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EMERGING OUTSOURCING TRENDS IN BIOPHARMA

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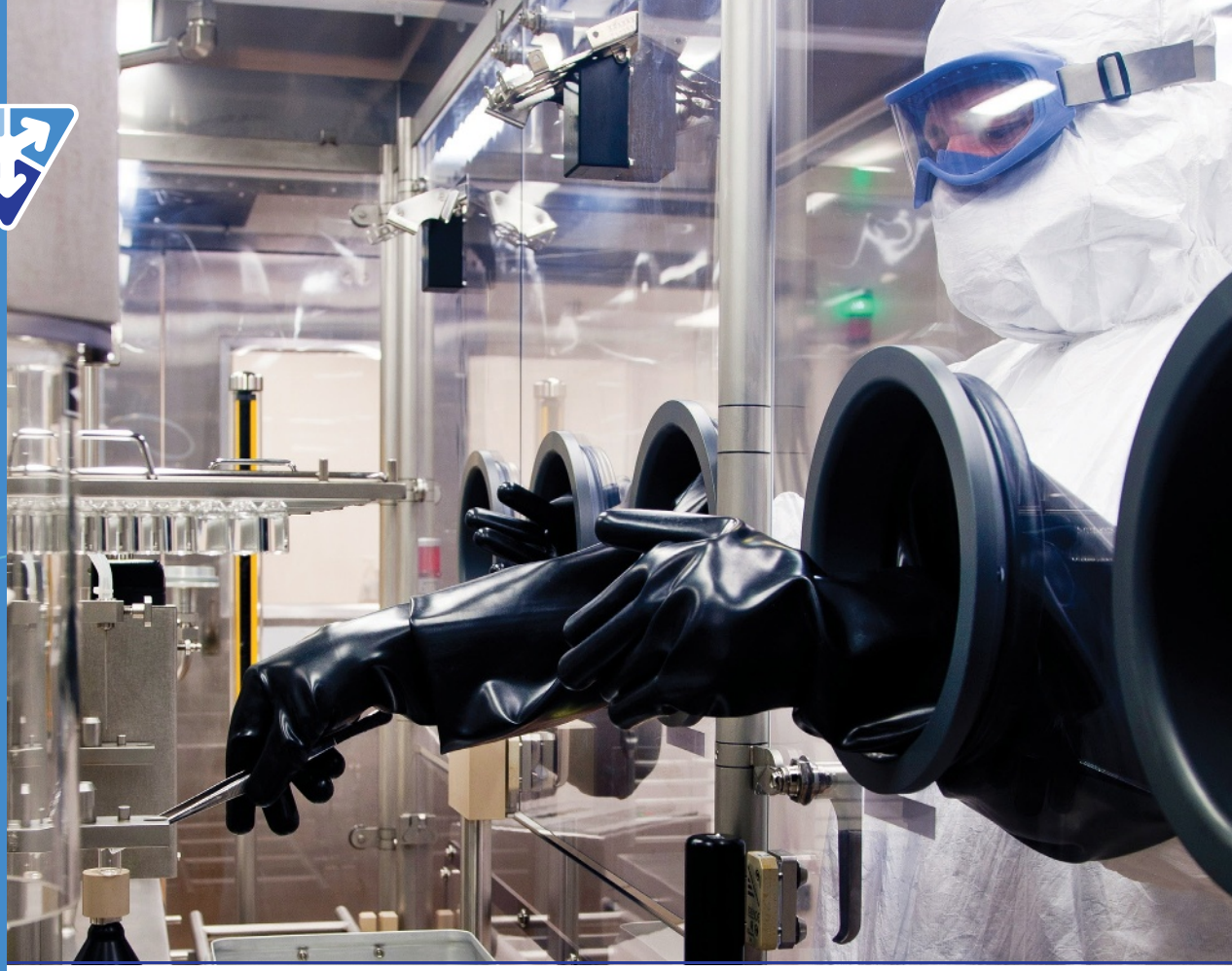

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Outsourcing Trends in Biopharmaceutical Manufacturing

A changing biopharmaceutical industry is going beyond typically outsourced activities and is using CMOs for more challenging processes. The author highlights the top 10 outsourcing trends found during a survey of biopharmaceutical manufacturers.

ERIC S. LANGER

The biopharmaceutical industry is changing the way it manufactures. According to BioPlan Associates' *10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (1), outsourcing and off-shoring have migrated into much more high-value areas of opportunity over the past 10 years. BioPlan's annual studies receive input from between 300–400 global respondents and facilities, on a broad range of issues. Outsourcing and offshoring are some of the many key areas analyzed. Over the past decade, BioPlan has found that developing regions, including China, India, and Brazil, as well as the substantial investments in technologies that improve productivity and efficiency are making outsourcing more strategic. Beyond typically outsourced activities like fill-finish, validation services, and assays, companies are increasingly relying on their suppliers to address more challenging processes. From expertly packing chromatography columns, to providing higher-quality liquid

