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CDMO STRONG CMO/CDMO MARKET OUTLOOK FOR 2016, BUT BEWARE MODERATING FACTORS
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 outsourcing 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 contract service. Whether you agree or disagree, please share your feedback.
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 their 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 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 Sherya, 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 facilitate 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 CDMO/CROs 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 Hoevin’s VP of R&D Filip Gasper, General Manager INU, USA Marco Gi, and Head of Continuous Manufacturing R&D Nuno Matos.

[6] Syed T. Husain, Chief Commercial Officer at Allipharma 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, other 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 Frye, 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] GMC Biologics President and CEO Gustavo Maher 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 Margalit Moss, Business Development Manager for Contract Manufacturing with Geffols 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.

[11] Guy Tiene, Director of Strategic Content and Robert Leonowens, 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 critical 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 ECO Annette 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 CDMO/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 Mazz, 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.

SPECIALIZED EXPERTISE ESSENTIAL FOR PHARMACEUTICAL OUTSOURCING PARTNERS

INTRODUCTION Pharma’s Almanac

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FOR PHARMACEUTICAL OUTSOURCING PARTNERS

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ESSENTIAL FOR PHARMACEUTICAL OUTSOURCING PARTNERS

BY CYNTHIA A. CHALLENER PH.D., THAT’S NICE

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.
### OPPORTUNITIES ABOUND FOR CONTRACT SERVICES IN 2016

**BY NOGEL 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 shape 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 pipeline and largest numbers of drug approvals seen in many years. While these successes are leading to greater investment in internal production facilities and MA&VA 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 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 manufacturing organizations (CMOs 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 synthesis require the use of low-temperature or hazardous chemicals
- 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 Administration (FDA). 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 has never been more apparent. 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 hope of streamlining 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.

[1] CMOs/CDMOs that employ automated processing and/or analytical solutions offer integrated services across discovery, development, and manufacturing, leading to more consistent products and processes. CMOs/CDMOs can achieve reduced resource consumption and greater efficiency for lower operating costs. Smaller footprints and the elimination of storage capacity can result in lower capital costs. Scale-up is simpler and more flexible, 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.

[2] 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.
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.

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 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 AAI Pharmaceuticals, are 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 Research’s 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 & MORE

CMOs/CDMOs/CMOs can find additional opportunities for expanding their client base by providing services that support branded biopharmaceutical and biosimilar developments, formulation, and manufacturing. Outsourcing partners with flexible, small-scale manufacturing facilities, designed to provide safe, efficient acceleration to 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 stiller competition though, with a limited number of large, 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 design to ensure the rapid development of cost-effective, robust processes, yielding high-quality, safe, and efficacious medicines will end up as winners in 2016.

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 (CISD), while seeking ways to better serve public and patient communities by reducing 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.

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In 2014 for example, Cambridge Major Laboratories, a full-service CDMO, combined with 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.

**OUTSOURCING PARTNERS OFFER CONSIDERABLE CHALLENGES**

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 mechanism 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 spent more than $50 million on outsourcing has remained fairly stable over the last three years (24% to 23%) 2013-2015. The 2016 survey shows that 43% spend $1-100M 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%).

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.

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 molecular clinical and commercial products.

The new facilities and equipment complement the CMOs dosage-form capabilities, which include minitabs, pediatric products, sublingual tablets, extrusion granules, and extrusion spheronization. Extrusion spheronization makes spheroïds uniform with dense granules for enteral market, including quality concerns, 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.**

**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.

Outsourcing parenterals is anticipated to increase and continue to benefit established companies in this market.

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 coordination and 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 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 soluble 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 parenteral biologic drug products. Sponsors expect advanced filling lines that can rapidly identify and characterize particles 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 prescriptive 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.

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**REFERENCES**

4. Morell T. Continuous Investment in Advanced Oral and Parenteral Drug Delivery Technologies. AAICML 03.15.16 Malaci Liacam Malalac
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 integrating these capabilities into fully integrated service providers. 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 differentiated, advanced technologies.

Effective process development in, in fact, essential for achieving cost-effective, robust biopharmaceutical manufacturing operations. In particular, processes designed with scale 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 efficiency 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 methods 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 via demonstrated viral inactivation—+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.

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, characterizing enough to model equipment at a site of choice. Laboratory-scale cell culture is carried out in shake flasks, and 2L and 15L bioreactors, Pilot-scale runs are performed in a 200L stainless bioreactor. All bioreactors maintain the aspect ratio and impeller design used at manufacturing scale. Future capabilities will include 200L disposable bioreactors. Upstream analytics include Viscell, Ysi, BCA, and Cedex BioHT.

