisfied and 39% Somewhat Satisfied), 6% expressed dissatisfaction (1% Unsatisfied and 5% Somewhat Unsatisfied), and the rest remained Neutral. The foremost disappointing trait is Product/Service Quality. Other top-ranked most disappointing traits include Cost Overruns, Inflexibility, Customer Service, Security/Confidentiality, Timeliness of Resolving Issues, and Products/Services Availability. Furthermore, many factors can prompt service sponsors to change CROs. Among these factors, Better Quality at Competing CRO is the most appealing reason to trigger the change, followed by Better Price Offered by Competing CRO, Better Timeline Promised by Competing CRO, Improved Logistics, and Operational Expertise offered by Competing CRO.

OUTSOURCING EXPENDITURE WILL CONTINUE TO GROW IN THE NEXT FIVE YEARS

Another exciting trend observed in the 2016 survey is the prominent increase in buyers' annual outsourcing expenditure. In 2015, 62% of buyer companies had an annual outsourcing expenditure between $10M and $50M, 23% over $50M, and 16% less than $10M.[†] The landscape changed completely in 2016: more buyers are in the category of more than $50M (56%; a 32% increase). Consequently, fewer companies are in the categories of $10M to $50M (32%) and Less than $10M (10%). The category of More than $50M can be further broken down into two categories: Annual Expenditure between $51M to $100M of 38% and More than $100M at 18%. This expenditure increase aligns with the global pharmaceutical outsourcing market growth trend: the entire market with a current value of $130.65 Billion is projected to reach $215 Billion by 2020 at a compound annual growth rate (CAGR) of 8.7% within the period of 2015 to 2020.[1]

Correspondingly, the majority of the respondents hold quite a positive view on the alterations of their annual outsourcing expenditure in the next five years, with 71% in favor of increase and only 6% in favor of decrease. The positive perspective is also reflected in buyers' prediction of the number of CROs their company will work with in the next three years. Currently, the respondents companies work with a wide range of CROs, varying from 0 to 99, with 76% of respondents falling into the category of 0-10 CROs. The percentage dropped to single digit for the rest of categories: 11-20 (7%), 21-30 (5%), 41-50 (6%), 51-60 (2%), and 1% each for 31-40, 61-70, 71-80, 81-90, and 91-99. On average, each respondent worked with about 12 CROs. Looking into the future, 64% of the respondents predict an increase in the number of CROs their company will work with in the next three years, while only 1% foresee a decrease. The main drivers behind the number increase are: Positive Experiences with CRO(s) (61%), Company Strategy {to move to larger proportion of outsourced relationships in supply chain} (56%), and General Increase in R&D portfolio (55%). The decline in CRO numbers is largely due to Decline in R&D Portfolio and Negative Experience with CRO(s).

CAUTION REMAINS IN ENGAGING CROs LOCATED IN EMERGING MARKET, ESPECIALLY FOR BIG PHARMA/BIOTECH SERVICE SPONSORS

Despite the growing importance of the emerging markets, in the NI 2016 survey, the respondents actually outsourced a smaller fraction of their projects to the emerging markets: a total of 47% of projects outsourced to the emerging markets (China: 10%; India: 9%; Eastern Europe & Turkey: 8%; Singapore & South East Asia: 7%; Argentina & Brazil: 7%; Middle East: 6%) vs. 61% in 2015 (China: 17%; India: 11%; Eastern Europe & Turkey: 10%; Thailand & Vietnam: 4%; Argentina & Brazil: 15%; Middle East: 5%). Even though in the 2016 survey, more respondents are located in Asia (19% vs. 1% in 2015), percentage wise, mature markets received more projects than last year: 31% of projects are outsourced to the U.S. & Canada vs. 23% in 2015 and 14% to Western Europe vs. 11% in 2015. Some possible explanations for this phenomenon could be that pharmaceutical makers in Asian countries are targeting the western markets, or service sponsors become more cautious in engaging CROs in the emerging markets.

This caution is further reflected by a decreased level of interest in buyers' consideration of outsourcing to CROs located

% Of Projects Contracted To Each Type Of Outsourcing Relationship

45% Preferred Provider

- 31% Tactical Service Provider
- 24% Strategic Partnership

% Of Outsourced Projects Assigned To Each Region (Among Respondents Who Engage Emerging Market Providers)

2015 to 2016 +8%

31% U.S. & Canada

- 14% Western Europe
- 10% China
- 9% India
- 9% Japan & Korea
- 8% Eastern Europe & Turkey
- 7% Singapore & South East Asia
- 7% Argentina & Brazil
- 6% Middle East

Among Respondents Who Consider Emerging Market Providers

30% Overall

Are aware of reliable CROs in emerging markets, but have not worked with one yet.

Big Pharma/Biotech	25%
Midsize Pharma/Biotech	36%
Small Pharma/Biotech	28%
Emerging Pharma/Biotech	11%

Respondents Who Do Not Consider Emerging Market Providers Mentioned The Following Concerns

Quality is too risky	47%
Regulatory compliance concerns	46%
Intellectual property concerns	42%
Communication concerns / challenges	37%
Logistics are too complicated	37%
Simply have not considered it	28%

QUALITY IS THE GREATEST CONCERN AMONG THOSE WHO WOULD NOT CONSIDER EMERGING MARKET PROVIDERS.

in the emerging markets: 71% of the respondents this year are interested, in contrast to an 84% interest rate among Pharma respondents and 86% among Biotech respondents last year. In addition, the Big Pharma/Biotech respondents demonstrated a "No Consideration" rate of 15% while the overall "No Consideration" rate was 19%. A variety of reasons contribute to the industry's hesitation in engaging CROs from the emerging markets. Similar to 2015, concerns on Quality (47%) and Regulatory Compliance (46%) remain the top two issues. Intellectual Property concerns (42%) jumped to the third place this year while it was the least issue of concern in 2015 (19%). Furthermore, except Quality (down by 3%), the degree of concerns in all other five surveyed areas have increased by a range of 5% to 20%: Regulatory Compliance, up by 15%; Intellectual Property, up by 23%; Communication Concerns/Challenges, up by 12% to 37%; Logistics, up by 15% to 37%; and Simply Have Not Considered It, up by 5% to 28%. On the other hand, among the "Yes" respondents, 65% of them have worked with CROs in the emerging markets, a 12% increase from the 2015 level. Meanwhile, the Emerging Pharma/Biotech sector showed the highest engagement rate of 85% with CROs in the emerging markets. Nevertheless, it is going to be a long way for service providers in the emerging markets to gain trust and build rewarding partnerships with pharma/biotech companies worldwide. P

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CRO INDUSTRY LEADERS

Nice Insight's Top Companies lists are comprised of the highest scoring companies, as rated by buyers of outsourced services, with respect to customer perception within each category. Customer perception describes how a current buyer or prospect rates a company based on the information they have been exposed to — from marketing materials to word-of-mouth influence, as well as experience with the company. Nice Insight uses six key drivers of outsourcing — quality, reliability, productivity, affordability, innovation and regulatory history — to measure customer perception; the number listed is the average of the six individual scores, down to the decimal point.