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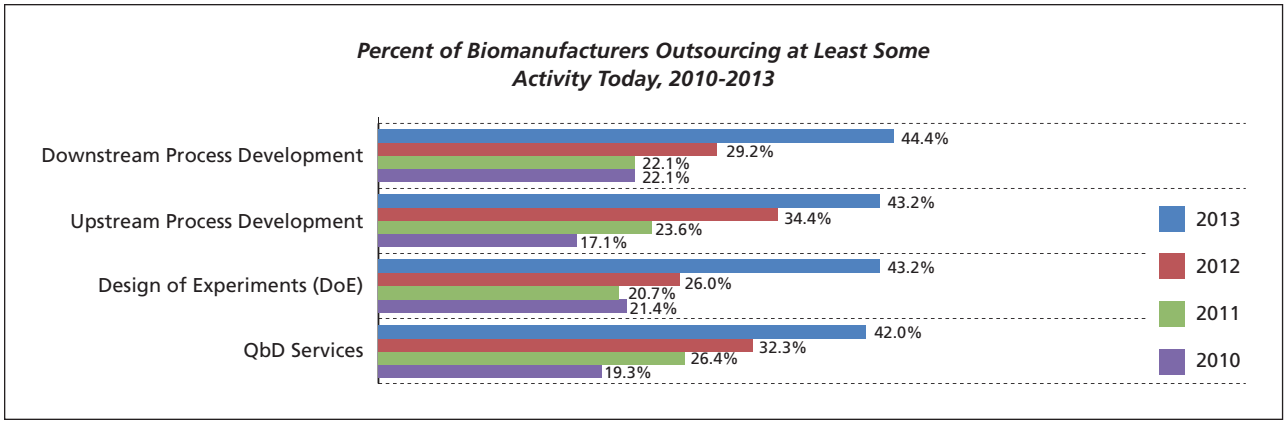
Figure 1: Growth in outsourcing of core activities.



media and buffers at large-scale, suppliers with technical competence are taking on some of the industry's most challenging operations.

Access to targeted expertise is changing the outsourcing landscape. Commercial-scale media and buffer prep, for example, has long been performed in-house. Although large-scale preparation of liquid cell culture media and buffers for biopharmaceutical manufacturing has been discussed for decades, only recently have the economics changed enough to warrant outsourcing of this process.

BioPlan surveyed 50 biopharma decision-makers in July 2014 and found that 47% of this industry would consider outsourcing large-scale media and buffer prep. Interest in local outsourcing of this normally 'core' operation is an indication of the depth in activities that outsourcing appears to be achieving. Outsourcing of culture media and buffer preparation primarily involves hydration of media or buffer powder ingredients under GMP conditions. The economic currents today are changing the make-vs-buy equation and are beginning to favor buying locally prepared liquid culture media and buffers vs. end-users preparing their liquids to cGMP standards from powders in-house. Of course, economics are just one of many factors. Other factors include regulatory, documentation, integration of inventory management, space availability, utilization of classified space, staffing, training, preferences for flexible and lean operations, and demand for bioprocessing sterility.

TREND ONE: OUTSOURCING IS GROWING ACROSS ALL PRODUCTION SYSTEMS

Before looking at the finer details of the outsourcing landscape, it's worth taking a broader view, and data from BioPlan's studies confirm that biomanufacturing outsourcing is a growing market. Part of BioPlan's industry-wide census involves the percentage of facilities that are outsourcing at least some of their production. The results over the past 10 years show that outsourcing is not only increasing across traditional systems including mammalian cell culture and microbial fermentations, but also across newer systems such as plant and insect cells.

Specifically, this past year found:

- Only 46.2% of facilities involved in mammalian cell culture were keeping all manufacturing in-house, down from 57.6% in 2006
- An even smaller share (34.8%) of facilities involved with microbial fermentation were manufacturing 100% in-house, with that down from 58.1% in 2006
- For yeast systems, exactly half claimed to keep all their production in-house, down from 86.2% in 2006
- For plant cells, a strikingly small 28.6% of respondents kept all production in-house, down from a range of 68.6–88.9% not outsourcing any production from 2006 through 2012
- A similar story emerged for insect cells: only 37.5% kept all production in-house, down from a range of 64.7–100% from 2006 through 2012.

TREND TWO: MORE CORE ACTIVITIES ARE BEING OUTSOURCED

There is a growing trend towards outsourcing of activities previously deemed too core to be outsourced. In this latest survey, for example, 44.4% of respondents said that they outsourced downstream process development, a significant increase from 29.2% a year earlier and 22.1% in each of the prior two years.

Similarly, the proportion of respondents reporting having out-

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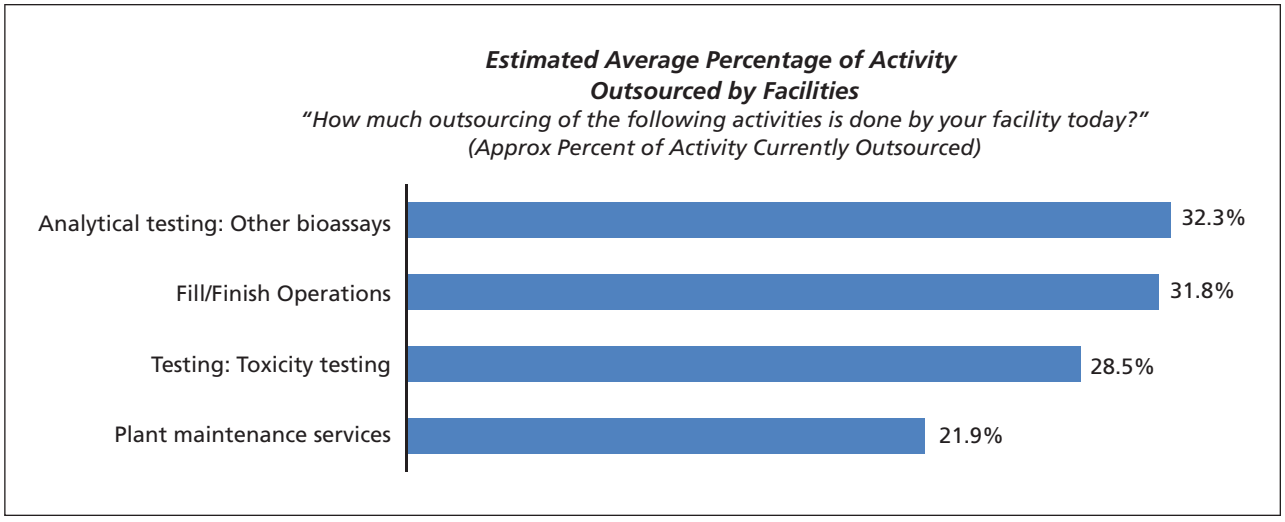
Figure 2: Current outsourcing: Average percent of activity outsourced today.



sourced upstream process development has more than doubled since 2010, from 17.1% to 43.2%. Comparable rates of growth are also seen with outsourcing of design of experiments (from 21.4% to 43.2%) and quality-by-design (QbD) services (from 19.3% to 42%). These activities are still at the bottom of the list in terms of outsourcing popularity, but they are growing rapidly, signaling a greater degree of comfort on the part of clients with the technical expertise of their partners (see **Figure 1**).

