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Inking the Deal

Mastering the art of lasting outsourcing relationships in the pharmaceutical industry

By Karen Langhauser, Chief Content Director

Responsible drug manufacturers and contract organizations share the common goal of producing the best possible product in the most efficient way. The two have shared mutually beneficial relationships for decades in the pharmaceutical industry and will no doubt continue to do so for years to come. The numbers support that continued success as well: according to an IntelliROI 2016 report, the global contract pharmaceutical manufacturing market is expected to reach $84 billion by 2020, up from $58 billion in 2014[1].

What follows is an in-depth look at pharma's outsourcing relationships from the contract manufacturing perspective — what works, what doesn't, and how to both build and maintain the optimum dynamic for ongoing success.

ONE SIZE DOES NOT FIT ALL

When trying to qualify the relationships between contract organizations and their customers, generalizations are ill-advised. Asked about the challenges and frustrations of their client relationships, the resounding response from CMOs was — "it depends."

Drug manufacturers have a broad range of outsourcing experience, and naturally some companies are better-versed in the process than others. Additionally, project complexity, scale, goals and timelines vary. However, in order for the process to run smoothly, it is pivotal that drug manufacturers do not lose sight of why they are outsourcing. Essentially, is the need functional or strategic or somewhere in between?

"I think it's important for our potential customers to keep in mind why they went to a CDMO in the first place," says Mike Valazza, VP global business development, Catalent Pharma Solutions. "Was it speed or technical advancements or a specific delivery

platform, for example. If they keep that in the forefront of their minds, they will find a partner that is a good fit."

Project complexity can change the nature of relationships as well. Drug manufacturers who approach contract organizations with products that are easy to make, with well-characterized processes and well-defined systems naturally create a smoother, simpler relationship. But complex pharmaceutical products are becoming increasingly more common.

"These complex products require a much higher level and frequency of communications as the CMO works through the various challenges that will be confronted. There needs to be mutual trust and responsiveness from both parties to get these challenges resolved quickly and efficiently," says Lonnie Barish, executive director, business development, Wellspring Pharma Services.

But just because the product is complex, does not mean the outsourcing relationship has to be complex, says Simon Edwards, VP global sales and business development, Cambrex. "The project may be complex, but relationships only get complicated by people. A good relationship is a bond based on the individuals who are involved. Where it gets complex is when there are people involved behind the scenes who aren't active in the day-to-day interactions. If all those working directly together respect one another and develop a degree of goodwill, there is a natural tendency to sort out problems," says Edwards.

Manufacturing semi-solids at WellSpring.

STRATEGIC PARTNERSHIP?

Much has been written about the role of contract manufacturers evolving from an "extra set of hands" to a more high-level, strategic partnership. But is the term "strategic partnership" truly the best way to describe the contract organization/drug manufacturer relationship? Again, the answer is: it depends.

"I don't like the term strategic partners. It's true that if it's going to work well, the relationship should be strategic in nature. But we are definitely not talking about a formal strategic partnership on paper — it is more strategic *behavior* as opposed to a strategic partnership. The strategic behavior comes

out of the relationship you build, not out of formalizing a strategic partnership agreement," says Edwards.

A cleanroom producing powder-based Rx products at Pharma Tech Industries' manufacturing facility in Royston, Georgia.

Tee Noland, CEO of Pharma Tech Industries, echoes that sentiment and is realistic about the varying nature of the relationship.

"The word 'partnership' just gets thrown around a lot," says Noland. "The reality of some of our relationships can be 'you're the vendor and we are the customer,' which can make solving problems and communication challenging," acknowledges Noland.

When drug manufacturers are content with working tactically — purchase order after purchase order — and aren't seeking a strategic relationship, savvy contract organizations adapt to the situation.

"We tune our execution protocol to suit individual client requirements. Some of our longest partnerships have been with clients where we demonstrated flexibility and commitment to fine tune our approach to meet their needs," says Vivek Sharma, CEO of Piramal Pharma Solutions.

Perhaps it's a problem of logistics more so than semantics. It isn't necessarily the case that the entire pharmaceutical industry is opposed to significant, high-level relationships with their outsourcing partners — but getting there can be a struggle.

Supply chain optimization is at the forefront of today's pharmaceutical industry agenda, playing a key role in addressing current cost, performance and quality challenges. According to an A.T. Kearney Pharma Supply Chain Panel survey[2] of pharmaceutical companies, the single biggest barrier to improving performance is supply chain complexity. And while 92 percent of respondents of that survey saw simplifying their supply chains as a strategic priority, nearly 40 percent of the surveyed firms were not yet doing anything about it.

"Many large pharma companies are in fact saying they want 'strategic partnerships' with CMOs. They don't want to work with 150 CMOs, they just want the 50 best CMOs. But to get there is not an easy thing to do. There is a tremendous amount of time and complexity involved in shifting

products in order to consolidate suppliers," says Noland.

As drug manufacturers continue to pare down their vendor numbers and establish preferred/strategic partnerships with fewer, integrated suppliers, contract organizations are establishing competitive advantages by understanding the individual needs of each customer and maintaining a flexible approach to the relationship.

FINDING "THE ONE"

The contract services market has enjoyed healthy growth in recent years, no doubt a reflection of the robustness of pharmaceutical pipelines and the drug industry's overall greater need for support. In fact, Nice Insight's 2016 CDMO Outsourcing annual survey[3] revealed that pharma/biopharma execs expect spending on outsourcing to increase for the fourth year in a row.

However, consolidation, increasing offshore outsourcing alternatives and pharma's tightening purse strings means that competition for outsourcing bids is alive and well — and pricing, like it or not, is a factor in contract services selection. But according to CMOs, it is not the leading factor in the process.

"I don't think price dominates — it's not necessarily the number one. Customers talk to at least 3-6 suppliers, and often kick out the highest and the lowest bid. If price was dominating, drug manufacturers would just pick the lowest bid," points out Edwards.

So what is dominating the selection process? First and foremost, is a contract organization's quality reputation, followed closely by its ability to execute projects against promised timelines.

Part of Catalent's Pressurized Metered Dose Inhaler (pMDI) filling suite at RTP, North Carolina.

"Customers do look at your quality record and do try to get a feel for your technical expertise. I don't think I've ever won any business where our customers haven't gone to look at our sites first," says Edwards.

Sharma echoes this sentiment: "The degree of confidence that the CMO can provide to the customer on supplying the product on time, at the right quality, quite often directly correlates to the probability of winning the

proposal. Of course, the CMO still needs to be within a certain range of the bids that the customer receives."