586 SURVEY RESPONDENTS

74 CROS IN THE SURVEY

6 KEY DRIVERS OF OUTSOURCING

Quality, Reliability, Productivity, Affordability, Innovation & Regulatory

CP CUSTOMER PERCEPTION SCORE

Average of six individual key driver scores

PreClinical

General Toxicology

1	Worldwide Clinical Trials	87.33% CP Score Mean
2	ICON	86.33%
3	MPI Research	85.83%
4	BRI Biopharmaceutical Research	85.67%
5	PPD	85.50%
6	MedPace Inc.	85.33%
7	Toxikon Corporation	85.00%
8	Lambda Therapeutic Research	84.83%
9	American Preclinical Services	84.33%
9	JRF Global	84.33%
9	PRA Health Sciences	84.33%

PreClinical

DMPK

1	Evotec	90.50% CP Score Mean
2	Worldwide Clinical Trials	88.67%
3	MPI Research	87.33%
4	CiToxLAB	87.00%
4	ICON	87.00%
6	Seventh Wave Laboratories	86.50%
7	Parexel	86.33%
8	JRF Global	85.83%
9	PRA Health Sciences	85.50%
10	Battelle	85.33%

PreClinical

Analytical Testing

1	Blue Sky BioServices	88.00% CP Score Mean
2	Quest Diagnostics Clinical Trials	87.33%
3	Seventh Wave Laboratories	86.50%
4	Parexel	86.33%
5	Evotec	85.67%
5	MicroConstants	85.67%
7	ICON	85.50%
7	MPI Research	85.50%
7	Surpass	85.50%
7	PRA Health Sciences	85.50%

PreClinical

Bio-analytical Testing

1	Blue Sky BioServices	87.33% CP Score Mean
2	Novotech	87.00%
3	Quest Diagnostics Clinical Trials	86.83%
4	ICON	86.00%
4	Toxikon Corporation	86.00%
6	Evotec	85.83%
6	Smithers Avanza	85.83%
8	PRA Health Sciences	85.67%
8	CNS Network	85.67%
10	Surpass	85.50%

PreClinical

Method Development & Validation

1	BASi	88.33% CP Score Mean
2	Blue Sky BioServices	87.67%
2	Worldwide Clinical Trials	87.67%
4	InnoPharma S.r.l.	87.50%
5	Parexel	87.00%
6	Evotec	86.83%
6	ICON	86.83%
8	PRA Health Sciences	86.67%
9	Quest Diagnostics Clinical Trials	86.33%
10	CiToxLAB	85.83%
10	Product Safety Labs	85.83%

Clinical

Clinical Data Management

1	Quest Diagnostics Clinical Trials	88.33%
2	Novum Pharmaceutical Research Sciences	87.67%
3	InnoPharma S.r.l.	87.33%
4	CNS Network	87.17%
5	InVentiv Health	87.00%
6	ICON	86.50%
7	Parexel	85.83%
7	Worldwide Clinical Trials	85.83%
9	Novotech	85.50%
10	BioSkin GmbH	85.00%
10	Janix	85.00%

Clinical

Clinical Trial Recruiting

1	CNS Network	87.50% CP Score Mean
2	InnoPharma S.r.l.	87.17%
2	Janix	87.17%
4	Chiltern	86.83%
5	INC Research	86.17%
5	PRA Health Sciences	86.17%
5	Spaulding Clinical	86.17%
8	Novum Pharmaceutical Research Sciences	85.83%
9	MedPace Inc.	85.67%
10	Envigo	85.33%

Clinical

Clinical Trial Design

1	InnoPharma S.r.l.	87.17% CP Score Mean
2	Worldwide Clinical Trials	86.67%
3	InVentiv Health	86.50%
4	Intertek	86.00%
5	PRA Health Sciences	85.67%
6	Parexel	85.50%
7	Novotech	85.33%
8	MedSource	85.17%
9	MedPace Inc.	84.83%
10	CNS Network	84.50%
10	ICON	84.50%

Clinical

Clinical Trial Monitoring

1	Parexel	88.67% CP Score Mean
2	InnoPharma S.r.l.	87.83%
3	Piramal Pharma Solutions	87.33%
4	Novum Pharmaceutical Research Sciences	87.17%
4	PRA Health Sciences	87.17%
6	MPI Research	86.83%
6	Novotech	86.83%
6	Premier Research	86.83%
6	Worldwide Clinical Trials	86.83%
10	BRI Biopharmaceutical Research	86.50%

Clinical

Project Management

1	Worldwide Clinical Trials	89.67% CP Score Mean
2	Piramal Pharma Solutions	88.00%
3	InnoPharma S.r.l.	86.50%
3	Blue Sky BioServices	86.50%
3	Janix	86.50%
6	SanaClis	86.33%
7	Quest Diagnostics Clinical Trials	86.17%
8	Spaulding Clinical	86.00%
9	MPI Research	85.67%
10	Rho	85.50%

Where scores are equal, all companies are listed.

EQUIPMENT TRENDS TRANSFORMING PHARMACEUTICAL MANUFACTURING

→ BY **NICE INSIGHT**

In response to factors affecting drug pricing around the world – such as shifting markets, government healthcare mandates, the end of the blockbuster era, and the linkage of insurance reimbursement with medical outcomes – pharmaceutical companies are taking many different actions to reduce their costs and increase efficiency and productivity. Equipment needs across the supply chain are changing, from initial discovery efforts to the packaging of final products. The Nice Insight 2015 Pharmaceutical Equipment Annual Study found that 54% of respondents (n=560) spent over $100 million on equipment per year (see Figure 1). And suppliers of research and development and production equipment, analytical instrumentation, and packaging systems are responding with innovative technologies that meet these needs.

SINGLE-USE TECHNOLOGY

Single-use, or disposable, technology (SUT) is widely used in biopharmaceutical drug development, and more recently has begun to gain acceptance in biologics production at increasingly larger scales, including commercial manufacturing. This interest is driven by the advantages that SUTs provide in terms of decreased capital expenditures and operating costs due to the reduction of cleaning and sterilization steps and the need for validation. In addition, processes based on single-use equipment are more flexible, require shorter set-up times, and have significantly reduced cross-contamination risk, all of which translates to a faster time to market and more robust and reliable production.

CONTINUOUS BIOPHARMACEUTICAL MANUFACTURING

Continuous manufacturing is appealing because it leads to more consistent products and processes, which equates to the consumption of fewer resources (raw materials, energy, water) and less waste generation, thus lowering operating costs – capital costs may be lowered as well. For upstream biopharmaceutical manufacturing, perfusion has become a well-established process that affords high-quality biologic drug substances with high productivity. Other types of upstream equipment under development include continuous centrifuges, acoustic resonance devices, and cell settlers. For continuous downstream bioprocessing, simulated moving bed (SMB) chromatography and tangential flow filtration (TFF) systems are also available and being adopted by the industry.

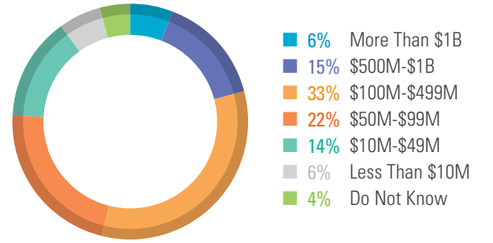
CONTINUOUS PROCESSES FOR SMALL-MOLECULE DRUGS

The industry has recognized the value of flow-through chemistry for the production of active pharmaceutical ingredients (APIs) and continuous tableting for many years. In addition to enhanced process and product consistency, flow chemistry enables manufacturers to perform hazardous reactions or use challenging conditions not possible in traditional batch modes. Reduced resource consumption and waste minimization are additional benefits, as with continuous biopharmaceutical processes, above.

HIGH POTENCY

One of the fastest-growing segments of the pharmaceutical market comprises formulated drugs based on highly potent active pharmaceutical ingredients (HPAPIs). This rapid growth is largely attributed to the growing number of antibody-drug conjugates (ADCs) that have recently been approved or are in development. These drugs are attractive because they are targeted therapies that deliver highly potent and often cytotoxic drugs (payloads) to selective sites in the body, linking them to antibodies that are taken up by only specific types of cells with the right antigens. Because the active drug is only released at the site of action, ADCs can be delivered systemically without causing harm to healthy cells.

→ **FIGURE 1** COMPANY ANNUAL EQUIPMENT EXPENDITURE



→ **FIGURE 2** PERFORMANCE METRIC RANKING

UTILIZING USED EQUIPMENT

At the same time that demand for innovative equipment for continuous processing, single-use technology, and systems for the manufacture of highly potent compounds is being driven by the need to reduce costs and increase efficiencies, demand for used pharmaceutical equipment is also rising as the result of increased levels of industry consolidation and outsourcing. As large companies acquire smaller firms or merge with larger entities, they often turn to resource recovery (the sale of redundant facilities and surplus equipment) to achieve initial and ongoing cost savings. In fact, high-quality used equipment is often sold at 40%-50%, and sometimes as little as 20%, of the original price. In addition, used equipment is immediately available, compared to new equipment, which, in some cases, can take weeks or even months to obtain if back-ordered. Used equipment can also serve as cost-effective back-up materials for critical processes or can help keep a process running in the event of an unexpected equipment failure.