Recovery is accomplished with a centrifuge and scaled-down filter train. Purification is performed using AkaPure, Pilot, or Bioprocess skid, depending on the scale. Filtration development is facilitated by automated data capture. UF/DF development is aided by an automated custom skid that is configured to simulate manufacturing scale. Downstream analytics include HPLC, SDS-PAGE, and CCE. The lab capabilities include process development, characterization, process-scale-up, small-scale process validation, and performance of viral clearance studies. Demonstration lots and Toxicology lots are typically performed at 200L scale.

Viral safety consultation is also available as a standalone service. Using a customized approach, GSK can provide dedicated technical consultation on facility segregation, study design, and regulatory documentation support.

GlaxoSmithKline Biopharmaceuticals serves as a manufacturing knowledge center, enabling the launch, supply, and management of GSK biopharmaceutical products around the world. We leverage these capabilities to provide contract manufacturing services with market-leading quality, cost benefits, and timelines.

We have the proven history, technologies, facilities, systems, people, and corporate support you need to get your biologics products into development and out to patients efficiently, and with maximum safety and quality.

• Independent business of GlaxoSmithKline
• Support GSK and external customers with drug substance (DS) and drug product (DP) manufacturing
• Two facilities in the U.S. for biologics
• DD production (fermentation and cell culture)
• State-of-the-art process development laboratory
• Two facilities in Europe for formulated DP manufacturing
• Fully integrated supply chain support

As a CDMO that operates as an independent business within a large pharmaceutical company, GlaxoSmithKline Biopharmaceuticals offers many advantages to manufacturers looking for a strong, stable partner with extensive experience in biologics development and commercialization, and access to expansive resources, including a wide range of analytical capabilities and in-depth regulatory expertise.

In 2014, a state-of-the-art process development laboratory was commissioned in Rockville, Maryland. The laboratory was specifically engineered to model manufacturing-scale equipment at GSK but flexible enough to model equipment at a site of choice. Laboratory-scale cell culture is carried out in shake flasks, and 2L and 15L bioreactors. Pilot-scale runs are performed in a 200L stainless bioreactor. All bioreactors maintain the aspect ratio and impeller design used at manufacturing scale. Future capabilities will include 200L disposable bioreactors. Upstream analytics include Viscell, Ysi, BCA, and Cedex BioHT.

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COMPANY HIGHLIGHTS

GLAXOSMITHKLINE BIOPHARMACEUTICALS

“DEVELOPING AND MANUFACTURING YOUR PRODUCTS LIKE OUR OWN”
Scale-down models, which can mimic and predict large-scale operations, are instrumental in the characterization and validation studies, including media stability, generation of Cells at the Limit (CALs) of in vitro Cell Age (VICAs), 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 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 mini-screening 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 public 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 processes that can then be used to further explore the process operating space without the need for additional experimental 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.

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Greg Flyte is the Director of Contract Manufacturing Organization (CMO) Alliance & Program Management at GlaxoSmithKline (GSK). He brings over 18 years of technical and business experience in engineering, validation, process development, alliance/project management, manufacturing operations, and business development. During his 16 years at the Rockville, Maryland, USA site (14 with Human Genome Sciences, which was acquired by GSK in August 2013), Greg has also been involved with managing the design through validation phases during the construction of all of GSK’s manufacturing facilities, in addition to managing the large-scale manufacturing (LSM) facility validation team from inception through commercial production. He holds a BS in chemical engineering from Drexel University.

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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 systems and technologies, manage all forms of shipment and information, and allow the sponsor to avoid the need to obtain import licenses for every country.

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

EXISTING SYSTEMS HAVE MANY LIMITATIONS

Supply chains managed by third- and fourth-party clinical logistics organizations (CLOs) need to include interactive response technology (IRT) and other advanced IT systems. Supply chains must be more effective and efficient, and their reliability must increase. 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 efficiency and to 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment 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 systems and technologies, manage all forms of shipment and information, and reduce waste and inefficiencies in the global supply chain.
### 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 delivering clinical trial materials. First, gene- and cell-based bio-hazardous materials require specific 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; deliver within short timeframes to the manufacturing site for patient-specific drug product preparation, and final delivery back to the patient for treatment in 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 meeting 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 (EDCs) 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 ability 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 and regulators believed that the use of lower-cost facilities and in-home testing (which would be facilitated by direct-to-patient material delivery and home treatments) and increased use of mobile technologies and EDCs.

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.”

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. 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.

### REFERENCES

2. Sacks L. , “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. Sacks L. , “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.”
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In many cases, contract development and manufacturing organizations (CDMOs) play a critical role in facilitating the successful development of innovative small-molecule drug candidates, since the 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 seen as essential partners in the global API market.