Upon further dissection, the "price" discussion should really be a discussion of value — exactly what are drug manufacturers getting for their dollars spent? "At the end of the day, the least expensive car on the market isn't going to be a Mercedes, but if you are going to spend the money on a Mercedes, you are expecting that the value is there for what you are spending," points out Valazza.

Contract organizations caution drug makers against chasing lower numbers. And the precautionary words are not merely self-indulgent: Lower initial prices could ultimately equate to bad service, bad quality and supply disruptions.

"It is up to the pharma companies to decide if they want a reliable supply chain — one where they are not constantly having to put out fires — or do they want to chase a lower cost and, as a result, have to micromanage their supply chain," says Noland.

Scope creep — a challenge ubiquitous to all project management — needs to be taken into consideration during the initial price screening. Scope creep occurs when a project is not properly defined, controlled or documented, and deliverables and project boundaries are not properly laid out.

It's helpful to be aware that different contract organizations take different approaches to handling scope creep. "Some will come in with barebones project scope and then issue change orders as the project moves forward, while other companies will do more of a full-service proposal and lay out what they anticipate to be all the costs, preferring to minimize change orders," explains Barish.

A new manufacturing plant at Cambrex's facility in Charles City, Iowa.

"It's not always the case that others are less expensive; sometimes they just scope less work," agrees Valazza.

"What we do at Catalent is to anticipate the work the client will need based on all our experience and build that into the

proposal. We try to be upfront with what we think would be the best way to run the program if we were the decision maker," Valazza adds.

As drug manufacturers narrow down their choices of outsourcing partners, thorough due-diligence and drilling down to understand how the project is truly going to run ultimately helps inform the decision much more than just figures on a page.

PLANNING AHEAD

Contract organizations cannot stress enough the criticality of advanced planning. There is universal agreement that the clearer the vision for the project upfront, the smoother it will go down the road, and the opposite is equally true: poor planning will cost both sides time, money and frustration.

"One of the leading causes for tension in the CMO/ pharma relationship is lack of clarity and vision upfront," says Barish.

Planning needs to come from both sides of the relationship.

"Ideally pharma companies lay out exactly what they want, what their regulatory strategy is and how they see the project rolling out. Companies that do not provide the basic info for developing a quotation — safety data on APIs or packaging info for example — create a back and forth as contract organizations struggle to get all of the needed information. And ultimately, pharma companies can regret decisions that were made early on that were not strategically thought out upfront and instead decided on the fly," says Barish.

When expectations are clearly defined upfront, contract organizations can then provide the pharma manufacturer with a clearer understanding of full cost and timelines.

"In general, customers are prepared. It is even more helpful if they are clear on the difference between what they want and what they need. Often drug manufacturers are looking to get to the next step, but the bigger question is, what do you NEED to get there?" says Edwards.

A widely used tool for laying out such expectations is the Request for Proposals (RFP). The RFP document should effectively communicate the pharma organization's key deliverables and timelines in detail and ask questions specific to the proposed project.

"A well-written RFP and an effectively managed RFP process form the foundations for a productive relationship with the chosen CMO — a relationship that may last for the entire lifecycle of your product," says Ron Herman, senior partner, NexGen Consulting Group. (For more on RFPs, see Herman's

The Art of the Request for Proposals on page 11 of this eBook.)

RFPs mean all potential outsourcing partners see the same package, at the same time. While it standardizes the playing field, there can be downsides to the on-paper process.

"RFPs tend to take the relationships out of a lot of sourcing decisions. I worked with Bob on the last project and it went really well, but Bob is now replaced by a RFP committee. On the one hand, it's a way of doing things fairly, but it's also a bit of a loss because it removes the relationship from the initial equation," says Edwards.

Ideally, drug manufacturers reach back out to CMOs after receiving proposals, seeking further clarification and asking questions about the proposal. The personal relationship element should, at this point, re-enter the picture.

While a carefully written and thought-out RFP can take the human element out of the equation, "on another level it clarifies the direction, and does a better job of setting expectations on both sides," concludes Barish.

THE NATURE OF WORKING WITH PHARMA

Each industry comes with its own unique set of challenges. Savvy contract organizations are well-versed in the struggles indicative of pharma and have established methods of working through these challenges.

One such challenge in the pharma industry is culture. As pharma's business models shift, its cultural models are failing to adjust accordingly. Frequent mergers, acquisitions, and relocations further complicate the matter. PwC went as far as to use the term "cultural sclerosis," stating that "prevailing management culture, mental models and strategies on which the industry relies are the same ones it's traditionally relied on, even though they've been eclipsed by new ways of doing business."[4]

Companies struggling to build a strong culture within their own organizations will invariably be challenged when trying to form working partnerships.

"You need to be sure of your own culture before you can find a cultural fit with an outsourcing partner," says Noland.

But this struggle has helped some contract organizations to reflect inward and work to improve their own cultures. A poor cultural fit can result in awkward CMO-drug manufacturer relationships, which means CMOs also need to have a clear vision of their own capabilities.

"Our reputation is paramount to us. If I take on a program that isn't a good fit culturally and the customer has a bad experience, it can affect our ability to work with that customer on other programs in the future," says Valazza.

Pharma Tech speaks of the time spent building their own cultural focus. "To get the culture we believe is in the shared interests of our employees and our customers, we've had to invest a lot in our cost structure in terms of the right leadership. To grow, we need a certain level of volume and profitability to sustain the culture we want," says Noland.

Contract organizations can be challenged to take such a position, as the core reason for outsourcing has traditionally been lower costs — meaning CMOs have to exercise some frugality, at least at the start, and need to reach a certain scale before investing heavily in top talent. But the investments seemingly pay off, as contract organizations with strong cultures and values are able to provide structure and consistency to their customer relationships.

COMMUNICATION, FLEXIBILITY AND PLANNING

There is much variability involved in pharmaceutical outsourcing relationships and tremendous pressure surrounding these relationships.

"In our industry, time is money. Delaying the launch of a product can result in the loss of tens of thousands, sometimes millions of dollars. We, as CMOs, are constantly being reminded of that fact," says Barish.

Building a good outsourcing relationship is the responsibility of both parties, and the best relationships have these three things in common: communication, flexibility and planning.

"Every project and customer is a learning experience. It's a complex business to be in. The pace and challenges in the pharma world can be eye-opening," concludes Noland.

For two sectors that rely on each other for industry success, mastering the art of building and maintaining relationships is proving to be worth it.