CONCLUSION

Taken together, these equipment trends are an effective response to the changing landscape of the pharmaceutical manufacturing industry across the supply chain. In addition to being pragmatic and cost effective, these revolutionary tactics have already yielded results for the many companies that have employed them. And with pharma equipment evolving at a rapid rate, decreased costs and greater efficiency will be the rule – not the exception – for drug companies going forward.

The Nice Insight 2015 Pharmaceutical Equipment Annual Study found the following purchasing criteria to rank very closely for both Pharmas and Biotechs, as well as for CDMOs and CROs: Quality/Performance, Durability/Reliability, Regulatory/Validation, Price, Customer Service, and Service Agreement (see Figure 2). P

THE IMPORTANCE OF CONVENIENT DOSING FORMULATIONS FOR ELDERLY PATIENTS

BY **KEVIN HAEHL,** UNITHER PHARMACEUTICALS

Poor adherence to patient treatment plans is a widely recognized and significant issue in healthcare today. Because elderly patients often take numerous medications and can suffer from cognitive impairment and physiological problems, correctly following prescribed regimens can be challenging.

INCORRECT USE OF MEDICATION HAS BEEN ASSOCIATED WITH AS MANY AS **125,000 DEATHS PER YEAR** IN THE U.S. ALONE.

While active involvement of physicians and pharmacists and greater support from family can help improve adherence, simplification of medication regimens and access to affordable medications in easy-to-use dosing formats are also crucial to improving the treatment outcomes of geriatric patients.

Greater insights into the role of various biochemicals combined with advances in chemical synthesis and biotechnology are resulting in the development of safer, highly efficacious drugs for the treatment of both rare and prevalent diseases. Surprisingly, the results observed in clinical trials for these novel therapies do not always translate to the marketplace. One of the key reasons is poor patient adherence; drugs cannot be effective if they are not taken properly.

Poor patient adherence takes many forms, including not filling or picking up prescriptions, missing doses or taking them too frequently, and halting treatment too soon. There are also many factors contributing to medication nonadherence: patients' lack of knowledge; preconceived ideas and beliefs about different types of diseases and medications; expectations for results (i.e., side effects, time to see improvement); mental and psychological state, and cost concerns; treatment timeframes; lack of appropriate education and communication from physicians and pharmacists; and for the elderly in particular, the number of medications and dosing frequency. In 1986, approximately 90% of people receiving Medicare took medications, with half of them taking five or more drugs.[1] In addition, different factors may influence adherence for different medications.

In the U.S., over 50% of prescribed medications are taken incorrectly or not at all.[2] Of 800 American adults surveyed in 2013, 64% of those who took medications said they didn't take them as prescribed.[3] The consequences of such poor patient adherence are numerous and can be quite severe and costly. In one study, 33%-69% of drug-related adverse events that resulted in hospital admissions were linked to poor medication compliance,[2] while other researchers found that up to 40% of nursing home admissions can be attributed to nonadherence.[4]

Overall, nonadherence results directly in reduced efficacy of the treatment, which leads to more rapid disease progression and an increased need for physician and hospital visits. Overtreatment can also occur if physicians are unaware of lack of adherence and prescribe higher doses to achieve desired results.[5,6] In fact, incorrect use of medication has been associated with as many as 125,000 deaths per year in the U.S. alone.[2] In addition, the IMS Institute for Healthcare Informatics estimated that at over $200 billion annually, or 8% of the U.S. healthcare expenditures in 2013, the year of the study.[7] According to the U.S. Congressional Budget Office, a 1% increase in the number of prescriptions filled by beneficiaries would cause Medicare's spending on medical services to fall by roughly one-fifth of 1 percent.[8]

MORE COMPLEX ISSUES FOR THE ELDERLY

The fact that elderly patients take many different medications for the treatment of multiple diseases, in some cases prescribed by numerous different doctors who may not be communicating well with one another, makes compliance more difficult for this segment of the population. Studies have shown that as the number of prescriptions increases, the likelihood of nonadherence also increases.[9] The frequency at which a medication must be taken also influences patient adherence. Studies have shown that, on average, adherence drops significantly when medications must be taken four times per day (80% for one/day to 50% for four/day).[10]

The ease of use for self-administered drugs is also an important issue. Elderly patients that suffer from arthritis may find it difficult to open certain types of pharmaceutical packaging. Others who suffer from memory and cognitive problems may have difficulty remembering when to take pills, whether or not they have taken them already, or how to measure the correct dose.

MANY STRATEGIES ARE REQUIRED

Education of patients about their diseases, the action of the medications, the expected response time and the consequences of failing to adhere to prescriptions are crucial for increasing adherence. Physicians must consider their patients carefully and learn how best to communicate with each individual, taking into account his/her risk factors for nonadherence. Similarly, modern technology allows pharmacists to more actively monitor adherence for customers who regularly purchase medications from them.

Simplification of medication regimens and increasing the convenience and access to medications are two key strategies for improving patient adherence. The number of medications can be reduced by using combination therapies and finding alternative drugs that can treat multiple diseases. Switching to extended-release versions of current medications can reduce the frequency at which medications must be taken.

Prescribing the appropriate dosage form in pharmaceutical packaging designed to encourage adherence is important as well. The use of easy-access containers, and particularly single-unit dose formats, can have a significant and positive impact on geriatric patient adherence. Both physicians and pharmacists can help to identify alternative medications and appropriate dosage forms/packaging, as well as lower-cost medications, including generics where appropriate. The pharmaceutical manufacturing industry needs to support these efforts by using advanced manufacturing technology to provide affordable, convenient and easy-to-use drug forms.

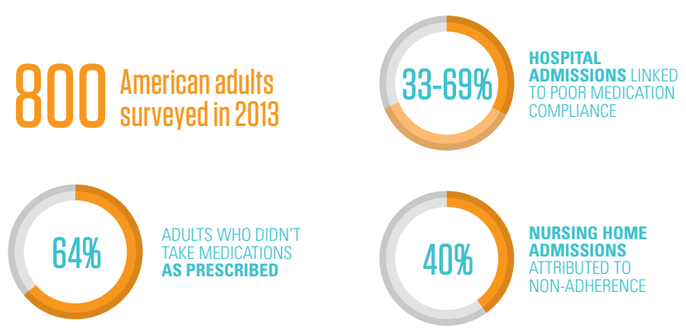
Family members can also help ensure effective treatment by actively monitoring the medication adherence of their elderly relatives and intervening with physicians and pharmacists to obtain more appropriate medications.

CONVENIENT SOLUTIONS

Unit-dose delivery of medication is widely used in healthcare facilities in the U.S. and Europe to prevent medication errors. Many of the benefits of single-dose packaging can also be realized by elderly patients. Single-dose delivery systems are accurately filled to hold only the quantity of drug

UNIT DOSE DELIVERY OF MEDICATION IS WIDELY USED IN HEALTHCARE FACILITIES IN THE U.S. AND EUROPE TO **PREVENT MEDICATION ERRORS.**

ELDERLY FACE COMPLEX ISSUES



intended for a single dose and are meant to be opened only once. Many dosage forms – oral, topical, and injectable – can be packaged as unit doses: blister or pouch packages for oral solid formulations, plastic syringes with rubber tips and squeeze tubes for oral liquid medications, sterile blow-fill-seal forms for ophthalmics and inhalation therapies, pre-filled syringes and cartridges for injectables, and stick-packs for liquids, suspensions, and gels for oral and topical administration.

Single-dose packaging can help elderly patients reduce medication errors. They can be clearly labeled with the product name and also include information on the dosing regimen, such as calendars to indicate when medication should and has been taken. They can also be designed to be easily opened, even by patients with limited dexterity. For active patients that are often away from home, single-dose packaging provides greater convenience because such medications can be easily put in a purse or backpack. There is also reduced concern over contamination when traveling because each dose is surrounded by protective packaging.

The Healthcare Compliance Packaging Council (HCPC), established in 1990 to promote the many benefits of unit-dose packaging, highlights several case studies demonstrating increased patient adherence for various types of medications (e.g., birth control pills, certain antibiotics, hormone replacement therapies, steroids, etc.) through the use of modern packaging solutions, and particularly compliance-prompting packaging that reminds people whether they have taken their medications.[11] With the advent of smartphone and networked homes today, the opportunities are even greater.