DEMAND FOR SMALL-MOLECULE DRUGS REMAINS STRONG

Small molecule drugs accounted for 84% of pharmaceutical industry revenues in 2014. In addition, small-molecule drugs still account for the majority of molecules in 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. This strong demand for HPAPI manufacturing services is having significant impact on the contract manufacturing market. Companies with existing HPAPI capabilities have been expanding their facilities, while many without have sought to acquire existing businesses or add HPAPI capacity. HPAPI manufacturing services offered by CDMOs today are seen as essential partners in the global API market.

DEMAND FOR CDMO SERVICES OFFERING HIGHLY POTENT API (HPAPI) MANUFACTURING SERVICES

Another area of strong demand for innovative small-molecule drug development services is in the highly potent API (HPAPI) segment. HPAPIs make up one of the fastest-growing segments of the global API market. Ash Stevens supports all aspects of drug substance development and CDMO manufacturing, from de novo process development to commercial API production. The company’s state-of-the-art manufacturing facility located in Riverview, Michigan is an FDA-regulated facility and has the capability to develop and manufacture APIs from grams to batch sizes up to 250 kilograms. In addition, Ash Stevens is a fully GMP-compliant operation, offering regulatory support spanning early stage drug substance development through NDAs and post-approval manufacturing. The company’s history of successful HPAPI inspections by the FDA and European authorities includes many successful inspections by the U.S. FDA and those in the European Union (EU), Australia, Japan, Korea, and Mexico. The company offers expert services for managing regulatory filings according to current standards. Pre-approval inspections (PAI) for the last three API manufacturing approvals did not generate any form 483.
IN 2014, 84% OF PHARMACEUTICAL DRUGS SMALL-MOLECULE is most efficient when integrated with process development and optimization services, which generally include syntheses to cGMP processes. Development pathway going from laboratory chromatographic purifications. Consequently there exists a growing gap in the API asements 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.

GROWING DEMAND FOR PROCESS DEVELOPMENT CDMO SERVICES

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.

REFERENCE


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Dr. Stephen A. Munk is the CEO of Ash Stevens Inc., a full service Active Pharmaceutical Ingredient (API) development and manufacturing contractor. He is experienced in drug discovery, development, and manufacturing both as a scientist and as a manager. Under his leadership, Ash Stevens has received eleven regulatory approvals to manufacture novel drug substances. He earned his Ph.D. in organic chemistry from the University of California at Berkeley and was an American Cancer Society Postdoctoral Fellow, conducting studies in medicinal chemistry and molecular biology, at Purdue University. Dr. Munk served on the “Chemistry in Cancer Research Working Group” of the American Association for Cancer Research (CICR-IACR; Chairman 2014).

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SMALL-MOLECULE DRUGS ACCOUNTED FOR 84% OF PHARMACEUTICAL INDUSTRY REVENUES IN 2014.
Continuous processing is gaining significant interest in the pharmaceutical industry, driven by the need to improve productivity, reduce costs, and meet regulatory requirements. This approach involves the use of continuous processes throughout the manufacturing cycle, from raw material processing to product formulation and packaging. Continuous processing offers several advantages over traditional batch methods, including improved efficiency, reduced waste, and the ability to conduct real-time monitoring and control. This allows for more consistent product quality and faster time to market, which is crucial in the fast-paced pharmaceutical industry. Continuous processing also aligns with current trends towards more integrated and sustainable manufacturing practices, and it supports the development of new regulatory frameworks that recognize and promote continuous manufacturing approaches. As such, continuous processing is becoming increasingly important for companies looking to stay competitive and meet the demands of the 21st-century drug development landscape.
A CONTINUOUS FUTURE

The pharmaceutical industry is in a period of rapid change and innovation. Those companies—their brand manufacturers and contract service providers—will need to adapt to new technologies in their operations that result in better understanding, better control, and lower cost. Continuous manufacturing 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. 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. Continuous tableting may be a preferred route in this context, as minimal amounts of APIs will not compromise on 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.

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 knowledge 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 -45ºC; 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 reactors 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 developing 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.

REFERENCES

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 availability 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 for both reducing 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 cost or 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.
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 sites, 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/bio-technology 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. 

When you think equipment, think Federal Equipment

When you need to upgrade your facility or reduce the risk of equipment failure, Federal Equipment gets you online with the right machinery in the shortest time. As a trusted source of processing equipment for over 50 years, we have extensive industry expertise and a vast inventory viewable in pharma-dedicated warehouses.

Federal Equipment Company

Visit us at Interphex, Booth #3110

When you think equipment, think Federal Equipment

We sell high-quality machinery
We buy surplus equipment

Matt Hicks, Chief Operating Officer, Federal Equipment Company

Optimize Your Capability

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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 and 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 generic 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**

Vishingain (February 2015) estimates that the global contract manufacturing market will grow at an average annual rate of 7.5% from $54.54 billion in 2013 to $79.24 billion in 2019. 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, 29% 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 10% 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 respondents (n=560) indicated that their companies have dramatically increased year-over-year spending on outsourcing for the last four years.