RESOURCES

1. *IntelliROI. (2016). Global Contract Pharmaceutical Manufacturing Market - Market Size, Demand Forecasts, Industry Trends and Updates (2014-2020)*
2. *A.T. Kearney. (2014). Preparing the Supply Chain Pharma Needs.*
3. *Tiene, Guy. (2016). CDMO Market Continues to Expand. Pharmaceutical Manufacturing. Volume 15(3).*
4. *PwC Global. (2016). Pharma 2020: from vision to decision*

The Art of the Request for Proposals

A well-written RFP and effectively managed process is well worth the upfront time and effort

By Ron Herman, Senior Partner, NexGen Consulting Group LLC

The time has come to write a Request for Proposals (RFP) to outsource your latest contract manufacturing project. A well-written RFP and an effectively managed RFP process form the foundation for a productive relationship with the chosen contract manufacturing organization (CMO) — a relationship that may last for the entire lifecycle of your product.

Begin the process with basic reviews of CMOs that potentially have the capabilities you need for this specific project. Numerous published articles offer excellent tips for creating lists of suitable CMOs; usually between five to 10 candidates is a good starting point. Once you have your preliminary list, check the latest regulatory agency (e.g., FDA) databases to see if there are any recent negative reviews. Then contact a business development representative for each CMO remaining on your list. Explain the project in general terms, but do not reveal any confidential information. Make note of the questions they ask and be sure to address each of them in your RFP.

KEY POINTS FOR WRITING AN EFFECTIVE RFP

1. Timeline

Regardless of the product or service being outsourced, you should have a realistic deadline for the deliverables. Use that to develop a timeline for the entire RFP process including proposal reviews, plus all the other essential activities needed before the actual work starts (a Gantt chart can be very useful even at this early stage of

You should actively manage the entire RFP process to achieve the best possible outcome.

outsourcing). Be sure to include time to sign a Confidentiality Agreement (CDA) with each candidate CMO because CDAs frequently take a lot of time. Rushed RFPs and hurried CMO responses are bound to create confusion and misunderstanding.

2. Scope

It is essential that your entire team has input into preparation of the RFP. Each department or discipline may have different visions for the use, quantity and quality attributes of the product or service being outsourced. An effective RFP requests deliverables that can accommodate your entire team's anticipated needs at this stage of development. Time and money can be wasted if you modify the deliverables after the work has started.

3. Details

Everything in the RFP should be covered by the CDA, so share information freely. Clearly define your deliverables (quantity, quality, batch records, reports, regulatory filings, etc.) and the timelines. Include detailed technical data and a Safety Data Sheet(s). Ask key questions relevant to your specific project, e.g., about tech transfer, process development and engineering runs, equipment purchases and qualification, methods development, stability studies, services

outsourced to third parties, packaging, storage and distribution, etc., so you form a complete picture of the entire project at each CMO. Be sure to address the questions raised during your informal contacts with the CMOs.

The CMOs will evaluate your RFP based on the deliverables, timelines, fit with their capabilities, and available capacity so they can quote with reasonable accuracy. It

helps to include a small table at the end of the RFP so each CMO can capture the details of their quantities, costs and timelines in a uniform format. Provide contact information for the team member who will be responsible for answering questions about the RFP. The deadline and delivery address for proposals are essential parts of an effective RFP. Have your team review the RFP for clarity and accuracy. Convert the final RFP into Adobe PDF format to add a professional look and to ensure that the recipients can access the file.

MANAGING THE RFP PROCESS

Writing the RFP is only the first step in successful outsourcing. You should actively manage the entire RFP process to achieve the best possible outcome.

1. Distribution

The CMOs should receive identical RFP packages, all sent out on the same day. If the RFP is too large for an email attachment, use a CD, USB stick or a secure file sharing site, instead of hard copy. Use overnight delivery services for CDs, USB sticks or hard copies.

2. Update

It is inevitable that a CMO asks a question(s) not addressed in the RFP. Send written responses to such questions, as well as any other updates, to all CMOs. If you meet with one CMO to discuss the RFP, you should meet with all of them.

3. Due Date

Set a realistic deadline with all proposals due no later than a specific date. Too soon and you may get incomplete or inaccurate proposals; too long and your RFP may lose visibility. Three to four weeks is usually a reasonable timeline for proposals, keeping in mind that good CMOs may be working on proposals for several customers at the same time. Be sure to indicate how and where you want proposals submitted, e.g., in PDF format on a CD or USB stick, electronically via email or through a secure file-sharing site or as hard copy.

4. Follow-up

Contact each CMO about midway through the review period to ask if they have any questions about the RFP and to remind them of the submission deadline.

REVIEWING PROPOSALS

The due date has arrived and proposals have been received. Some CMOs may have missed the deadline, so it is good practice to follow up with them. They may not have submitted a proposal because they cannot provide the required services or are unable to meet your timeline. In unusual instances, a CMO may decline to submit a proposal because they have identified a problem or potential hazard that you may not have recognized.

1. Review

CMOs put their time and expertise into

writing proposals. Respect their efforts by reading all proposals carefully. CMOs have different experience and may have different approaches to your project. You can mine useful information from virtually every proposal. Be sure to contact the CMO if you have any questions about their proposal or if anything is missing, and it is always a good idea to check their math.

2. Compare

Compile the data from the RFP summary table that each CMO completed to simplify your side-by-side comparisons. Score cards can be useful, especially when more than one person is reviewing the proposals. Create a list of key project attributes, e.g., CMO experience, quality, timelines, regulatory compliance, cost, etc., and have the reviewers assign a grade for each key attribute to all proposals using a scale of 1-5 or 1-10.

3. Price

Costs are important, but should not be the defining factor when selecting a partner. Experience, quality and timelines are as important as price.

4. Selection

Based on the reviews and score cards, select one or a small number of CMOs for in-depth technical discussions, perhaps including a meet/greet visit at their site. Get to know their team. Be sure you can work effectively with them.

5. Decision

Using the proposals, in-depth discussions and a successful QA audit at the highest ranking site, you should be ready to select the CMO that best fits your overall project goals. Once a services agreement has been signed with that CMO, close the loop with the CMOs that were not selected. Feedback is usually well-received and helps the CMOs prepare better proposals for your next project. Be general in your comments, and do not reveal any confidential information obtained from the other CMOs.

These straightforward recommendations should simplify the outsourcing process and allow you to choose the best CMO partner to move your latest invention from the lab toward launch.