In all cases, of course, unit-dose packaging for pharmaceuticals must meet regulatory requirements and ensure the stability and efficacy of the medications they enclose. In many cases the use of unit-dose technology allows for the removal of artificial preservatives and longer shelf life. The most effective pharmaceutical packaging designs also serve as deterrents to counterfeiting and incorporate child-resistant features, while still allowing easy access for elderly patients.

Specialists in the development and contract manufacturing of sterile single-dose vials using blow-fill-seal (BFS) technology and liquid stick-packs, Unither Pharmaceuticals is committed to offering innovative and convenient single-unit dosage forms that simplify the lives of patients. Packing of medications via BFS is ideal for elderly patients, because it is possible to create many different shapes and incorporate premolded, presterilized inserts to achieve a variety of delivery methods. Liquid stick-packs offer versatility in terms of volume and barrier properties, and they are compatible with many different processing and filling methods. They are ideal for liquids and suspensions in particular, because no device is required for measurement or delivery. Both technologies allow for preservative-free formulations and provide single-dose packaging that is convenient, portable, and cost effective.

CONCLUSION

Nonadherence by elderly patients is a significant issue contributing to declining health, greater numbers of hospital admissions, and higher healthcare costs. While there are many factors that contribute to poor geriatric medication adherence, simplification of therapy regimens and easier access to affordable medications have been shown to have a positive influence. Convenient dosing formulations, particularly single-dose options, help reduce dosing errors and can be designed for easy access for patients with limited dexterity and mobility. In addition, blow-fill-seal and stick-pack products can be designed to provide elderly patients with a means for keeping track of when to take and when they have taken their medications. For these reasons, they also offer pharmaceutical companies an opportunity to differentiate their products and better serve their patients. P

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Kevin Haehl is responsible for developing and growing Unither Pharmaceutical's contract pharmaceutical manufacturing business for North America in niche fields such as sterile unit dosage forms using Blow-Fill-Seal technologies and Unistick® single-dose liquid stick-packs, and the strategic leadership of the newly acquired manufacturing site in Rochester, NY. He has over 25 years of broad experience across pharmaceutical manufacturing, sales support, engineering, process development, financial, quality, and supply chain. Prior to Unither, Mr. Haehl held management positions at Evonik and Eli Lilly & Company, and worked in engineering at DuPont.

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CUSTOMER EXPERIENCE: KEY TO GROWTH IN THE OUTSOURCED SERVICES INDUSTRY

BY **GUY TIENE, MA** AND **ROBERT LEEUWENDAL, MSc,** NICE CONSULTING

This article reviews alternative approaches to improve the customer experience that can be taken by both growing and established contract manufacturing organizations (CMOs), and contract development and manufacturing organizations (CDMOs).

In October 2015, **Haig Barrett, Inc**. Management Consultants (Los Angeles) and **That's Nice LLC** (New York) a science agency announced the launch of **Nice Consulting**, a partnership designed to offer strategic and specialized consulting tailored to the marketing needs of life science companies; to help them to drive value in their brands, pricing, competitive positioning and capacity utilization.

Building a client relationship that results in repeat orders and leads to a long-term partnership between the CMO and Sponsor requires the "customer experience" to meet or exceed client expectations. Customer experience is not the same as customer satisfaction, which is often measured. A CMO's ability to respond effectively to a client's needs and demands shapes the customer experience. This article looks at the impact of communications, adaptability, and ways to improve the customer experience.

THE BUSINESS VALUE OF CUSTOMER EXPERIENCE

Customer experience is the product of an interaction between an organization and a customer over the duration of their relationship. This interaction includes a customer's attraction, awareness, discovery, cultivation, advocacy, purchase, and use of a service. It has become evident that, despite the habit in many consumer retail industries to routinely measure customer satisfaction, high customer satisfaction metrics do not correlate with increased customer retention or increased customer referral patterns.[1] In contrast, companies that have been able to successfully implement the customer experience approach have been found to be 4%-8% more profitable than their peers. In these companies, a customer experience metric known as the Net Promoter Score® (NPS®) (e.g., How likely is it that you would recommend our company/product/service to a friend or colleague?) has been implemented successfully, not as a one-off metric, but as a process and system for building a greater customer experience. Research has shown that an NPS acts as a leading indicator of growth (www.netpromoter.com).

So, are the customer experience results from these consumer markets and other B2B industries relevant to the contract manufacturing segment? The answer is a resounding yes. In both our professional/business and private consumer lives, we are continuously exposed to, and demanding for ourselves, increasingly positive customer experiences in buying cycles.[2]

THE DIMENSIONS OF CUSTOMER EXPERIENCE IN THE CMO/CDMO MARKET

Which of the new insights in customer experience are relevant to the CMO industry, and what are some options to improve the customer experience? There are critical differences between large consumer market segments and the customers for CMO services.

[1] In large consumer market segments, customer satisfaction is systematically and routinely tracked, creating consistent observations that, in turn, lead to suggestions for how to improve customer interactions and the supporting processes.

[2] Historically many CMO services have been offered in a project-to-project fashion for particular customers with unique requests, and the value of empirical approaches to improve processes that enhance customer experience is limited.

[3] The CMO-Sponsor relationship often involves specialized staff both from the CMO and customer's organization.

Important dimensions that have shaped the customer experience for decades are cost (obviously), delivery date/supply reliability, and product specifications.

Nice Insight has developed the Customer Awareness (CA) and Customer Perception (CP) scores to further detail what constitutes customer experience dimensions in the CMO market. For purposes of the Nice Insight survey, Customer Awareness describes a potential or current buyer's knowledge of a particular company, product, or service offering. Customer Perception reflects how a current buyer or prospect rates a company based on information he/she has been exposed to, such as marketing materials and word-of-mouth influence, as well as personal experience.

The CP score is based on six drivers in outsourcing: Reliability, Quality, Innovation, Affordability, Productivity, and Regulatory Track Record. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences, as well as barriers to strategic partnerships among buyers of outsourced services.

Other dimensions may include intellectual property, process compliance, and traceability, depending on the complexity of the customer's request.

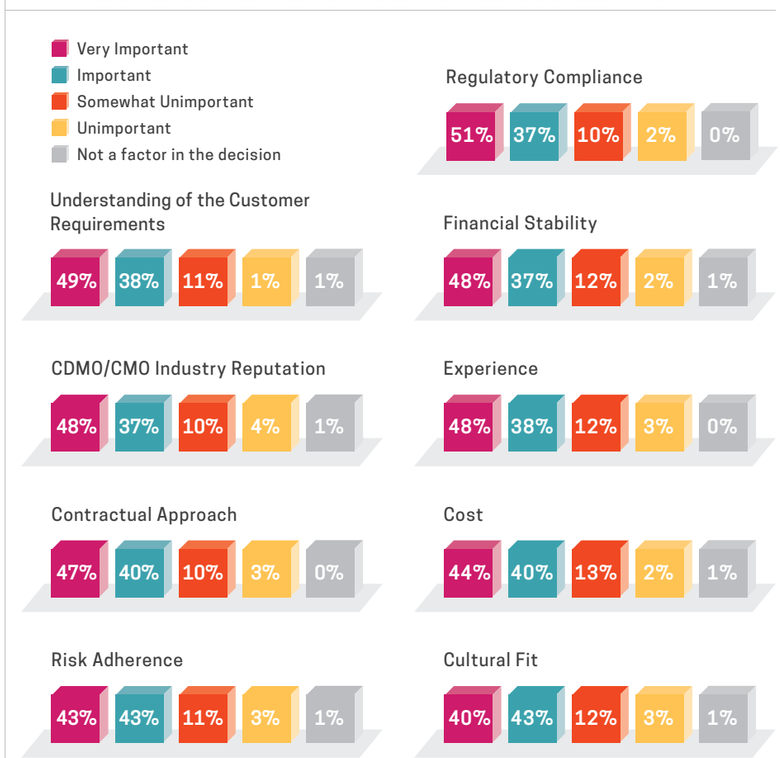
The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to pharmaceutical and biotechnology executives seeking outsourcing on an annual basis. Since 2010, Nice Insight has randomly selected respondents from a group of over 40,000 qualified individuals who are key industry influencers and decision makers to complete its Nice Insight Pharmaceutical and Biotechnology Survey (CRO/CMO/CDMO). Survey respondents answer a range of questions based on their outsourcing needs and behaviors. The data provides ratings of company strengths for providers offering similar services based on various criteria, such as buyer group or service type.