<table>
<thead>
<tr>
<th>Region</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>28%</td>
</tr>
<tr>
<td>Europe</td>
<td>16%</td>
</tr>
<tr>
<td>Asia</td>
<td>28%</td>
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</tbody>
</table>

#### By Annual Outsourcing Expenditure

<table>
<thead>
<tr>
<th>Expenditure</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than $100M</td>
<td>28%</td>
</tr>
<tr>
<td>$10M - $50M</td>
<td>23%</td>
</tr>
<tr>
<td>Less than $10M</td>
<td>3%</td>
</tr>
</tbody>
</table>

#### By Department

<table>
<thead>
<tr>
<th>Department</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market Research</td>
<td>36%</td>
</tr>
<tr>
<td>Management</td>
<td>9%</td>
</tr>
<tr>
<td>Corporate</td>
<td>12%</td>
</tr>
<tr>
<td>Small Pharma</td>
<td>36%</td>
</tr>
<tr>
<td>Big Pharma</td>
<td>9%</td>
</tr>
<tr>
<td>Midsize Pharma</td>
<td>43%</td>
</tr>
</tbody>
</table>

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</tr>
<tr>
<td>Asia</td>
<td>28%</td>
</tr>
</tbody>
</table>

#### By Buyer Group

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotech</td>
<td>41%</td>
</tr>
<tr>
<td>Biotech</td>
<td>33%</td>
</tr>
<tr>
<td>Biotech</td>
<td>33%</td>
</tr>
<tr>
<td>Biotech</td>
<td>32%</td>
</tr>
<tr>
<td>Biotech</td>
<td>32%</td>
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<tr>
<td>Biotech</td>
<td>28%</td>
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<tr>
<td>Biotech</td>
<td>27%</td>
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<tr>
<td>Biotech</td>
<td>27%</td>
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<tr>
<td>Biotech</td>
<td>26%</td>
</tr>
<tr>
<td>Biotech</td>
<td>22%</td>
</tr>
<tr>
<td>Biotech</td>
<td>22%</td>
</tr>
</tbody>
</table>

### SURVEY PROFILE INFORMATION

**NEW NICE INSIGHT SURVEY FOCUSES ON CDMOs**

A comprehensive study of 123 CDMOs for strategic use by both buyers and sellers of contract services. That’s Nice Insight 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 includes input from representatives of both pharmaceutical and biopharmaceutical 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.

#### % Of Respondents Who Will Attend The Following Industry Events

<table>
<thead>
<tr>
<th>Event</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID International</td>
<td>41%</td>
</tr>
<tr>
<td>DCAT</td>
<td>36%</td>
</tr>
<tr>
<td>AAPS</td>
<td>33%</td>
</tr>
<tr>
<td>BIO Europe</td>
<td>33%</td>
</tr>
<tr>
<td>Contract Pharma</td>
<td>32%</td>
</tr>
<tr>
<td>EPI Europe</td>
<td>32%</td>
</tr>
<tr>
<td>ChemOutsourcing</td>
<td>28%</td>
</tr>
<tr>
<td>Interphex</td>
<td>27%</td>
</tr>
<tr>
<td>ChemOutsourcing</td>
<td>27%</td>
</tr>
<tr>
<td>Interphex</td>
<td>26%</td>
</tr>
<tr>
<td>Interphex</td>
<td>22%</td>
</tr>
<tr>
<td>Interphex</td>
<td>22%</td>
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</tbody>
</table>
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 (56%).