TREND THREE: MOST OUTSOURCING REMAINS WITH LOWER-VALUE ACTIVITIES

While the range of activities being outsourced is broadening into new areas, the heaviest levels of outsourcing activity are still centered on lower-value services.

From the responses gathered, BioPlan estimated the average percentage of outsourcing done by biomanufacturers across the various activities listed. On average, facilities outsource 32.3% of analytical testing/bioassays (up from 27.6% in 2012 year), 31.8% of their fill/finish operations (down from 34.5%), and 28.5% (27.3% in 2012) of their toxicity testing (see **Figure 2**). It's worth remembering that these numbers are averaged out among all facilities including those not outsourcing any of these activities. In essence, it's an estimate as to how much of the market's activity in these areas is kept in-house as opposed to being outsourced.

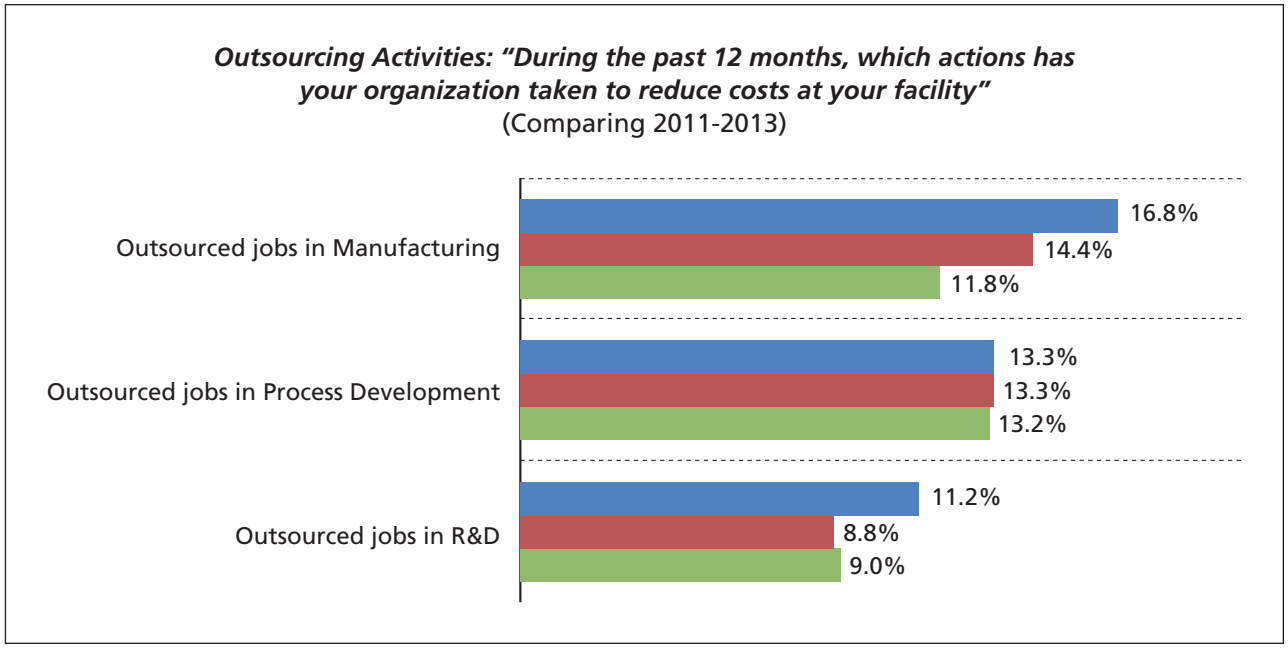
The numbers show that, not surprisingly, lower-value services are the ones that the industry is most comfortable outsourcing. On the other end of the curve, only 7% of design of experiments and 5.9% of QbD services activity is being outsourced.

None of the 24 areas identified were indicated as being outsourced at more than a third of their total activity. So, while it's fair to say that outsourcing is essentially universal, with most every company involved to some degree, it's also worth noting that in general, few areas of bioprocessing are predominantly outsourced activities. That threshold might at some point be crossed for some repetitive or less technical activities, such as performing analytical testing/bioassays, but it is not the case for the time being.

TREND FOUR: MAJORITY OF BIOSIMILARS PRODUCTION COULD BE OUTSOURCED

One area that might end up being mostly outsourced is biosimilars production. Contract manufacturing organizations (CMOs) are likely to see big benefits from the advent of biosimilars, with many CMOs already reporting double-digit increases in business. Given that a significant portion of larger companies will likely prefer to allocate what in-house manufacturing capacity they have to newer, higher-margin products, it's reasonable to foresee a scenario in which major players in biosimilars, at least from a marketing standpoint, will be using CMOs to manufacture their products. Companies will likely license biosimilars from a selection of small and foreign developers and then contract out the manufacturing of these products. It's possible that a slim majority of biosimilars and biobetters will be manufactured by CMOs.

Figure 3: Selected cost-cutting changes specific to outsourcing.



TREND FIVE: BUDGETS FOR OUTSOURCING ARE REBOUNDING

The data and trends point to an outsourcing industry that is expanding in scope, but to what extent are budgets following? One would presume that biomanufacturers would be spending more on outsourcing given their increasing desire to contract out higher-value activities. And data do show that budgets for outsourcing have swung positive over the past few years, as the range of activities being outsourced has swelled.