BEING GREAT IN 2016

The 2016 CDMO report includes responses from 587 participants representing Big Pharma and Biotech (36%), Midsize Pharma and Biotech (43%), Small and Emerging Pharma and Biotech (21%), and having positions in C-Suite (39%), Operations, Purchasing, and Drug Development (29%), Quality Assurance/Regulatory (11%), and R&D/Formulation (18%).[4]

The 2016 CDMO Nice Insight report found that 87% of CDMO customers across all customer segments (Big Pharma/Biotech, Midsize Pharma/Biotech, Small and Emerging Pharma/Biotech) look for strategic partnerships, while CDMO selection criteria include hard business requirements for understanding customer requirements, contractual approach, regulatory compliance, and cost (see Figure 1). Post-CDMO engagement satisfaction relies on the "soft" attributes that are related to good communication, being flexible, and the ability to adapt to customer protocols. It is clear that, apart from the great performance in busi-

FIGURE 1 ATTRIBUTES THAT FACTOR INTO INITIAL CDMO SELECTION



ness and manufacturing, a CDMO must also excel in service performance in order to retain strategic partnerships.

THREE CRITICAL FACTORS FOR IMPROVING CUSTOMER EXPERIENCE WITH CDMOS

Analysis of successful businesses in improving customer experience across many different industries tends to point out three critical factors.

[1] Understanding customer expectations during interactions at key touch points. Understanding the expectations of different client functions that are involved, and when they will be participating, is critical. It is useful to map out the "customer journey" to identify the touch points and what customer needs are along the way. It must be emphasized that, although identifying touch points is very helpful, customer experience dimensions transcends this issue. The Nice Insight report also found that cultural differences in how customers and CMOs communicate can be an important factor in making contract or strategic partnership decisions.

[2] Align internal processes to support the desired customer experience. Apart from looking at the customer journey, two key stages in which the customer experience is shaped are during "inquiry to contract" and "order to delivery." In both stages, the quote response time, quality audits, cost estimates, intellectual property and regulatory requirements, and batch validation demand the timely coordination of many specialized functions.

POST-CDMO ENGAGEMENT SATISFACTION RELIES ON THE **"SOFT" ATTRIBUTES** THAT ARE RELATED TO **GOOD COMMUNICATION, BEING FLEXIBLE AND THE ABILITY TO ADAPT** TO CUSTOMER PROTOCOLS.

Smaller CMOs with experienced staff may be able to do with less formal approaches to manage information and collaboration because of their "lean" integrated approach to doing business. Larger CMOs will find the need for being more disciplined in capturing, finding, and distributing information and introducing project management protocols and a "One Voice" approach to customers.

[3] Demonstrate leadership in order to make the necessary organizational changes. Improved organizations are only possible by improving people. While new practices and tools are required, they will only generate results if people make proper use of them. It is the responsibility of leadership to provide the direction and motivate staff to align their thinking and behaviors that will result in better overall customer experience performance. The most common factor in failed improvement initiatives is a lack of frequent and sustained communication.

SHOULD YOU INVEST IN CUSTOMER EXPERIENCE? THREE STEPS:

[1] A first step would be to review where your organization sits on the spectrum of transactional manufacturing relative to customer satisfaction and real customer-experience-based performance. Take into consideration the complexity of your specific CMO business, your competition, and future customer needs. Do you need to shift on the spectrum? Can you articulate the business case for the shift?

[2] Identify your (future) customers needs across the "inquiry to contract" and "order to delivery" stages and use your customer journey mapping to identify the new practices and tools that you need to shift the customer experience. If you conclude that your organization lacks basic project management, consider developing a project management champion. Once basic processes are in place and mastered by a few, you are ready to introduce project management principles throughout the organization.

[3] Appoint a small implementation team to oversee and drive the required changes. Ensure that the team is experienced in driving project management/process change, as first time "DIY" teams have a very high failure rate. P

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THE POWER OF "INBOUND" FOR DIGITAL MARKETING (& SALES!) SUCCESS

BY **AARON MAZZE,** THAT'S NICE

NEXT STEPS

PERSONALIZING MULTICHANNEL MARKETING

1. Consider how inbound marketing can positively transform your marketing to sales hand-off
2. Learn your market thorough market research
3. Set goals for your marketing efforts and tie them closely to your sales strategy
4. Define your ideal customer
5. Develop compelling thought leadership
6. Share your insights on all of your digital channels to build on your brand
7. Measure your results to be sure that what you're sharing is making an impact
8. Nurture your leads through the buyers journey with streamlined automation
9. Strike when the iron is hot and gain those opportunities, using both demand and lead-generation intelligence
10. Delight your customers through personalized / tailored experiences — both in-person and online

FOR OVER 10 YEARS, inbound marketing, as a concept and practice, has been the most effective marketing method for doing business online. In addition to traditional "outbound" marketing methods of buying ad space in print and online with various emarketing tools to nurture leads, inbound marketing focuses on creating content that pulls people toward your company or product.

Developing content to support customer needs and interests increases building awareness and credibility — and inbound traffic to nurture leads and grow your sales pipeline. Many companies do rather well at building awareness but fall short of following through on monitoring and best responding to the course of this customer experience.

Fundamental to inbound (and the outbound that supports it) is the understanding and development of the customer experience for your customer personas — those traits and buying behaviors, internal roles, and personal pain points that define your customer base. Developing content geared toward the needs and interests of unique personas further optimizes your true opportunities for success.

SO WHAT IS INBOUND?

Inbound is all about making a more meaningful connection with your prospects and customers through the creation and sharing of relevant content. By developing content that is specifically designed to appeal to your ideal customers, inbound marketing attracts better qualified prospects to your business like a magnet — engaging and retaining leads in ways traditional advertising can't.

Inbound marketing isn't "automation." It requires action. Deployed correctly, the Inbound Methodology provides a comprehensive approach to managing every interaction and stage of your buyer's journey — from total stranger to happy customer. Your end goal is to achieve and maintain the perfect marketing trifecta of precisely delivering the right content, in the right place at the right time. It takes experimentation and an open mind to learn what works and what doesn't when it comes to your audience. The good news is that there are many tools and best practices shared in the market that can make your inbound efforts easier to facilitate, monitor, and manage. P

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GOOD LABORATORY PRACTICES LEAD TO GOOD MANUFACTURING IN CDMOS

→ BY **CHRISTOPHER CONWAY** AND **RAJESH SHENOY**, ALBANY MOLECULAR RESEARCH INC.

With quality ranked as the main driver for contract development and manufacturing organization (CDMO) selection, the organization that consistently delivers is likely to be a key market player. In order to consistently provide high-quality products and services, certain CDMOs are placing an emphasis on Good Laboratory Practices (GLPs) that can be readily scaled to Good Manufacturing Practices (GMPs).

This article focuses on tech transfer in relation to strategic partnerships, with Albany Molecular Research Inc. (AMRI) as an example of an organization that feeds its commercial pipeline through robust capabilities in drug discovery and early phase development.

Although the pharmaceutical industry is experiencing record growth, the market size has narrowed. Globally, the pharmaceutical industry is valued at approximately $300 billion per year and is likely to grow to $400 billion within three years. Over thirty percent of this market is dominated by ten drug companies. This situation has translated into a market shaped by mergers and acquisitions (M&A). Contract discovery, development and manufacturing organization (CDMO) AMRI has contributed to this trend in a big way, announcing six acquisitions from 2014 through 2015. As a leading CDMO that has emerged fighting for greater market share, AMRI is looking to gain customers by forming strategic partnerships based on trust and emphasizing attention to quality, beginning with the use of Good Laboratory Practices (GLPs).

In Nice Insight's 2016 CDMO Outsourcing survey of nearly 600 outsourcing-facing pharmaceutical and biotechnology executives (2016), 60% of respondents indicated that they are very interested in strategic partnerships. As the dependence on outsourcing continues, the contract development organization that can position itself through partnerships will win out in the long-term.