79% of Respondents Who Outsourced Each Service Category

<table>
<thead>
<tr>
<th>Service Category</th>
<th>% of Respondents Outsourcing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product &amp; Manufacturing</td>
<td>68%</td>
</tr>
<tr>
<td>Small Molecule – New Chemical Entities (NCE)</td>
<td>50%</td>
</tr>
<tr>
<td>Small Molecule – Generics</td>
<td>40%</td>
</tr>
<tr>
<td>Large Molecule – Clinical Scale Manufacturing</td>
<td>40%</td>
</tr>
<tr>
<td>Large Molecule – Commercial Scale Manufacturing</td>
<td>39%</td>
</tr>
<tr>
<td>Large Molecule Active Pharmaceutical Ingredient (API) R&amp;D</td>
<td>33%</td>
</tr>
<tr>
<td>Large Molecule – Clinical Scale Manufacturing</td>
<td>30%</td>
</tr>
<tr>
<td>Large Molecule – Commercial Scale Manufacturing</td>
<td>28%</td>
</tr>
<tr>
<td>Advanced Intermediates</td>
<td>30%</td>
</tr>
<tr>
<td>Blood factors</td>
<td>26%</td>
</tr>
<tr>
<td>Vaccines</td>
<td>21%</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>20%</td>
</tr>
<tr>
<td>Capable of邨l and Manufacturing</td>
<td>19%</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>15%</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>14%</td>
</tr>
<tr>
<td>Blending</td>
<td>13%</td>
</tr>
<tr>
<td>Antibody Drug Conjugates</td>
<td>11%</td>
</tr>
<tr>
<td>Blood factors</td>
<td>11%</td>
</tr>
<tr>
<td>Vaccines</td>
<td>10%</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>7%</td>
</tr>
<tr>
<td>Small Molecule – Clinical Scale Manufacturing</td>
<td>7%</td>
</tr>
<tr>
<td>Large Molecule – Clinical Scale Manufacturing</td>
<td>5%</td>
</tr>
<tr>
<td>Large Molecule – Commercial Scale Manufacturing</td>
<td>5%</td>
</tr>
<tr>
<td>Advanced Intermediates</td>
<td>4%</td>
</tr>
<tr>
<td>Blending</td>
<td>2%</td>
</tr>
</tbody>
</table>

23% Respond They’ll Be Spending Between $10M-$50M on Outsourcing Annually

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 $560 billion acquisition of Allergan), the pharma-biotech companies are investing significantly in internal manufacturing capacities, through the expansion of existing or additional new manufacturing facilities and/or the acquisition of production capability. This is the case with Pfizer’s pending acquisition of Baxter’s pipeline and pharmaceutically capacity. This in-house expansion activity is largely due to pipelines that are much more robust than has 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 that a 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-biotech companies 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 Galaxis Biopharmaceuticals by the newly formed DPX Holdings, the merger of Cambridge Major Laboratories with AAIPharma, and the acquisitions of Bend Research and Excellence 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 in the case with internal investments by CMOs and CDMOs. Leading the pack in that area is Catalent, which also recently acquired several companies (Pharmaap 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, according to PharmaSource. These combined firms have developed a global footprint, with large-scale capabilities for greater cost efficiencies, service offerings (including development and full 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 long-term commitments, and customize protocols for different projects will also have an edge, according to survey participants. Specialized technical capabilities

20 PHARMA’S ALMANAC: GLOBAL PHARMACEUTICAL SUPPLY CHAIN LANDSCAPE | 01 2014

38 PHARMA’S ALMANAC: GLOBAL PHARMACEUTICAL SUPPLY CHAIN LANDSCAPE | 01 2014

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

<table>
<thead>
<tr>
<th>Service Category</th>
<th>% of Respondents Outsourcing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecule – New Chemical Entities (NCE)</td>
<td>57%</td>
</tr>
<tr>
<td>Small Molecule – Generics</td>
<td>57%</td>
</tr>
<tr>
<td>Over the Counter Medications (OTC)</td>
<td>37%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Service Category</th>
<th>% of Respondents Outsourcing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Drug Conjugates</td>
<td>57%</td>
</tr>
<tr>
<td>Vaccines</td>
<td>56%</td>
</tr>
<tr>
<td>Blood factors</td>
<td>54%</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>54%</td>
</tr>
<tr>
<td>Interferon</td>
<td>52%</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>51%</td>
</tr>
<tr>
<td>Interleukin-based products</td>
<td>44%</td>
</tr>
<tr>
<td>TNF factors</td>
<td>43%</td>
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</tbody>
</table>

Types of Biologics Included In Respondents’ Product Pipeline

<table>
<thead>
<tr>
<th>Type of Biologics</th>
<th>% of Respondents Outsourcing</th>
</tr>
</thead>
<tbody>
<tr>
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<thead>
<tr>
<th>Service Category</th>
<th>% of Respondents Outsourcing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecule API – R&amp;D</td>
<td>72%</td>
</tr>
<tr>
<td>Small Molecule API – Commercial Scale Manufacturing</td>
<td>56%</td>
</tr>
<tr>
<td>Large Molecule Active Pharmaceutical Ingredient (API) R&amp;D</td>
<td>33%</td>
</tr>
<tr>
<td>Large Molecule API – Clinical Scale Manufacturing</td>
<td>30%</td>
</tr>
<tr>
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<td>28%</td>
</tr>
<tr>
<td>Advanced Intermediates</td>
<td>26%</td>
</tr>
<tr>
<td>Ingredient Processing</td>
<td>13%</td>
</tr>
<tr>
<td>Blood factors</td>
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<tr>
<td>Monoclonal antibodies</td>
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</tr>
<tr>
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<td>5%</td>
</tr>
<tr>
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<td>5%</td>
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</tbody>
</table>
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 competitive 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/or fast track designations from the FDA, stand out for offering 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 competitive 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.