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The Evolving Biopharma Contract-Manufacturing Market

Once biopharma companies optimize operations in order to free up hidden capacity, they have four options: build, acquire, partner or face the realities of outsourcing

By Andrea Gennari, Martin Loesch, Alberto Santagostino and Ralf Otto, McKinsey & Co.

Biopharma companies have depended on contract manufacturing organizations (CMOs) to provide capacity and capabilities as needed; in some cases, CMOs have provided a great deal of a company's production. Yet the current market structure presents biopharmacos with a shortage of CMO capacity to produce biopharmaceuticals, especially in mammalian cell culture technology and new modalities, even as demand for outsourcing increases. As companies face today's evolving industry economics, they should first optimize their operations in order to free up hidden capacity. Once this is done, they have four remaining options: build, acquire, partner or face the realities of outsourcing.

WHY OUTSOURCE BIOPHARMACEUTICALS?

The large molecules that constitute biopharmaceuticals differ from small molecules not only in their size, but also in their behavior, their manufacture and the way they work in the human body. Manufacturing these molecules is significantly more complex than producing traditional pharmaceuticals.[1] In fact, biopharma is a true high-tech industry, with complex processes that relatively few players have entirely mastered.

Perhaps as a result, the industry is more profitable than the pharmaceutical industry, with relatively little pressure on cost of goods sold (COGS). Biopharma has also grown steadily for a number of years, and

the large pipeline of molecules in clinical trials promise continued growth.

Despite the industry's high complexity, however, outsourcing is extremely popular. In fact, the market share of biopharma CMOs has risen steadily in the past decade, reaching 20 to 30 percent of the industry's COGS in 2013, and is expected to grow to almost 70 percent for some companies over the next few years.[2] Not surprisingly, global CMO sales are growing steadily, fed not only by increased outsourcing, but by overall growth in new and existing products including clinical-trial supply. Further growth of more than 5 percent per year is projected over the next three years, leading to a total biopharma CMO market of $7 billion in 2019 — of which up to 30 percent will come from trial supplies.

Five factors are primarily driving this growth:

- Hedge risk: Biopharmaceutical companies often outsource to balance their risk and buy time until key milestones in clinical trials or market uptake are met and they can justify investing in-house.
- Lack of capacity: Many new market entrants. and start-ups developing biopharmaceuticals lack existing manufacturing capabilities. The same is true of some large pharma companies switching over parts of their pipeline to biopharma.
- Invest hurdles: The biopharma industry has high investment requirements. For example, a new biopharma plant with large stainless-steel vessels designed to produce high-volume biopharmaceuticals (500-1000 kg of active pharmaceutical ingredients, or APIs, a year) would require more than $250 million and lead times of four or more years.
- Lack of capabilities: Several experienced CMOs have strong technical capabilities in cell line development, process development and scale-up. These CMOs are very well-suited to production process development, able to increase yields while reducing COGS. In fact, a CMO's technical capabilities are one of the most important factors to consider when selecting an outsourcer, along with its track record of quality, compliance inspection and supply flexibility. Exhibit 1 illustrates one CMO's success in increasing yields, or titers, after optimizing the manufacturing process for a range of six products (monoclonal antibodies, or mAbs).
- Technology shift: Two major trends impact existing mammalian cell culture facilities:
  1. The production of large molecules moves to highly productive platforms composed of cell expression, media composition and process mode in up-and downstream processing (fed-batch vs. continuous, rise of single-use equipment). Not all existing plants are ready for disruptive productivity increase or use of disposables.
  2. New biologics modalities in the pipeline like multispecific mAbs, viral vectors,

oligonucleotides, peptides and other force biopharma plants into a multi-platform, multi-modality situation while most multi-product plants are still in a mono-modality and mono-platform setup.

THE CHALLENGES OF BIOPHARMA OUTSOURCING

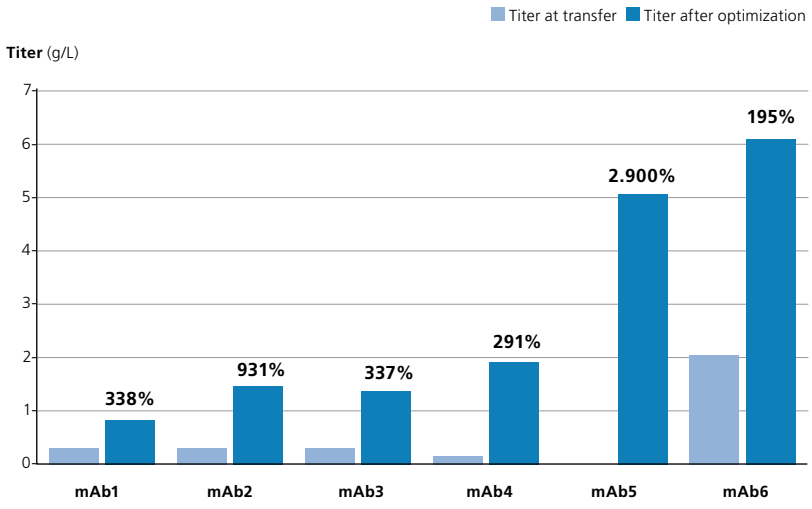
Transfer complexity

Looking at the market drivers and the value proposition offered by leading CMOs, the advantages of outsourcing from a biopharmaco's perspective seem clear. Yet biopharmaceutical outsourcing faces several challenges, one of the best-known — and most critical — is the molecules' high transfer complexity. All large, complex biopharmaceuticals (such as mAbs, receptors and enzymes) require extremely sensitive production conditions given their complex structure and unpredictable post-translational modifications. As a result, transferring this type of biopharmaceutical to a new production environment is extremely complicated — whether transferring from R&D to manufacturing, or from the originator company to a CMO. In fact, more than a hundred input parameters must be adjusted to accommodate the living biopharmaceutical organism and the purification of large complex proteins, because duplicating the original environment is next to impossible. If transfers fail into highly utilized CMOs, the next slot available might be several months later, having a huge impact on the launch forecast and impacting the top-line, as such it is clear that an excellent process transfer track record is a critical success factor.

Nonetheless, some biopharmacos have mastered this and other challenges and found compelling reasons to use CMOs, including the CMOs' strong processing capabilities, deep experience in production-process transfers, biomanufacturing

EXHIBIT 1

Case example: There are good reasons to outsource biopharma manufacturing



Source: McKinsey

excellence, high reliability, in-depth regulatory expertise, strong analytical capabilities and ability to adjust their facilities as needed.

Limited CMO capacity for large-volume biopharmaceuticals.
Beyond well-known challenges such as transfer complexity, biopharmacos face another pressing challenge if they are to outsource in today's market: a shortage of CMO capacity, in particular for large-volume biopharma drug substances.