In fact, over the past five years, respondents to BioPlan's annual studies have gone from forecasting moderate decreases in spending (of -1.3% in 2009) on outsourced biopharmaceutical manufacturing to +1.7% budget increases in 2013. Only hiring of new operations and scientific staff has undergone a bigger turnaround in budgets during the past five years—with that swing very likely due to a general loosening of budgets after recessionary staff reductions.

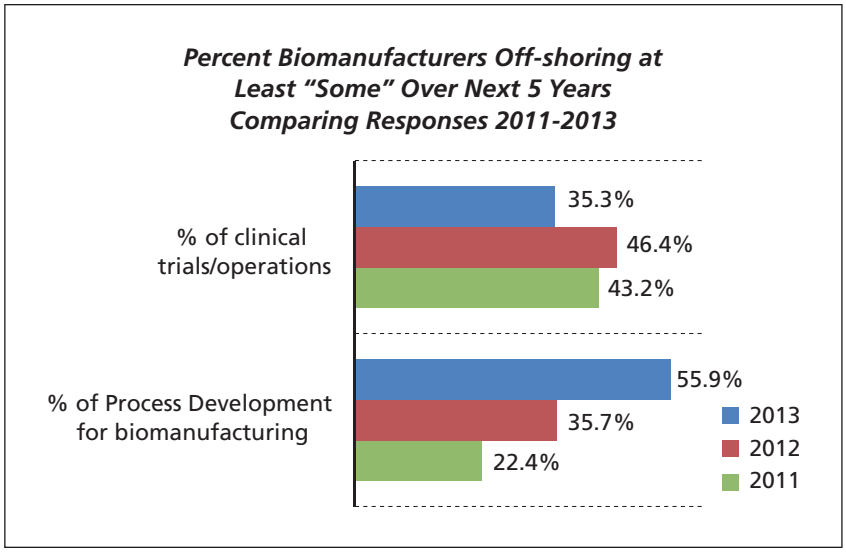
TREND SIX: OUTSOURCING'S GROWING ROLE IN COST-CONTAINMENT

Outsourcing is no longer a top priority when facilities are looking to reduce costs. This may largely be due to saturation and limited returns, with the easiest attainable tasks and those offering the most savings from outsourcing likely already outsourced in prior years. It's also another indication that outsourcing is moving to higher-value areas—with that calculus not driven by cost considerations but instead by the equipment and expertise that CMOs offer that may simply not be available in-house. In other words, use of CMOs is now, perhaps, viewed as a necessary unavoidable expense not affording opportunities or appropriate for further cost-saving. Rather than saving costs, CMOs are viewed as providing benefits including flexibility and low capital investment.

BioPlan asked organizations to identify which of several actions they had taken during the past 12 months to reduce costs at their facility (see **Figure 3**). The survey found 19 common actions associated with bioprocessing, and five of these were related to outsourcing. These five were near the bottom of the list. But it should be noted that they are growing. Last year, for example, 14% of respondents reported having outsourced manufacturing to domestic service providers to cut costs, while 12.6% offshored manufacturing as a cost-containment tool. Those percentages were roughly double the comparable figures from only two years earlier (7.1% and 5.7%, respectively).

So despite not being seen as offering major cost-saving, outsourcing still surely is used by some organizations for cost-reductions (although with these often already implemented, improvements are likely harder to see). But now, other benefits that are much harder to quantify as cost-savings, such as the flexibility outsourcing provides, may be more important.

Figure 4: Five-year off-shoring plans, 2011-2013.



TREND SEVEN: OUTSOURCING IS BECOMING MORE STRATEGIC

There are risks to high levels of outsourcing. Outsourcing can leave companies with fewer real assets, inadequate bioprocessing facilities and staff lacking needed in-house expertise. When activities that were previously considered essential to retain in-house become options for outsourcing, the calculus moves beyond a simple short-term balance sheet analysis and instead turns to a study of the long-term outcomes, since R&D cycles and production build outs are lengthy and risk-intensive. In this context, it is the additional strategic benefits, beyond just cost savings, that outsourcing can bring to drug development and manufacture that often swing decisions.

Those benefits must be weighed against the problems that come with reduced in-house capabilities and expertise that accompany outsourcing: these problems include companies having to hire CMOs and consultants to find and fix problems that classically would or should be resolved by in-house staff, with this potentially being costly. Other problems can arise, such as a lack of consistency in bioprocessing and regulatory documentation, which in turn lead to delays in product development, approvals, and manufacturing.

TREND EIGHT: OFFSHORING IS PART OF THE STRATEGIC DECISION

Companies appear increasingly willing to trust partners beyond those local to them. In fact, in last year's study, only 7% of respondents said that their CMO partner being local to them was a very important issue. Location of CMOs has never been important to facilities, with just 1 in 10 considering it very important back in 2006.

Data from the BioPlan study supports a growing trend towards international outsourcing of some activities. Responses were evaluated from 2011 to 2013 regarding the percentage of biomanufacturers that plan, within the next five years, to offshore at least some of various indicated activities ranging from process development to clinical trials and operations (see **Figure 4**). Significant growth was found in process development, a 33.5% numerical and 250% relative increase from 22.4% in 2011 to 55.9% this past year. Process development was the only area where over half of respondents plan to offshore in the next five years (although with increased emphasis on QbD and related quality issues, one would presume less offshoring of process design). Areas associated with biomanufacturing operations indicated a relatively smaller but still solid overall increase in expectations for offshoring, rising from 37.6% in 2011 to 50% in 2013.

TREND NINE: EMERGING MARKETS A BIGGER PART OF THE EQUATION

Biopharmaceutical facilities are being built by local companies in developing countries to serve their domestic, regional, or lesser-regulated international markets. Markets for biopharmaceuticals are growing in many developing countries, such as India and China, with increased incomes, a new middle class and improved healthcare. Indeed, China (8.6%) and India (8.1%) together account for about one-sixth of global capacity. Factor in hubs in other Asian countries (9.7%) and Latin America (6.6%), and these emerging regions now hold a combined third of estimated global concentration of bioprocessing capacity, employment, and productivity (2).