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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 (40%), and India (22%), 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.


REFERENCES
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.

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 proportionately. Along with the robust growth of the global pharmaceutical outsourcing market, buyers’ outsourcing expenditures will continue to increase in the next few 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/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%; Midsize: 27%; Small: 9%); Emerging 4% and 37% from the Biotech sector (Big: 15%; Midsize: 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 correspondents from Corporate Management, up by 20% to 32%; Clinical Trials Operations/Management up by 6% to 14%; and RDD/Formulation/Analytical up by 2% to 15%; Quality Assurance/Quality Control was down by 6% to 10%; Regulatory Affairs was down by 7% to 6%; and Contracting/Sourcing/Purchasing was down by 7% to 6%. Ninety percent of the respondents hold management positions: C-Level Executive — 6%; Senior Vice President — 10%; Senior Vice President/Senior Director/Scientist — 32%; 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 (40%), or being part of the team that establishes criteria/makes recommendations on the selection of CROs (20%), or supervising or coordinating with CROs (33%).

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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 Disorders (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%), Genomics (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.

### Pharmaceutical/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 (60%) and Clinical Trial Services (59%) was observed. The demand for Clinical Trial Services is much more evident among Big Pharma/Biotech and Midsize Pharma/Biotech sectors (66% respectively) than Small Pharma/Biotech and Emerging Pharma/Biotech respondents (48%) respectively.

Among a cluster of 13 Preclinical Trial Services, Bio-analytical Testing (53%), Analytical Testing (49%), Chemistry and Stability Testing (48%), and Biostatistics (45%, respectively) are the top 5 most needed services. For Clinical Trial Services, Clinical Trial Design (54%), Clinical Trial Phase I/IIa and Clinical Trial Phase I/II/III (51%, respectively), Clinical Trial Data Management (50%), and Clinical Trial Recruiting (49%) 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 Models (Animal Models) (39%) and In Vitro Assays (42%).

To fulfill their research and development needs, currently 75% of the respondents outsource services or operations to CROs (45%) 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%; Midsize Pharma/Biotech: 35%; 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 2%), 51% in Phase III (up by 2%), and 39% in Phase IV/Post-Launch (up by 1%).

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.
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 (23%), which may be due to their lack of products in the late stage, or due to mergers and acquisitions. Conversely, 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 leaner and focusing on 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 Technolodiges. 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 attributes are: Regulatory Compliance (85%), CRO Understands the Client's Requirements, CRO Industry Reputation (83%, respectively), Financial Stability and Experience (82%), Methodological, Therapeutic, Technical, and Risk Avoidance (84%, respectively), in favor of increase and only 6% in favor of decrease. The positive perspective is also reflected in buyers’ prediction of 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 digits for the rest of categories: 11-20 (7%), 21-30 (5%), 40-49 (6%), 50-60 (2), and 1% each for 61-70, 70-80, 80-90, and 90-99. 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 CROs (40%), Competitive Strategy (to move to larger proportion of outsourced relationships in supply chain) (56%), and General Increase in R&D portfolio (60%). The decline in CRO numbers is largely due to Decline in R&D Portfolio and Negative Experience with CROs.

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

Among Respondents Who Consider Emerging Market Providers

% Of CROs Contracted To Each Type Of Outsourcing Relationship

45% Preferred Provider

31% Tactical Service Provider

24% Strategic Partnership

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

Among Respondents Who Do Not Consider Emerging Market Providers

30% Overall

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

Among Respondents Who Consider Emerging Market Providers

36% Big Pharma/Biotech

32% Midsize Pharma/Biotech

28% Small Pharma/Biotech

28% Emerging Pharma/Biotech

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

Quality is too risky

47%

Regulatory compliance concerns

46%

Intellectual property concerns

37%

Communication concerns / challenges

36%

Logistics are too complicated

28%

Simple have not considered it

28%

REFERENCES

### General Toxicology

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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 tabletting 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 therapeutics 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.

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 level of capital 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 pharmaceutical 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 that 64% 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.

n 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 64% 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 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 single-use technology (SUT). For continuous downstream bioprocessing, simulated moving bed (SMB) chromatography and tangential flow filtration (TFF) systems are also available and being adopted by the industry.
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.

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 time frames; 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, 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 In fact, incorrect use of medication has been associated with as many as 125,000 deaths per year in the U.S. alone.6 In addition, the IMS Institute for Healthcare Informatics estimated that at over $200 billion annually, or 8% of the U.S. healthcare expenditures in 2012, the nonadherence to medications led to medical errors.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 once/day to 50% for four/day).9

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 accurate and easy to use.