LEVERAGING STRATEGIC PARTNERSHIPS

Building a successful strategic partnership begins with an understanding of the customer. Although large and mid-sized pharma, small biotechs, virtual companies and academia have many different needs and concerns, they do share a number of universal expectations for outsourcing experiences: partnerships that provide quality products and services at reasonable price points. Customers are attracted to organizations that produce products efficiently and who uphold the confidentiality of client molecules from start to finish. Timelines are also key; providers that can guarantee the availability of appropriate equipment, provide minimal batch cycle times, begin preparatory work before startup and implement timely release testing and QA review procedures will be viewed favorably.

Additional results of the same 2016 study by Nice Insight reinforce the importance of the above attributes when clients are selecting CDMOs. Quality was rated as the top factor by an overwhelming majority of 70%. Reliability, innovation, productivity, a positive regulatory track record and affordability also influence the CDMO selection process. These qualities define themes that are universally acknowledged in any strong business relationship and are expressed through trust, transparency and skill.

GLP LEADS TO GMP

The skill to take a molecule from the discovery phase into development is greatly dependent on the use of effective and appropriate laboratory practices. Early phase development performed diligently and with a view toward scale up in a reliable and safe manner significantly increases the likelihood of a successful commercial launch from the outset.

The organization that has a demonstrated history of employing Good Laboratory Practices is in a position to be highly successful at GMP; good work in the lab being a key stepping-stone to good work as a contract manufacturing organization. As an outsourcing services provider offering contract research, development and manufacturing support to the pharmaceutical industry, AMRI's GLP practices have been integral to its capabilities in medicinal chemistry and drug discovery for 25 years. By employing a heightened focus on early phase optimization to ensure easier scale-up, AMRI demonstrates the concept that GLP facilitates

PHARMACEUTICAL INDUSTRY IS VALUED AT **$300B PER YEAR** AND IS LIKELY TO GROW TO **$400B WITHIN THREE YEARS.**

COMPANY HIGHLIGHTS

AMRI TECHNICAL TRANSFER

For AMRI, tech transfer usually begins when a customer requests small-volume GMP manufacturing services for early phase clinical trials; projects can last from six months to a year, depending on the complexity of the chemistry. Taking extra time during this step ensures that scale-up to large-volume GMP production will be smoother. Both analytical and synthetic chemists are involved in the process development effort to ensure the simultaneous development of optimal manufacturing processes and the most appropriate analytical methods for them.

If early-phase clinical trials are successful, larger volumes of the API will be required for late phase trials, which require a transition to larger scale GMP manufacturing. A team effort involving process engineers and related operational technology as well as other experts (QA/QC, Regulatory, etc.) is established to ensure that validation and commercial manufacturing go smoothly.

This transition is the basis of AMRI's business model: to feed the pipeline through both discovery and chemical development. Initial due diligence of a program extends to a host of measurable successes. With a success rate of approximately 40%, AMRI's **API manufacturing** pipeline includes 50 compounds in Phase I and II and 14 in Phase III, with 27 DMFs and 148 commercial products. On the **drug product** side, there are 69 aseptic fill finish products in Phase I and II, 21 in Phase III, with 23 under regulatory review and 17 in commercial production. This success rate attests to the importance of diligence during the initial development efforts. An increased rate of scale-up success is linked to attentiveness during discovery and partially attributed to the fundamental controls available at the laboratory scale.

API COMPOUNDS

50	PHASE I AND II
14	PHASE III
27	DMFs
148	COMMERCIAL PRODUCTS

DRUG PRODUCTS

69	PHASE I AND II
21	PHASE III
17	COMMERCIAL PRODUCTION

GMP manufacturing. It may seem reductive, but when going from small-scale to large-scale, it pays to get things right initially; devoting more time early in the process development phase ensures that commercial batches are developed efficiently.

Indeed, efficient timelines are only one facet of successful CDMOs. The capability to develop and manufacture drug intermediates and Active Pharmaceutical Ingredients (APIs) at different scales is a key component of an effective program that is designed to meet various customer needs. AMRI intentionally established its small-scale GMP manufacturing group to address not only the paramount need for smooth tech transfer and facile scale-up of laboratory processes, but to provide small-scale GMP facilities for the production of small-volume APIs, such as highly potent cytotoxics and controlled substances. CDMOs that have such GMP capabilities located side by side with chemical development are positioned to best leverage their services for customer success.

TRANSPARENT COMMUNICATION

Of course, there are aspects of discovery, development and tech transfer that are universally challenging across all operations. In situations where a potential issue may arise, transparency stands out; it is better to work up front with customers and explain what might affect their programs later on. This approach mitigates any chances of surprise or upset; challenges are discussed before any chemistry has been performed. Open, two-way communication is central throughout each phase of a program and is essential for truly collaborative efforts. For example, at AMRI, project managers often communicate daily with customers. True transparency and the sharing of data, successes -- and failures -- openly and quickly build trust and enhance the overall program and customer-provider relationship.

CDMOs with advanced methodologies and the ability to develop optimal and readily scalable processes in minimal time gain the confidence of their customers. They also adopt leadership roles and are typically viewed as ideal strategic partners. Sponsor companies, whether big pharma or small biotech, are looking to their outsourcing partners to provide knowledge and guidance. Successful CDMOs are responding with the development of proprietary technologies or the acquisition of specialized expertise (through M&A and/or the hiring of subject matter experts).

Expertise is in no way one-sided, of course, and generally symbiotic relationships are established between clients and their strategic CDMO partners. The benefits of such interchanges are realized over time; a CDMO with years of experience working on hundreds of programs and numerous chemists on staff is more likely to identify unique solutions that a pharmaceutical company completely focused on drug discovery has overlooked.

Leading CDMOs have an extensive array of successfully completed projects that serve as a foundation for future success and enable efficient problem solving. Indeed, CDMOs that have a demonstrated history of employing a GLP approach to development work while considering the ultimate needs for commercialization will clearly be best suited for these types of relationships. Furthermore, collaborative strategic partnerships with such CDMOs reduce the risks typically associated with outsourcing performed through transactional relationships with tactical suppliers.

AMRI has evolved over the last quarter century as a leading CDMO and continues to do so, encouraging its employees to expand their areas of expertise while also bringing in new and different skill sets. Once focused on discovery, the CDMO is now positioned to provide support from discovery through development and commercial production, and has plans to add further capacity.

This commitment to expansion was mostly recently demonstrated with the opening of AMRI's Buffalo facility, which addresses the key market need for U.S. integrated drug discovery. AMRI's integrated drug discovery expertise in Buffalo – which also includes proprietary informatics that enable increased data analysis for accelerated process development, combined with its diversified chemical development capabilities, ensures that product knowledge is not only captured, but maintained at all levels of the organization and throughout a project's lifecycle. It is this highly collaborative approach to project management/technology transfer that advances lead compounds through the drug development process, from bench scale to commercial production. P

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PATIENT SAFETY AND PARENTERAL DELIVERY SYSTEMS

→ BY **MARGA VIÑES,** GRIFOLS INTERNATIONAL, S.A.

As active pharmaceutical ingredients (APIs) become more sophisticated, drug delivery options have followed suit. Innovations in intravenous administration have contributed to an increase in patient safety.

The premixed bag, an updated parenteral option, benefits manufacturers, caregivers, and most importantly, patients. This article describes the difference between leading parenteral drug delivery options with an emphasis on safety. The advantages of premixed parenteral delivery are considered in regards to overall patient and administrator benefit. The paper also discusses the importance of selecting a highly capable contract development and manufacturing organization in order to bring a parenteral product successfully to market.

DOSAGE FORM OPTIONS

Intravenous administration is the most common parenteral administration route, providing an immediate therapeutic effect by delivering a drug directly into circulation. Small-volume parenterals (SVP), those with a volume of less than 100 mL, and large-volume parenterals (LVP), 100 mL or greater, are both used for the intermittent or continuous infusion of fluids or drugs.

Injectable dosage forms are the preferred formulation of large molecule drug products, traditionally delivered via the intravenous (IV) admixture. A drug delivered intravenously is pumped directly into a patient's circulatory system and takes effect immediately. An admixture is dried or lyophilized drug product, packaged in a glass vial or ampoule. In order for a patient to imbibe the admixture, the dry powder concentrate must be diluted.