Today's shortfall can be traced to three key factors:

- Although there are plenty of CMO competitors in the area of small molecules, in large molecules there are only 10 to 20 biopharma CMOs from which to choose, leaving limited options to biopharmacos seeking the ideal outsourcing partner.
- As of 2015, large-volume mammalian cell-culture production based on six or more 12kL bioreactor lines (the current industry workhorse) were offered by only three suppliers — Boehringer Ingelheim, Lonza, and Samsung — while others such as Patheon Biologics or Sandoz owned only one or two 12 kL bioreactor lines.
- Several players take an opportunistic approach to the market, acting as CMOs only when their own brands are not generating enough sales to utilize their full capacity. As a result, there is a risk that they may not offer very stable business partnerships, because they may prioritize their own brands when those volumes increase.

SWING FACTORS IMPACT CMO CAPACITY FORECASTING

Global cell culture utilization rate stayed relatively stable and rather high in the past five years at an average of 65 percent, while CMOs are presumably even at >85 percent. Going forward, the capacity utilization will diverge depending on dominate factors. Utilization goes up driven by: Biosimilar uptake in general, their expansion into emerging markets and comparably low productivity levels (in favor of similar product quality), demand increase for new therapeutic areas especially in unmet medical needs like immune modulation and CNS disease treatment, and general adoption of multi-specific mAbs produced by lower productivity expression systems. Utilization goes down driven by: second generation manufacturing processes that increase yield manifold, converting to ADCs ultimately reducing volume due to higher efficacy additional investments by CMOs, opportunistic CMOs and big pharmacos, a drop in clinical success rates and, finally, a shift to new modalities and treatments that push large molecules off traditional indications like oncology.

Evolving industry economics and new modalities
Adding to the challenge, we expect the

economics for biopharma outsourcing to evolve over the next few years and thus further reduce CMO capacity. Although existing CMOs have been investing in large-scale capacity, they have only kept pace with existing needs and made no further expansions of any significance over the last few years. However, recently significant expansions by Lonza and Boehringer Ingelheim have been announced. Simultaneously, several formerly leading CMOs such as Boehringer Ingelheim and Celltrion Healthcare announced that they will rebalance their portfolios by adding to the development and launch of their own brands and biosimilars, even shifting away from contract manufacturing to do so.

Also, surprisingly few additional competitors are expected to enter the high-volume CMO market, despite profit margins of above 30 percent in the biopharma CMO business versus 5 to 10 percent in the pharma CMO business. The primary entry barrier is the high investment required — more than $350-400 million for a manufacturing facility with a capacity of six times 12kL and an additional $170 million for pilot facilities and labs — along with the development of enough skilled biopharma experts (likely in the hundreds) to manage start-up, biomanufacturing and product transfer.

As a result, only a few CMOs have the financial power and strategic direction to take on the risk of entering the biopharma market. One notable exception is Samsung, which entered the biopharma CMO market in 2013 with Samsung BioLogics. Wuxi Biologics is another rising player in biopharma CMO offering development and manufacturing in disposables based facilities.

The situation is likely to worsen for the production of next-generation biopharmaceuticals like antibody drug conjugates (ADCs), which require additional steps to make their active pharmaceutical ingredients (APIs) more effective in the body. Currently, no CMOs offer the conjugation technologies “one-stop shopping” — from drug substance supply, through conjugation, to drug product, which already account for 25 percent of the biopharma pipeline. Currently, there is almost no choice of CMOs for new modalities like cell therapy and viral vectors. Here, new manufacturing platforms and completely new ways for supply need to be established from E2E (e.g. personalized medicine).

Finally, with 83 percent of biopharmaceuticals consumed in the European Union and the United States, the industry’s high transfer complexity greatly limits the ability of biopharma companies to outsource to China or India, leading biopharma executives to view outsourcing there as less attractive than producing elsewhere, according to a recent survey.[3] In addition to transfer complexity, of course, executives looking at China or India must take

into consideration such issues as intellectual property protection, ensuring a high-quality product and gaining authorization from regulatory bodies such as the European Medicines Agency and FDA.

Without enough outsourcing options to meet demand, biopharmacos requiring large volumes have little negotiating power to help them capture value from a CMO. In addition, biopharmacos are in a weak position should they face capacity shortages, with little to no available internal backup production. And operating expenses tend to mount quickly, reaching $60 million to $80 million per year for 20 to 50 large-scale batches.

Small volumes

In contrast, CMOs operating on a smaller scale (up to 3kL) — whether for small volumes of biopharmaceuticals such as those needed for clinical supply or for small-volume commercial production, such as APIs for ADCs and biologics for niche indications — face fewer barriers to entry. The use of disposable reactors (up to 2kL) in particular has low investment requirements and therefore low entry barriers.

The value proposition of these smaller-scale CMOs will increasingly tend toward high-tech solutions such as high-expression cell lines (high titer) and next-generation protein purification (high-performance resins), which allow manufacturing on a lower scale (up to 3kL) and with high speed and flexibility. They are also starting to offer supplementary services such as production-process development or support for product transfers outside their companies, as well as the design and opening of disposables facilities globally.

Perhaps not surprisingly, therefore, market forecasts indicate a strong trend toward low-volume manufacturing as productivity continues to increase, biopharmaceuticals become more effective (requiring lower doses), and treat more niche indications. Nonetheless, we expect to see increased pricing pressure and consolidation, given that there are already quite a few small-volume CMOs in the market.

POTENTIAL STRATEGIC OPTIONS FOR THE NEXT THREE TO FIVE YEARS

As biopharmacos face the myriad challenges of outsourcing, they have several strategic options to consider, whether they have existing capabilities — and expected future growth — or are just entering the biologics arena. These options include building a new facility, acquiring an existing facility, partnering with a large pharmaco and continuing to outsource despite the challenges (Exhibit 2).

Every option has its price. As a result, assuming that biopharma operating assets are available, companies should try to

get the most out of these existing assets first, optimizing productivity and freeing up new capacity. An in-depth assessment of wait times such as product changeover, maintenance and unplanned downtime relative to industry benchmarks will help to identify this untapped capacity. In fact, McKinsey's experience shows that there is much more room for improvement than most companies believe. The meaningful use of new technologies can also help, including the new high-expression cell lines and the use of perfusion systems or high-performance resin for the purification of proteins.

When all optimization levers have been investigated, however, companies may still need to pursue other options.