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In the U.S. alone, 40% of adults admitted to nursing homes and 33%-69% of hospital admissions are linked to poor medication compliance.

1. Of 800 American adults surveyed in 2013, 64% of those who took medications said they didn’t take them as prescribed.
2. The consequences of such poor patient adherence are numerous and can be quite severe and costly.
3. In one study, 33%-69% of drug-related adverse events that resulted in hospital admissions were linked to poor medication compliance.
4. Other researchers found that up to 40% of nursing home admissions can be attributed to nonadherence.
5. 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.
6. Overtreatment can also occur if physicians are unaware of lack of adherence and prescribe higher doses to achieve desired results.
7. In fact, incorrect use of medication has been associated with as many as 125,000 deaths per year in the U.S. alone.
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9. 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.
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11. Simplification of medication regimens and increasing the convenience and access to medications are two key strategies for improving patient adherence.
12. The number of medications can be reduced by using combination therapies and finding alternative drugs that can treat multiple diseases.
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 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. 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 for lyophilized stick-packs, Unither Pharmaceuticals is committed to offering innovative and convenient single-dose unit-dosage forms that simplify the lives of patients. Packaging of medications via BFS is ideal for elderly patients, because it is possible to create many different shapes and incorporate premolded, perforated 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 dosage 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 serve better their patients.

REFERENCES

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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-dose forms using Blow-Fill-Seal technologies and Unither’s® single-dose lip-id stick-packs, and the strategic leadership of the newly acquired manufacturing site in Rochester, NY. He has over 20 years of broad experience across pharmaceutical manufacturing, sales support, engineering, process development, financial, quality, and laboratory services. Prior to Unither, Mr. Haehl held management positions at Scivio and Eli Lilly & Company, and worked in engineering at DuPont.

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Unither® single unit dose liquid stick packs are user-friendly, convenient, and affordable. They help patients take their medicine on-time and in the right amount, and can reduce the need for artificial preservatives.

Speak to Unither Pharmaceuticals today to differentiate your products and improve your patient’s experience without increasing costs.

Unither is a global development and manufacturing partner for pharmaceutical dosage forms, with facilities in Europe and North America.
In October 2015, Haig Barrett, Inc (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 and cost effectively to demands that shape 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. In contrast, companies that have been able to successfully implement the customer experience approach have 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

[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, data/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 positive opinions on the contract manufacturing organization (CMO) performance and what are some options to improve the customer experience.

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 business growth (www.netpromoter.com).
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 transcend 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. 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 “GUT” teams have a very high failure rate.

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.

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REFERENCES


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

BY AARON MAZZE, THAT’S NICE

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 “out-bound” marketing methods of buying ad space in print and online with various advertising 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.

NEXT STEPS

PERSONALIZING MULTICHANNEL MARKETING

1. Consider how inbound marketing can positively transform your marketing to sales handoff
2. Learn your market through 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 buyer’s 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

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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).

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 stopping-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
In situations where a potential issue may be universally challenging across all operations, development and tech transfer that are unique to a company. Of course, there are aspects of discovery and development and tech transfer that are typically seen as separate entities, but when going from small-scale to large-scale GMP manufacturing. It may seem reductive, but 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 methodologies or the acquisition of specialized expertise through M&A and/or strategic partnerships. AMRI intentionally established its small-scale GMP manufacturing group to address the rapid expansion of its clients and generally symbiotic relationships 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 most recently demonstrated with the opening of AMRI’s Buffalo facility, which addresses the key market need for US-based, integrated drug discovery. AMRI’s expanded 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.  

**DIVERSE, END-TO-END OUTSOURCING SOLUTIONS**

**The Right Elements for Complex & Next-Generation Discovery R&D**
- Biology & Pharmacology
- World Class High-Throughput Screening Capabilities
- In vitro Pharmacology & Pharmacokinetics
- Fast-Track Hit-to-Lead & Lead Optimization Medicinal Chemistry

**Diversified Chemical Development & Small Scale Manufacturing**
- Commercial-Focused Process Chemistry
- Reaction Modeling/Simulation
- Continuous Flow Chemistry

**Small Scale (Non-GMP & cGMP Synthesis)**

**cGMP Manufacture of Complex API**
- Potent/Cytotoxic Compounds
- Controlled Substances
- Biotics, Peptides, Steroids & Hormones
- Stable APIs

**Sterile Dosage Form Development & Manufacturing**
- Pre-formulation & Formulation Development
- Lysophilisation Process Development & Optimization
- Clinical & Commercial Supply
- Injectable, Ophthalmics & Inhaled Nasal
- Non-Cytotoxic & Cytotoxic/Highly Potent
- Liquid & Lysophilized Products – Solutions & Complex Formulations
- Vials, Syringes or Dropper Bottles

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Christopher Conway, in Senior Vice President, Discovery and Development at Albany Molecular Research, Inc. Conway, who leads all of AMRI’s Global Discovery Development, Analytical and Small Scale Manufacturing businesses, joined AMRI in 2009. In 2010, Conway was promoted to Senior Director of the North American Discovery market and then to Vice President of North American and European Business Development in 2012. Conway was promoted to Vice President of Global Sales & Marketing in 2013 and Senior Vice President in 2015.