Premixed bags, however, can be injected into a patient without any mixing; they are packaged in plastic bags and ready-to-use. These premixed IV solutions eliminate the need for human intervention in the drug product and are therefore the safest option for administration.

REDUCING RISK DURING DRUG DELIVERY

It is unsurprising that admixtures pose a risk to patient safety. The opportunity for error is present throughout all stages of the process, from preparation through to dose calculation and injection. A lack of control when reconstituting the admixture powder is one opportunity for error. In this situation, the patient is solely reliant on their clinician, pharmacist or nurse to create an identical formulation repeatedly. The training and ability of this individual is an immense variable, as are the circumstances under which dilution and dosage calculation occur.

The margin of error this causes has been acknowledged as a critical issue among medical professionals. The Institute For Safe Medication Practices National Medication Error Reporting Program (ISMP-MERP) frequently receives reports regarding IV admixtures. An observational hospital study confirmed that at least 1 in 10 of these parenteral products were improperly prepared.[3]

The more complicated the solution, the greater the margin of error – nutritional injectables gleaned an alarmingly high error rate of 37% when prepared manually.

THESE PREMIXED IV SOLUTIONS **ELIMINATE THE NEED FOR HUMAN INTERVENTION** IN THE DRUG PRODUCT AND ARE THEREFORE **THE SAFEST OPTION FOR ADMINISTRATION**.

Even when preparation was partially automated, formulations had a 22% error rate. The State of Pharmacy Compounding Survey, conducted in 2009, found that 30% of hospitals had experienced a patient event attributed to an admixture compounding error over a period of 5 years. The use of premixed IV solutions could have reduced such life threatening or damaging incidents.[2,3]

ADVANTAGES OF THE PREMIXED IV SOLUTION

In order to ensure patient safety, the ISMP recommends the use of commercially prepared premixed bags over manually compounded sterile products. Similarly, opting for premixed bags as opposed to admixtures ensures compliance with the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) standards and U.S. Pharmacopeia 797 guidelines. These guidelines state: **[1]** medications should be available in ready-to-administer form whenever possible; **[2]** drug concentrations should be standardized; **[3]** medications should be available to meet patient needs when the pharmacy is closed; and **[4]** preparation of admixtures by nursing staff should be minimized.[1,4]

By eliminating the need for admixtures, premixed bags manufactured in a cGMP compliant facility provide the highest level of safety available. In addition to reducing the risk of medical error, premixed bags greatly decrease the threat of microbial contamination. Admixtures prepared in pharmacies are particularly vulnerable to process contamination. This is due to inconsistent staffing and the variant environment of the compound area; variables that are eradicated when using premixed bags.

Premixed bags produced in facilities that are highly automated, in addition to meeting all other requirements, benefit from an assured level of quality. This is attributed to minimal human intervention, a low chance of container manipulation and accurate labeling. Received directly from the manufacturing organization, premixed bags ensure little opportunity for the mislabeling of the final product or illegibility – often a source of confusion or cause of mistakes with admixtures. Prior to shipment, the manufacturer of the premixed product further confirms its

COMPANY HIGHLIGHTS

GRIFOLS INTERNATIONAL, S. A.

Grifols is a global healthcare company with a 75-year 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 and its headquarters are located 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.

constancy through a series of required tests. The physical, chemical, biological, microbiological and functional attributes of the product are evaluated for the ability to function in diverse environments, including those with low humidity.

GROWTH OF THERAPEUTIC CLASSES

The demand for premixed solutions is therapeutically led. Premixed IV solutions are the preferred mode of delivery for antibiotics globally – a market segment that continues to grow. The world's usage of antibiotics has risen approximately 36% since the year 2000.[5] Pain management and cardiac medications, regularly delivered intravenously, also contribute to the demand for premixed bags.

Packaged in plastic to ensure flexibility, premixed solutions deliver a fixed dose in 50 mL to 1 L containers. The bags are terminally sterilized, aseptically filled or aseptically filled and frozen, again to guarantee the utmost safety. This specific dose feature not only guarantees that the patient receives an accurate amount of drug product, but also helps reduce waste. Another positive outcome of premixed solutions over admixtures is that reasonable dosage limitations are likely to encourage providers to write more cost-effective orders. Additionally, admixtures must be used within 24 to 48 hours – premixtures can be utilized up to two years or more. This enhances the hospital's ability to manage stocks and increases patient treatment options on-hand.

CDMO SELECTION FOR PARENTERAL DRUG PRODUCTS

Deciding between admixture and premixed IV solutions is dependent on the intended use of the drug product and most importantly, how each form will aid patients, with an emphasis on safety. Administrators must also consider the level of efficiency and convenience associated with each; the pros and cons of either is a deciding factor when developing and manufacturing parenterals.

It is both complex and costly to advance a parenteral drug product. In order to achieve success in this area, a range of specific requirements must be met. This includes expertise, resources, technology, market knowledge, a highly sterile environment and automated facility as well as aseptic manufacturing conditions. In order to reap the benefits of manufacturing parenterals without assuming the majority of the risk, sponsors are tasking specialized contract research and development organizations (CDMOs) with switching drug product from in-vial admixture to a premixed IV bag.

CDMOs have experience meeting regulatory specifics worldwide, are versed in parenterals throughout the product lifecycle and can provide strategic advice needed to go to market. Sponsors are engaging in the outsource trend, preferring to work with an organization that is equipped to take the product from start to finish. CDMOs with this capacity can take a parenteral into the commercial market from development. As innovations in delivery – exemplified by premixed bags – arise to meet the growing interest, selecting a CDMO is often the most economical and informed decision that a sponsor driven by growth can take. P

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ADVANCING BIOLOGICS DEVELOPMENT AND MANUFACTURING

→ BY **GUSTAVO MAHLER**, CMC BIOLOGICS

The vigorous growth of the biopharmaceutical market has boosted the demand for biopharmaceutical contract manufacturing services.[1] Today, pharmaceutical and biotechnology companies outsource a broad spectrum of services from early-stage drug development (e.g., cell line, process, analytical, and formulation development) all the way to commercial-scale manufacturing. The outsourcing decision is often made by the need to expedite research and development, shorten the time to market, gain access to novel technologies and regulatory expertise, and minimize risks, at competitive cost.

Complexity in biologics development and production, an obligation to better understand the product, and implementation of quality by design (QbD) have driven drug innovators to engage with their contract manufacturers much earlier than prior conventional practice. This shift in buyers' behavior has given rise to the contract development and manufacturing organization (CDMO). Generally, a full-service CDMO offers a comprehensive set of services that connect all the aspects of the development stage of drug production through to commercial manufacturing in an integrated process, whereas traditional contract manufacturing organizations (CMOs) focus mainly on large-scale manufacturing. To some degree, an experienced CDMO can serve as a one-stop-shop for drug innovator development and manufacturing needs.

BIOLOGICS MARKET EXPANSION

The debut of the first recombinant protein, human insulin, in 1982 marked a new era of modern medicine: therapeutic biologics. Biologics have profound clinical performance and a better regulatory approval rate than small-molecule drugs. They can generally offer better efficacy and thereby command a high premium price. Together these major boons have pushed therapeutic biologics into the center of drug discovery and development. The development pipeline for biologics looks strong: the U.S. alone hosts over 900 clinical-stage biologic molecules targeting more than 100 diseases.[2] In the last two years, FDA's Center of Drug Evaluation and Research (CDER) has approved record-high numbers of novel medicines since 1996 with 41 in 2014 and 45 in 2015. The number of new biological approvals is also steadily increasing: 13 new therapeutic biologics were approved in 2015, up by 2 from 2014. Additionally, nine of them were recognized as "First-In-Class," an indicator for the innovative nature of a drug.[3, 4] The innovation in biologic therapeutics is unlikely to slow down any time soon.