It's true that these regions have yet to provide the institutional knowledge, facilities, and quality systems to compete in terms of commercial cGMP manufacturing infrastructure, and they have yet to contribute substantially in terms of manufacturing products marketed in the US and European Union. However, products made in India by Biocon may soon become available in European markets, and

multiple South Korean companies can be expected to be among the leaders in launching biosimilars in the United States and EU markets. But China, Singapore, and other countries may have a long way to go, perhaps another decade, before substantially providing products/APIs for the EU and US markets. These countries, however, have become attractive destinations for outsourcing over time, and there's reason to believe that they will grow to become more competitive with the established players.

TREND TEN: BETTER COMMUNICATION ENABLES BETTER OUTSOURCING

Data point to a growing comfort on the part of biomanufacturers with strategically outsourcing core activities—and with the potential to contract this business out to companies in emerging locations. Ultimately, though, these broad trends will only take root if both partners are comfortable with the relationship.

Indeed, as outsourcing becomes more complex, and less familiar, clients and their partners will need to work harder than ever to ensure that they are able to communicate effectively to sort out any real and potential issues. The biomanufacturing community seems to recognize the importance of these "soft issues." When asked to choose from a list of issues they consider "very important" when considering outsourcing to a CMO, a leading 53% cited "stick to a schedule." Roughly half also cited "establish a good working relationship."

These issues have little to do with the type of activity being outsourced or the country they are being outsourced to. What they do indicate is that for international outsourcing—of highly technical activities nonetheless—to become a more seamless proposition for companies and their clients, both parties will need to pay good attention to the underlying relationships that will make their partnerships a win for both sides.

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Biopharma Contract Manufacturing Prices Go Up—and Down

A dynamic market, industry consolidation, and demand fluctuations lead to a mixed picture of pricing results and expectations.

WILLIAM DOWNEY

Over the past two years, the change in prices for biopharmaceutical contract manufacturing services has been mixed. For mammalian cell culture production, prices for small-scale projects have dropped, while prices for medium-scale projects have increased. In addition, the prices charged by CMOs for ancillary services, such as process development, have also increased over the past two years.

In the near-term, biotechnology companies expect to pay higher prices for raw materials, consumables, analytical, and other consulting services. The expectation of higher prices for consulting services is consistent with the trends seen with full-time equivalent (FTE) rates charged by CMOs for process development services.

BACKGROUND

The information and analysis for this article comes from HighTech Business Decisions' latest report, *Biopharmaceutical Contract Manufacturing: Best Practices Pricing Study 2013/2014* (1). This report is based on primary research including surveys and interviews from 27 respondents at pharmaceutical and biotechnology companies (users) who outsource some or all of the production of biopharmaceuticals, and from 18 biopharmaceutical CMOs. All respondents in this study are senior-level executives or scientists. This study focuses solely on biopharmaceutical manufacturing sold on a fee-for-service basis by CMOs. For purposes of the study, biopharmaceuticals are defined as complex molecular structures created through the genetic manipulation of living cells or organisms used for therapeutics, diagnostics, or vaccines. The respondent companies participating in this study are located in North America, Europe, and Asia.

RECENT PRICE CHANGES

Based on the observations from the respondents, overall prices for biopharmaceutical contract manufacturing services show an upward trend. While a plurality of respondents observed stable prices over the past two years, more respondents reported higher prices versus lower prices. In total, 49% of the respondents reported stable prices, 31% of the respondents reported higher prices, and 20% of the respondents reported lower prices (see **Table I**). For this analysis, stable prices are defined as changes of 3% or less. It is assumed that small price changes result from either currency fluctuations or general economy-wide inflation levels. And they are not necessarily specific industry price changes. Further analysis of observed price changes by the respondent group shows that users observed more price increases than did CMOs.

There are differences in observed price changes between users and CMOs. Fifty-two percent of the users observed stable prices, compared to 44% of the CMOs. Furthermore, 37% of the users observed higher prices over the past two years, while 22% of the CMOs observed higher prices over the same time period. Conversely, only 11% of the users observed lower prices compared to 33% of the CMOs who observed lower prices. While the observations between users and CMOs are different, these differences are not significant, based on the chi-square test for independence between the users and CMOs. The chi-square test for independence shows a p-value of 0.17; therefore, we cannot reject the null hypothesis for independence. Thus, while there are some differences between users' and CMOs' price observations, these differences are not significant.

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Table I. Price changes by respondent group.

Respondent group		Change in prices			
		Higher	Stable	Lower	Total
Users	Observed	10	14	3	27
	Adj. Residuals	1.05	0.49	-1.83	
CMOs	Observed	4	8	6	18
	Adj. Residuals	-1.05	-0.49	1.83	
Total		14	22	9	48

Chi-Square Analysis
H_0: $\pi ij = \pi i+ + \pi +j$
$X^2 = 3.55$; p-value= 0.17
Cannot Reject H_0: N_0 significant difference between respondent groups

While in total the two respondent groups' observations are similar, the category of lower prices shows a significant difference between the two groups. Only 11% of the users observed lower prices, while 33% of the CMOs observed lower prices over the past two years. Respondents from the CMO group were three times more likely to observe lower prices than respondents from the user group. This difference is significant, as can be seen by the adjusted residual of 1.83. This difference is most likely the result of different project scales and product phases between users and CMOs.

Several respondents gave specific examples or details about their price observations. A few respondents mentioned lower prices associated with either new CMOs or CMOs using single-use technologies. Other respondents noted that greater demand for contract manufacturing services has resulted in higher prices. Similarly, other respondents noted that consolidation and mergers have reduced excess capacity; thereby lessening the need to offer steep discounts in an effort to fill unused capacity.