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Rajesh Shenoy, Ph.D., Vice President, Global Chemical Development at Albany Molecular Research Inc., is responsible for AMRI’s Development, Analytical and Operations. Joining AMRI in 1998, Shenoy has held positions of increasing responsibility, including Manager/Director of India Operations, Director of Global Project Management, Senior Director of Global Project Management and in 2014, Senior Director of Global Chemical Development. He earned Ph.D. in Organic Chemistry at the University of Akron and postdoctoral research at Kent State University.

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**REFERENCES**

2. The Real Reasons for the Pharma Merger Boom. Fortune.  
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 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 infuse 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-MERF) frequently receives reports regarding IV admixtures. An observational hospital study confirmed that at least 1 in 10 of these parenteral products were improperly prepared.

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

**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 US. Pharmacopelia 707 guidelines. These guidelines state: 113 medications should be available in ready-to-administer form whenever possible; 121 drug concentrations should be standardized; 131 medications should be available to meet patient needs when the pharmacy is closed; and 144 preparation of admixtures by nursing staff should be minimized.

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 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 due to consistent staffing and the variant environment of the compound area; variables that are eradicated when using premixed bags.

**These Premixed IV Solutions Eliminate the Need for Human Intervention in the Drug Product and Are Therefore the Safest Option for Administration.**
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 2000.³ 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 specifications worldwide, are versed in parenterals throughout the product lifecycle and can provide strategic advice needed to go to market. Sponsors are engaging in the outsourcing 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.

ABOUT THE AUTHOR

Marga Viñes Business Development Manager, Contract Manufacturing, Grifols Partnership Marga holds a Degree in Pharmacy and an MBA in Pharmaceutical Management from the University of Barcelona. With more than fifteen years of sales and marketing experience in the pharmaceutical industry and healthcare business, including Anesthesia, Interventional Cardiology and Neurology, producing and implementing marketing plans for international and domestic markets, Marga has been in the field of strategic marketing for contract manufacturing parenteral solutions on an international level for the past seven years.

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REFERENCES

The vigorous growth of the biopharmaceutical market has ‘cy’ed the last few years. Currently, 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 to conventional practice. This shift in buyers’ behavior has given rise to the contract development and manufacturing (CDMO) market.

**BIODIVERSITY 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 trends have pushed therapeutic biologics into the center of drug discovery and development. The development pipeline for biologics looks rich. Four hosts over 900 clinical-stage biologic molecules targeting more than 100 diseases. In the last two years, FDA’s Center for 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. The innovation in biopharmaceuticals is unlikely to slow down anytime soon.

The fervor in searching for new biological entities (NEBs) 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. 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. By 2020, this market is expected to reach approximately $328 billion at a current compound annual growth rate (CAGR) of 9.4%, twice of the overall pharma market growth rate. To date, most of the development-stage and marketed biopharmaceuticals are protein-based products with monoclonal antibodies (mAbs) forming the mainstream. The following is a snapshot of the monoclonal antibodies (mAbs) developed through a complete suite of services from clinical drug development to delivery of commercial-scale cGMP manufacturing processes. CMC Biologics’ remarkable strength in mAb development is attributed to two technologies: the proprietary CHEF® 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 capability. CMC Biologics developed first-in-class cancer immunotherapeutics, 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, and 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 troubleshooting 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 IMM-g103, a novel first-in-class cancer immuno-oncology compound 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 molecules — ImmTACs.

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

Unlike small-molecule drugs, which contain active pharmaceutical ingredients (APIs) with well-defined chemical structure, biopharmaceutical APIs do not always have well-defined or even static structures. These molecules are hundreds to a thousand times larger than small molecules. A molecule in the developmental stage may be hundreds of thousands of times larger than an active pharmaceutical ingredient, and have different stability issues, 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 technologically advanced operational expertise.

With more biological products and biosimilars entering the market, the competition within the biopharma 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
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.

Perfusion Manufacturing

Another trend in biomanslufacturing 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).

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.20 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 adoption of 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.

References


About the Author

Gustavo Mahler
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’s degree in management from MIT Sloan.

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Superhuman team for superhero clients.

Powerful Separately, Unstoppable Together.

That's Nice is moving into its 22nd year in 2016, so our approach reflects more than two decades of accumulated experience and knowledge in life sciences.

Research. Strategy. Results.