The fervor in searching for new biological entities (NBEs) is undoubtedly linked to the revenues already realized in the market. The biopharmaceutical market has experienced robust growth in recent years and the momentum continues to build. Being the fastest-growing sector of the pharmaceutical industry, the global biopharmaceutical sales generated a revenue of nearly $162 billion in 2014, accounting for about 20% of the entire pharmaceutical market.[5] In the same year, 7 of the 10 best-selling prescription drugs in the world were biologics earning a combined revenue of more than $60 billion.[6] By 2020, this market is expected to reach approximately $278 billion at a current compound annual growth rate (CAGR) of 9.4%, twice of the overall pharma market growth rate.[1, 5]

To date, most development-stage and marketed biopharmaceuticals are protein-based products with monoclonal antibodies (mAbs) leading the market growth, followed by recombinant proteins. Niche specialty areas, such as antibody-drug conjugates (ADCs) and bispecific antibodies are also gaining attention. Of the top 10 best-selling biological drugs of 2014, five were mAbs (Humira – No. 1, Remicade – No. 2, Rituxan – No. 3, Avastin, and Herceptin). Four recombinant proteins (Lantus, Enbrel, Avonex, and Neulasta) and one vaccine (Prevnar) made up the remaining five.[7] The majority of these top-selling biopharmaceuticals are used in two therapeutic areas: five for autoimmune diseases (Humira, Remicade, Rituxan, Enbrel, and Avonex) and three for cancer and cancer-related diseases (Avastin, Herceptin, and Neulasta). In the next few years, breakthroughs in immunotherapy, gene, and cell therapy will bring more novel, diversified biologics into the market.

In addition, the biosimilar market is expected to gain significant growth in the next five years, especially in the U.S. By 2020, most of the top-selling biologics will fall off patent, which opens up tremendous opportunities for the biosimilar market. As a result, innovative pharma and biotech companies have entered competition with generic manufacturers to develop biosimilars. The United States is slower in adopting biosimilars than other developed countries. 2015 was a turning point for the U.S. biosimilar market: the FDA approved its first biosimilar drug, Zarxio, which was developed by Sandoz, the generic branch of Novartis. It was launched six months later at a 15% discount to its reference drug, Amgen's Neupogen.[8] With a regulatory framework in place and 29 biosimilars currently in clinical trials, more biosimilars will launch in the U.S. market in the coming years.[9] Overall, the global biosimilars market is expected to grow rapidly in the next five years at a CAGR of 22.1% and reach $6.22 billion by 2020.[10]

DEVELOPING BIOLOGICS REQUIRES STATE-OF-THE-ART FACILITIES AND AN ARRAY OF TECHNICAL AND OPERATIONAL EXPERTISE

Unlike small-molecule drugs, which contain active pharmaceutical ingredients (APIs) with well-defined chemical structures, biopharmaceutical APIs do not always have well-defined or even static structures. These molecules are hundreds to a thousand times larger than small molecules with inherent structural instability, which poses a constant challenge to the production process. In addition, the biopharmaceutical manufacturing process is more complex and costly to develop, operate, and maintain than the chemical process for small molecules. Successfully developing biologics requires a combination of state-of-the-art facilities and a broad array of technological and operational expertise.

With more biological products and biosimilars entering the market, the competition within the biopharmaceutical sector will continue to be fierce. Biopharmaceutical makers strive to reduce manufacturing cost, improve process efficiency, deliver high quality and efficacy, and accelerate speed to market. The latter is more critical for biosimilar developers. As for

COMPANY HIGHLIGHTS

CMC BIOLOGICS

CMC BIOLOGICS, A GLOBAL FULL-SERVICE CDMO FOR BIOPHARMACEUTICALS, IS WELL-VERSED AND EXPERIENCED IN THE AREA OF BIOPHARMACEUTICAL PROCESS DEVELOPMENT AND MANUFACTURING. Founded in 2001, the company is one of the twenty CMOs in the world that manufacture biologics, according to Eric Langer and Ron Rader of BioPlan Associates.11 Over the course of 14 years of operation, CMC Biologics has successfully developed more than 120 mammalian, bacteria, and yeast-based products for pre-clinical studies through commercial production. Some of the monoclonal antibodies (mAbs) were developed through a complete suite of services from clone development to delivery of commercial-scale cGMP manufacturing processes. CMC Biologics' remarkable strength in mAb development is attributed to two technologies: the proprietary CHEF1® expression system and the 2.012 Accelerated Monoclonal Antibody Development Platform, which allow CMC Biologics to deliver 500g of a monoclonal antibody manufactured under cGMP in just 12 months.

Another strength of CMC Biologics lies in its industry leading in-house analytics capabilities, which is somewhat rare as many CMOs outsource analytics development to the third parties. Analytical characterization is critical for the preparation of comparability data and the Chemistry, Manufacturing, & Controls (CMC) section of regulatory filings. CMC Biologics has extensive experience in developing and validating analytical methods for a wide range of proteins, including mAbs, Fc-fusion proteins, enzymes, growth factors, glycoproteins, and novel recombinant constructs as well as for a variety of functions, including product release, product characterization and process development support. Within CMC Biologics, the analytical unit is highly integrated into a comprehensive process development and manufacturing program, resulting in direct and efficient communications internally as well as with clients. This structure also allows fast trouble shooting and problem solving thus eliminating any unnecessary lag in development time.

In order to better serve biopharmaceutical clients and meet evolving market demands, CMC Biologics invested in state-of-the-art clinical and commercial manufacturing facilities and has strived to expand their expertise into niche areas. For instance, in October 2015, the company entered an agreement with Immunocore Limited for process transfer, scale-up and commercial-scale manufacturing of IMCgp100, a novel first-in-class cancer immunotherapeutic based on proprietary platform T-cell receptor (TCR) technology. In this partnership, Immunocore will benefit from CMC Biologics' extensive expertise in microbial manufacturing and their ability to meet aggressive clinical and commercial manufacturing timelines. For CMC Biologics, they will gain first-hand experience in manufacturing the first drug of a novel class of biologics — ImmTACs.

> "CMC Biologics remains vigilant in addressing growing market demand in Europe and the U.S. for increasingly scalable biologics production, states Gustavo Mahler, CEO of CMC Biologics. Combining capacity with our proprietary technologies allows us to best serve customer needs for meeting market demand for critically needed medicines. Likewise, our company maintains a healthy corporate stability and profitable growth ensuring our continued ability to invest and grow with the market."

biopharmaceutical CMOs/CDMOs, they have to be agile in adopting technological advances in order to lead process innovation and operational efficiency. As the industry is gradually shifting away from large scale production (10,000 – 20,000 Liters) to smaller scales for more niche and targeted therapies (e.g., personalized medicine), flexibility in operational capabilites, production scales, and multiple-product operations can be a great advantage for CMOs/CDMOs.

PERFUSION MANUFACTURING

Another trend in biomanufacturing is the increasing adoption of continuous bioprocessing with perfusion being the leading technology. The advantage of continuous bioprocessing is evident. First, in a perfusion system, cell culture lives in consistent optimal conditions with a constant flow of media and removal of waste. High cell density (i.e., 100 million/mL) can be achieved and operated for extended periods, resulting in higher volumetric productivity than traditional fed-batch manufacturing. The product is harvested continuously, enabling continuous downstream purification at a small scale. Second, continuous bioprocessing is more capital-equipment efficient. Perfusion bioreactors are smaller in size, requiring less space, infrastructure, utilities, and labor. Third, perfusion technology is quite flexible and can be adapted to various cell types and applications, including vaccine, mAb, and cell therapies (e.g., stem cells).[12, 13]

There are two major factors in adopting perfusion manufacturing. First, perfusion processes require more process knowledge, equipment, and technology. Second, as a result of the increased need for highly specialized technical equipment, perfusion-based manufacturing is more complex from a development, manufacturing, and regulatory perspective than fed-batch bioprocessing.[13] Assisted by CMC Biologics' expertise, these challenges can be managed with good science, experience, advanced analytics, and technical expertise. The biopharmaceutical industry is going to see more advances in perfusion technology, as well as wider adoption of continuous bioprocessing in the future. CMC will be at the forefront of these advances as it continues to develop innovative perfusion processes for its clients. P

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Chief Executive Officer and President

Gustavo Mahler, PhD, joined CMC Biologics in 2008 as president. In 2010, he was named global Chief Operations Officer and in January 2016 he became Chief Executive Officer. Prior to joining CMC Biologics, Gustavo worked for 15 years at Bayer in the United States, Europe, and Latin America, serving in various manufacturing and general management positions. He received his PhD in biochemistry from the University of Buenos Aires, and he also has a master of business administration degree from the University UNED of Madrid and an executive certification in management from MIT Sloan.

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