1. Build

The first option will be to set up a new, large-scale facility. This option will require a substantial investment of time and money, but of the four options available, this one will ultimately ensure the most flexibility and control of supply and improve agility in launch situations. Over the course of a couple years, it will be financially attractive if the facility is built in a tech-advanced location, filled up and run with operational excellence.

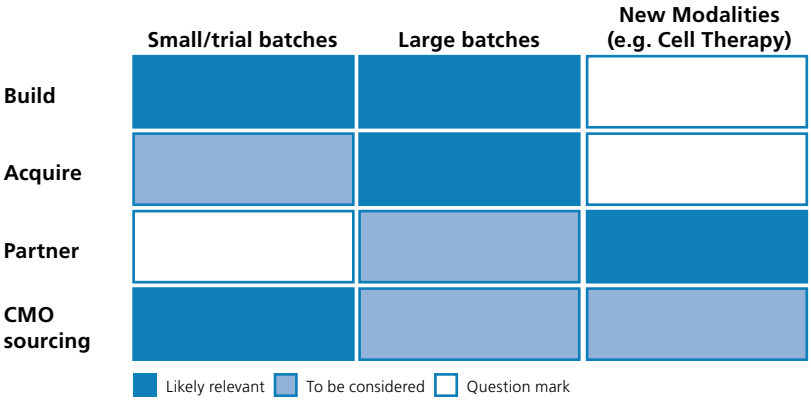
To begin, a six-month macro-design phase will allow capacity and technology choices to be carefully developed, because decisions at this stage will affect capacity, flexibility and capabilities for the next 20 years. Another important decision during this period will be the location: the company must choose between proximity to its existing owned infrastructure and more aggressive expansion to new locations, allowing access to markets, talent or technology.

Next, a nine-month basic engineering stage will allow the company to gather more details on facility design, investment and future operating cost.

Finally, it will take approximately three years, from

EXHIBIT 2

Strategic options for orginator companies going forward



SOURCE: McKinsey, Experts interview

ground break to the first validation batches, for the plant to be market-ready. Keys to success during this period will include developing the right skills in engineering and manufacturing, establishing high-quality training programs for new hires and attracting experienced leadership.

Despite the amount of time and effort required, building a new facility will be the right choice for experienced biopharmacos with a balanced product portfolio on the market and a sustainable pipeline of products to be launched.

2. Acquire

Although the biopharma industry is on the rise, a relatively high number of assets sit idle owing to attrition in the product pipeline. However, acquiring these assets will not be an easy solution, given that the buyer will require certain in-house capabilities or else be forced to partner to gain these capabilities.

On the positive side, an acquisition would speed access to both capacity and talent, while potentially enhancing the buyer's capabilities. A number of acquisitions have taken place in recent years, including the purchase of Amgen's high-tech biologics bulk manufacturing facility by AstraZeneca[4] and Baxter's facility in Minnesota by Takeda.[5] To succeed, a company must have the internal biotech skills to adjust its facility design, transform the acquired facilities and transfer its biotech processes.

On the downside, the existing facility design will often be too inflexible, requiring additional investments to adapt it to the necessary production process. In addition, facilities and a team sitting idle, for sale, for a certain period of time may result in the need to substantially remodel equipment and re-employ talent, along with the transformation of business processes and mindsets, before the facility can be useful again. Phasing out the previous owners' systems and paying off liabilities while integrating existing networks will also be required, along with change management and product transfer. Finally, an acquisition of any size will necessitate a significant amount of the acquirer's talent, which may be missed elsewhere.

3. Partner

A third option will be to take advantage of idle capacity within large biopharmacos. If the facilities have not been idle for too long, capabilities may still be strong and equipment well-maintained.

Partnerships work particularly well when the partners have a historical relationship or complementary skills that make it mutually beneficial. One example is the partnership that took place between Lonza and Genentech. Lonza built and launched a biopharma facility in Singapore and then Genentech

transferred the production processes and took over the facility.[6]

On the downside, there is a risk that the new partner's priorities will shift if its own molecules become successful, affecting the terms and conditions of the supply contract. There is the additional risk that large pharmacos will not be flexible in accepting existing contractual conditions, such as quality agreements. It is important to note that even large pharmacos sometimes lack experience with multiproduct operations and product-transfer excellence; as a result, the partnership could harm existing relationships and reputations.

4. Outsource

Large volumes: As described, the market structure is beginning to make large-volume outsourcing difficult, with few large-scale CMOs available. In addition, selection and management of CMOs requires appropriate organization and talent; the situation is quite different from that of chemical and pharmaceutical companies' CMO relationships.

With such limited capacity available biopharma companies have little negotiating power and must either accept the conditions laid out by the CMO or choose another option, whether acquisition of assets or partnering.

Small batches and clinical supply: Originator companies may prefer to invest internally in low-cost assets such as disposables, particularly if they already have strong in-house capabilities for developing cell lines and production processes. However, for small batches and clinical supply, whether in-house or external, outsourcing is not difficult: enough choices exist to meet demand. This option would also be attractive for new entrants that lack basic biopharma capabilities but wish to learn the technologies and ensure speed to market.

Whether large volumes or small, outsourcing to a biopharma CMO should be considered to be more of a partnership and less of a pure supplier interaction. With this in mind, companies should consider establishing contractual agreements once a product is outsourced —agreements that allow them to learn and benefit from the opportunity by getting regular updates, aiming for joint production-process improvements, and gaining the right to send their own staff into the CMO's facilities (called person-in-plants [PiPs]).

Biopharma contract manufacturing today faces steadily increasing demand because it offers biopharmacos both much-needed capacity and strong technical capabilities. At the same time, the large-volume CMO market expects capacity shortages over the medium term that will keep costs high and reduce the negotiating power of participants. As a result, companies should work to get the most from existing assets,

introducing new technologies where available and taking advantage of any untapped capacity.

Where existing capacity is still insufficient, they must consider the four possibilities open to them: building, acquiring, partnering and outsourcing. Each option should be considered carefully; not every choice is suitable for every company. If, for example, a company can build on strong biopharma expertise, transformational skills, a lean organization and a global talent pool, then asset acquisition and partnering can be very promising alternatives. If the company lacks certain skills or a historical relationship with a potential partner, however, it may be forced to focus on the CMO market, seeking out scarce CMO capacity when moving toward biologics manufacturing.