A few insightful comments from the biomanufacturing directors regarding the price changes for contract manufacturing services are shown as follows: (1)

- "There has been consolidation in the industry that has driven prices up. Some small start-ups are offering lower level pricing, but the mainstream CMOs are increasing their prices."—*Pharmaceutical/Biotechnology Company*
- "Pricing for single-use has decreased more than 10%. Pricing for manufacturing in stainless steel has remained consistent for the past seven years."—*Pharmaceutical/Biotechnology Company*
- "Pricing has been stable for the last three or four years. There was a downturn around 2008/2009. Since then, the volume of projects has been going up but balancing that, there are more CMOs and some CMOs are making large investments in infrastructure. Single-use bioreactors are making it easier to get into the industry."—*Contract Manufacturing Organization*.

GMP PRODUCTION PRICE CHANGES

The mixed observations about changes in prices observed by the respondents can also be seen in the change in prices for mammalian cell-culture production. Detailed price information for GMP manufacturing—collected in current and past studies from both users and CMOs—was used evaluate current industry pricing. From quantitative analysis of pricing, the per-batch prices for mammalian cell culture have declined for small-scale production and increased for medium-scale production over the past two years (**Figure 1**).

The average per-batch price for small-scale mammalian cell culture production is down 8% from two years ago. While over the same period, the average per-batch price for medium-scale production is up 21% over the same time period. The average price for large-scale production has stayed relatively flat; it is up 1%. As noted earlier, the lower prices for small-scale mammalian cell-culture production most likely results from new CMOs entering the market coupled with the adoption of single-use technologies at these smaller scales. The higher batch prices for medium-scale production most likely results from consolidations and adjustments in industry capacity to better match supply with demand.

FTE RATES

Besides production prices, the respondents in this study also provided the annual FTE rates for the various consultative-type services provided by CMOs. These rates are for services using staff in functions such as process development, manufacturing, quality, regulatory support, and project management. From the CMOs' inputs, annual FTE rates for process development services range from less than $100,000 to greater than $400,000. The average annual FTE rate charged by CMOs for process development is $248,000, which is an increase of 19% from two years

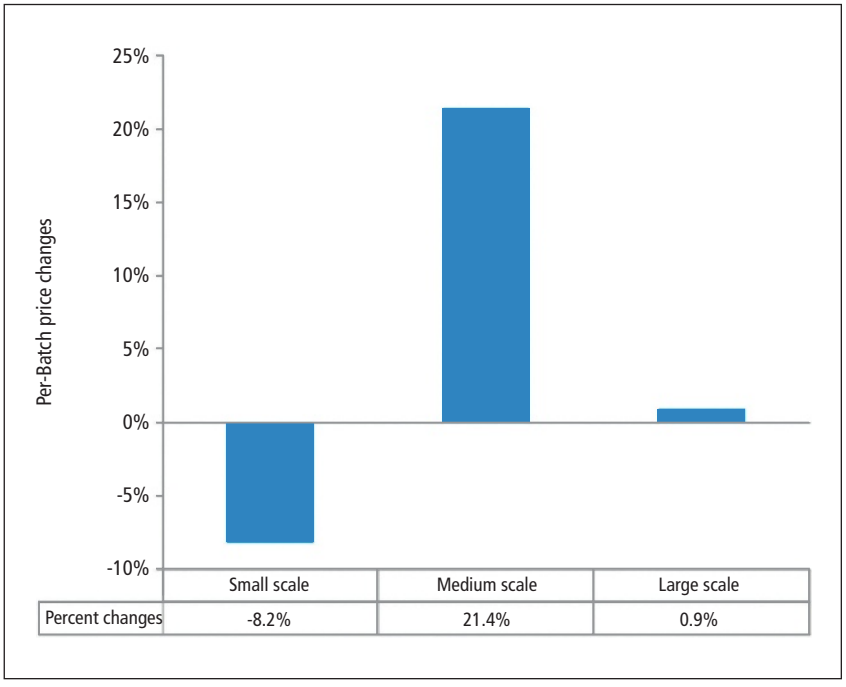
ago. This large increase in average FTE rates results from the distribution of FTE rates being more positively skewed in 2013 compared to 2011. From the analysis, there are fewer CMOs charging for process development services at the lowest FTE rate category, and more CMOs are charging at higher rate categories. As an example, in 2013, 75% of the CMOs charged an FTE rate of $350,000 or less, while in 2011, 78% of the CMOs charged an FTE rate of $300,000 or less.

FUTURE EXPECTATIONS

In addition to providing details about current prices paid for contract manufacturing services, the respondents in the study also discussed their expectations about future price changes. Over the next two to three years, a majority of users expect higher prices. The reasons given by the users for higher prices include higher demand for contract manufacturing services, greater regulatory and quality requirements being placed on CMOs, and general inflationary pressures. They expect higher demand over the next few years to increase industry capacity utilization rates and thus reduce excess supply. Currently, slightly more than half the users (52%) are now experiencing higher prices or seeing proposed price increases from their CMOs. Additionally, about one-fifth of the users (18%) expect to see higher prices in certain services and lower prices for other services offered by their CMOs, while approximately one-quarter (26%) of the users expect stable prices in the future.

In addition to sharing their expectations about future price changes, the users also provided details about specific products or services where they expect to see future price changes (see **Figure 2**).

Figure 1. Changes in batch prices 2011 versus 2013.



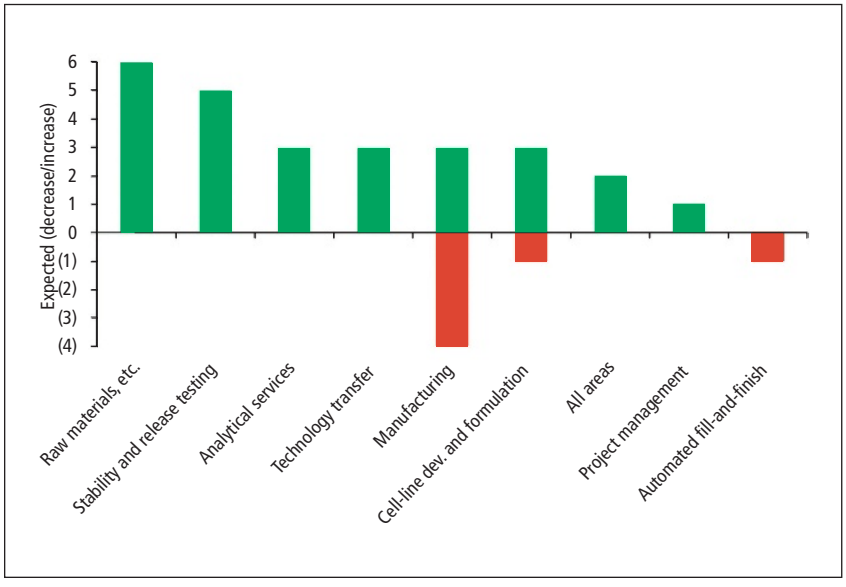
The users expect to pay higher prices for raw materials and consultative-type services. They specifically mentioned higher prices for raw materials and consumables, stability and release testing, analytical services, and technology transfer. Higher prices for raw materials and consumables were mentioned most often by the users, while higher prices for consultative-type services correspond to the higher average FTE rates reported by the CMOs. On the other hand, the users stated they have a mixed outlook for changes in manufacturing prices. In this case, more users expect to see lower prices than higher prices.

The following are comments from both pharmaceutical and biotechnology companies and CMO respondents regarding their future price expectations: (1)

- "We are seeing increased requirements for testing for adventitious agents but this is usually testing outsourced by the CMO so they pass through the costs to us so it is not really an increase from the CMO." —*Pharmaceutical/Biotechnology Company*
- "We're seeing higher prices for ancillary services such as project management and supply chain distribution."—*Pharmaceutical/Biotechnology Company*
- "Materials costs seem to be higher, things like resins, chemicals, and components. Transportation costs are higher and sourcing takes more effort now because vendors are not keeping as much inventory on hand. It may be that we had very good agreements in the past and now vendors are realizing they need to charge more."—*Pharmaceutical/Biotechnology Company*
- "FTE rates are going up which will affect all services. The FTE inflation rate is higher in Asia than in US and Europe. The capacity utilization rate is increasing so we can expect

ALL FIGURES COURTESY OF THE AUTHOR

Figure 2. Expect price increases and decreases.



prices to go up."—*Pharmaceutical/Biotechnology Company*

- "Raw materials, our vendors' pricing is going up higher than inflation. It is not clear why, maybe because of consolidation among suppliers or maybe because of the cost of implementing quality systems. Testing pricing is stable, but we are doing more testing. Regulators and consultants at the biotechs are requesting the extra testing. There is a good database for different kinds of products now, tests that have proved to be useful so the regulatory bodies expect them to be done."—*Contract Manufacturing Organization*
- "For any monopolistic situation, pricing is higher, for example column materials. Consolidation at places like Thermo Fisher and Life Science Technologies are contributing to this monopolistic situation. Equipment maintenance costs are going up. Suppliers realize customers are bound to them."—*Contract Manufacturing Organization*

ANALYSIS

An interesting observation can be seen from the changes in prices for both production and consultative-type services offered by CMOs. First, lower prices for small-scale production and the expected higher costs for raw materials and consumables suggest that the benefits from adopting single-use production technologies will not accrue to the CMO itself. But rather, the financial benefits of adopting single-use technologies will accrue to either the CMO's supplier or client. The lower upfront capital cost of single-use production reduces the barriers of entry for new CMOs. As noted by a few respondents, there are more CMOs entering the market using disposable technologies. The lower entry barrier results in a more intensely competitive market resulting in greater price competition and lower margins for those CMOs that cannot effectively differentiate their service offerings. Thus, we see lower prices for small-scale production where single-use technologies are being adopted. In addition, expected price increases for consumables and raw materials show that larger raw material suppliers are also able to derive some of the financial benefits of using disposable technologies from their CMO clients. This is most likely the result of the limited bargaining power that smaller CMOs have with its raw material suppliers.

The other observation pertains to higher FTE rates. The rates paid by the users for consultative-type services have remained flat over the past two years; however, average rates have been charged by CMOs increasing dramatically over the past two years. The average rates are increasing because fewer CMOs now charge rates at the lowest tier. These higher rates most likely reflect the narrowing salary differences between geographic areas.

SUMMARY

The market for biopharmaceutical contract manufacturing services is dynamic and prices are both increasing and decreasing. Smaller-scale production prices have dropped over the past year, while mid-scale production prices have increased from two years ago. In addition, consultative-type service prices are continuing to increase. Some of these increases are the result of higher wage inflation in emerging markets compared to the wage inflation in developed markets. Overall, pharmaceutical and biotechnology companies expect to pay higher prices for raw materials and consumables, and consultative-type services in the future.

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Ensuring Sound Bioanalytical Methods Transfer

A Q&A on bioanalytical method integrity with Roger Hayes of MPI Research.

THE EDITORS OF *BIOPHARM INTERNATIONAL*

For a drug-development process that relies on outsourced services for key research and development functions, special considerations are needed to ensure the proper transfer of technology and information from one phase to the next, across multiple vendors or facilities.

Drug discovery, preclinical, and development phases can take years, cross multiple organizations, facilities, researchers, and technologies. Maintaining the integrity of bioanalytical methods is paramount. Roger Hayes, PhD, vice-president, general manager of Laboratory Sciences at MPI Research, shares best practices to ensure successful bioanalytical methods transfer from preclinical to Phase I development, data/information sharing, and guidance that can establish terms for acceptability of method transfer in an interview with *BioPharm International*.