RESOURCES

3. *See the article, "Time for a New Prescription: Adapting to the Complexity of Biopharma Operations," by Otto, Santagostino, Schrader.*
4. *High Tech Business Decision – Biopharmaceutical Contract Manufacturing Report 2012.*
5. *BioPlan Associates, Biopharma managers, survey carried out by HighTech 2012-2013.*
6. *https://www.astrazeneca.com/media-centre/press-releases/2015/astrazeneca-biologics-manufacturing-boulder-colorado-11092015.html*
7. *https://www.takeda.com/news/2016/20160106_7262.html*
8. *"Roche and Lonza Announce Opt-in for Singapore Manufacturing," August 31, 2009, http://www.roche.com/investors/ir_update/inv-update-2009-08-31.htm.*

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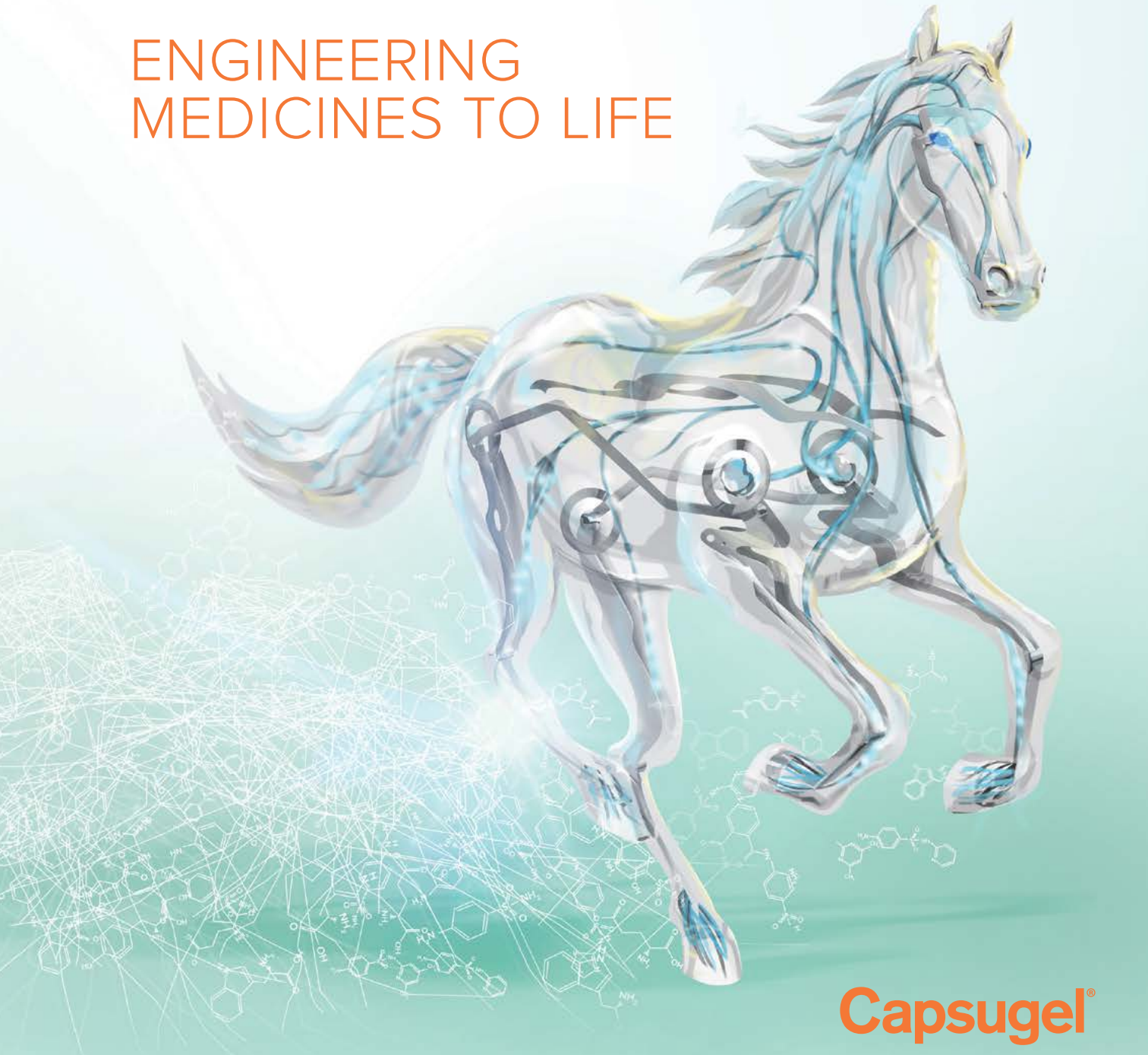

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CDMO Market Continues to Expand

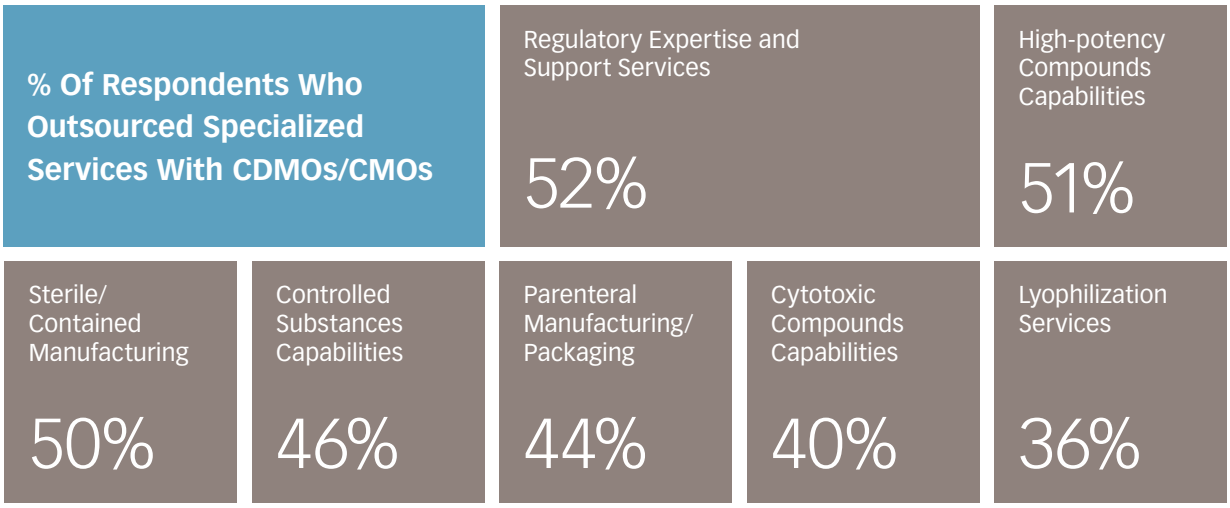
Recent survey results indicate that outsource spending has nearly tripled, with further future spending expected

by Guy Tiene, Director of Strategic Content, That's Nice LLC / Nice Insight

Respondents to Nice Insight's annual survey of outsourcing-facing pharmaceutical and biotechnology executives expect spending on outsourcing to increase for the fourth year in a row. This result fits well with estimates that the global contract pharmaceutical manufacturing market is growing at an average annual rate of 7.5%. There are many factors driving this growth in 2016 — increasing consumption of medicines around the world; a more robust pipeline of drug candidates and an increasing rate of FDA NDA/BLA approvals; the increasing focus on biologic drugs, including by traditional pharma companies that lack biotech expertise; the entrance into the market of numerous small, virtual startups that have no manufacturing capacity; the rise in patent expiries and increasing generics competition, which is driving a greater need for cost efficiencies and access to novel, proprietary technologies for achieving product differentiation; and the increasing complexity of both small- and large-molecule drugs such as antibody-drug conjugates and highly potent compounds.

DRAMATIC INCREASE IN SPENDING

This strong growth is supported by the results of Nice Insight's 2016 CDMO Outsourcing 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 to 23% from 2012-2014, the number of respondents nearly tripled to 71% in the new 2016 Nice Insight CDMO Outsourcing survey of nearly 600 outsourcing-facing pharmaceutical and biotechnology executives. Meanwhile, the percentages of respondents whose companies spend less than $10 million and $10 to $50 million on outsourcing both decreased from 2015 to 2016 from 16% to 3% (down from 43% in 2010) and 62% to 23%, respectively. 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.

Survey results also indicate that further spending can be expected. Nearly 95% of respondents expect that their companies will either maintain (18%) or increase (75%) their spending on contract development and manufacturing services over the next five years. Furthermore, while three-quarters of respondents currently use 0-10 CDMOs and/or CMOs, 7% use 11-20 and 5% use 21-30, 69% of participants in the 2016 CDMO survey expert to increase the use of CDMOs and CMOs going forward, with 29% expecting the number of manufacturing partners to remain the same, and only 1% expecting to decrease the number of partners.

These numbers reflect the robustness of pharmaceutical pipelines and an overall greater need for support. Slightly more than half (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. Survey participants also indicated that their companies are

Survey Background & Methodology

For the first time since That's Nice began gathering data on the pharmaceutical and biopharmaceutical contract services markets, in 2016 the original Nice Insight CRO/CMO outsourcing survey was divided into two separate surveys in order to focus on the differing aspects of the contract [development and] manufacturing (CDMO) and contract research markets (CRO/Clinical Services). In addition, in recognition of the key trend in this sector toward companies that provide integrated development and manufacturing offerings, the new manufacturing survey specifically explores the use of CDMOs and CMOs for both drug substance and product.

The Nice Insight 2016 CDMO Outsourcing Survey includes responses from 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 with 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.

These statistics clearly suggest that the results of the 2016 Nice Insight CDMO Outsourcing survey should be highly indicative of the conditions in the global pharmaceutical contract development and manufacturing sector. Initial analysis of the data also indicates that survey participants utilize contract services in all key pharmaceutical and biopharmaceutical markets around the world.

The Nice Insight Contract Development & Manufacturing Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2015-2016 report includes responses from 587 participants. The survey is comprised of 225+ questions and randomly presents ~50 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 123 CDMOs servicing the drug development cycle. Four levels of awareness, from "I've never heard of them" to "I've know them very well" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity and Reliability.

Emerging markets, value-added generics and biosimilars will provide potential opportunities for growth.

increasing the use of outsourcing as part of their manufacturing strategies (60%) due to the need to address patent life issues, the need for novel delivery forms and other specialized capabilities, and a desire to increase decentralization for greater flexibility. Companies are also expanding the use of service providers because they have had positive experiences with outsourcing to CDMOs and CMOs in the past (59%).

Interestingly, outsourcing is not highly focused at any one particular development stage, although the percentage of respondents outsourcing Phase II projects (63%, up from 42% in 2014) to CDMOs and CMOs is slightly higher than those using manufacturing services for Phase III (54%, up from 29% in 2014), Phase I (53%) and pre-clinical, including discovery phase, (51%) projects. The distribution is fairly even, however, and is another reflection of the robust drug pipeline resulting from significant investment in innovation; many candidate drugs are now steadily moving toward commercialization. Phase IV/Post-Launch projects are outsourced by 39% of survey respondents; the lower level of outsourcing compared to those at earlier phases reflects the attrition that occurs as safety and efficacy are evaluated. However, the number is nearly double that for outsourcing on Phase IV/Post-Launch projects in 2014 (22%). The much higher percentages of respondents outsourcing phase II, III and IV projects strongly suggest that new programs designed to weed out unlikely candidates as early as possible in the development process and well before they enter into clinical trials are achieving the desired results.

WHO WILL BE THE WINNERS?

Not all contract manufacturers will benefit from the increased spending anticipated by the participants in this year's Nice Insight CDMO Outsourcing survey. Indeed, the percentage of respondents that elect to work with "Preferred Suppliers" rose to 43% from 35% last year, while the preference for tactical suppliers dropped from 35% to 31%.

What does it take to be preferred? Such firms tend to have more global footprints,

large-scale capabilities for greater cost efficiencies, a broad range of service offerings including development and final formulation/drug delivery in addition to API manufacturing, and access to advanced technologies. In particular, successful CDMOs make it possible for drug manufacturers to more efficiently and cost effectively develop and produce increasingly complex drug candidates and extend the product lifetimes of off-patent products using novel, proprietary technologies. Consequently, technological capabilities will equate directly to competive advantage as drug manufacturers continue to pare down their vendor numbers and establish preferred/strategic partnerships with fewer, integrated suppliers.

It should also be noted, however, that preferred suppliers must continually earn their position with ongoing high levels of performance. For instance, half of the 2016 Nice Insight CDMO Outsourcing survey respondents indicated that they would switch CDMOs if they do not continually meet quality and on-time delivery expectations.

So where will the opportunities lie for CDMOs in 2016? Companies with truly integrated offerings and unique technical capabilities will enter into collaborative capacity management and long-term, multiproject relationships. Emerging markets, value-added generics (so-called supergenerics), and biosimilars will provide other potential opportunities for growth. Those that are positioned to leverage these opportunities will survive the more competitive contract manufacturing marketplace.

To learn more about Nice Insight, contact Guy Tiene at guy@thatsnice.com or visit www.niceinsight.com.