BEST PRACTICES: PRECLINICAL TO PHASE I

BioPharm: What would you identify as some key best practices to ensure successful bioanalytical methods transfer from preclinical to Phase I development?

Hayes: The preclinical space incorporates both discovery and safety assessment phases, each with differ-

ent requirements of bioanalytical method quality and sensitivity. A common term is fit-for-purpose, which refers to the quality of the method required to answer questions or regulatory requirements at a particular stage of drug development. Safety assessment studies are normally performed in accordance with GLP regulations and, as such, require fully validated bioanalytical methods. In contrast, methods that support candidate selection or lead optimization are not validated, but the methods do require sufficient quality to provide confidence in the results.

Because preclinical safety assessment involves higher drug exposures than those anticipated in the clinic, the bioanalytical method has a higher limit of quantitation that offsets the limited volumes typically available for sample extraction and subsequent concentration. Moreover, the number of samples collected for preclinical analysis is much lower than the high-throughput environment of clinical drug development. Therefore, assay robustness is not of high concern up until the transition to clinical bioanalysis.

Assay robustness is best achieved by adequate sample cleanup and chromatographic selectivity that separates matrix interferences and biotransformed products from the analyte of interest. Chromatography method development following preclinical bioanalysis is usually sufficient for first-in-human clinical trials. Some consideration is typically given to shorter analytical run times to accommodate higher sample numbers and a desire for more rapid data turnaround. If the first clinical studies use normal, healthy volunteers, the sample composition is not likely to be much different from preclinical studies, but patient samples will likely be more heterogeneous. Sample cleanup will, therefore, require more sophistication; a simple protein precipitation approach used in preclinical bioanalysis may give way to solid phase extraction or phospholipid removal methodologies. To achieve lower limits of quantitation, higher sample volumes are typically extracted and concentrated. Fortunately, sample volume is not normally a limitation in clinical bioanalysis, with the exception of pediatric or certain oncology trials.

Even with adequate sample cleanup and chromatographic selectivity, it is important to sufficiently compensate for analyte recovery or ionization differences by an appropriate internal standard, most often a stable isotope-labeled analog of the drug. Indeed, a stable labeled internal standard is essential for clinical analysis because of the heterogeneity of humans compared to preclinical species.

SPECIALIZED TRANSFER

BioPharm: Can you outline specialized considerations for bioanalytical methods transfer when the drug substance is a macromolecule, such as pharmacokinetic and immunogenicity measurements, or the use of specific reagents (i.e., antibody pairs) in the method development?

Roger Hayes

Hayes: Two key elements in successfully transferring a bioanalytical method for a protein therapeutic are the identification and sourcing of critical reagents. The identity of the test article will have a direct impact on the complexity of the ligand-binding assay (LBA), whether the assay is to support pharmacokinetic (PK) measurements or determine anti-test article antibody (ADA) response. Moreover, critical reagents used for capture and detection in PK assays, or as surrogate positive controls for ADA assays, need to be reliably sourced. The success of the LBA method is highly contingent on the quality and integrity of the critical reagents. When critical reagents are not commercially available, a sponsor will be expected to initiate the generation of critical reagents either internally or externally (outsourced).

Over the lifetime of the assay, there needs to be monitoring and quality control of the reagents. Reagent lot-to-lot differences may lead to significant variability in assay performance. When such variability is observed, the assay may require modification to return assay performance to established acceptable limits. The lot-to-lot variability may be substantial when the reagent is a polyclonal antibody that was generated from different immunizations or different animals. Alternatively, the use of monoclonal antibodies, where all lots are obtained from the same hybridoma cell line, is one approach that sponsors and CROs may choose to mitigate such differences.

SHARING DATA

BioPharm: What are some problems in data/information sharing that might be encountered in bioanalytical methods transfer and how may they be resolved? For example, how are laboratory variations (e.g., methods of pipetting, storage of reagents, analyte stock solution, specialized equipment, reagent purity and preparation) addressed that might influence method variability?

Hayes: There are many different reasons for a sponsor to outsource bioanalysis. But once an outsourcing relationship is established, the level of communication must align with the sponsor. At its foundation, the relationship requires the exchange of information in an accurate and timely manner. Over the course of the relationship, various activities occur, including assay development,

validation, and sample analysis. The sponsor will expect that these activities are performed by well-trained bioanalytical scientists. The CRO will provide individual training, and because efficiency is a key requirement of CRO operations, harmonizing techniques and streamlining bioanalytical processes across the laboratory will likely be implemented. To reduce and even eliminate technical differences in pipetting, for example, using dependable automated liquid handling systems is strongly recommended. With automation, analyst fatigue resulting in human error is dramatically reduced and productivity is increased.

The success of preclinical and clinical bioanalysis is determined by the quality of an assay's critical reagents.

The assay format and platform chosen for a given method are influenced by many factors. For instance, preclinical assay formats are largely dependent on availability of critical reagents, while dose and sensitivity may dictate the platform used. Clinical programs, on the other hand, require specific human protein recognizing reagents capable of selectively detecting human protein therapeutics. Because of the need to ensure method transferability across different facilities, it is unlikely that novel assay platforms will be selected for the initial method.

As discussed above, the success of preclinical and clinical bioanalysis is determined by the quality of an assay's critical reagents. During preclinical development, the life span of an assay is often short term and predictable; therefore, reagent availability is the only concern best mitigated with effective relationships with reagent vendors. Over prolonged clinical studies, implementation of more stringent physicochemical and biophysical characterization methods for critical reagents is essential to ensure the integrity of the bioanalytical method and data quality.

ACHIEVING ACCEPTABLE STANDARDS

BioPharm: How is the acceptability of a method transfer best evaluated? How are factors such as site transfer considered?

Hayes: The pharmaceutical industry is highly regulated and regulatory authorities normally offer guidance documents that describe best practices for the validation and subsequent application of bioanalytical methods. The fundamental parameters of a method that require being in control include accuracy, precision, selectivity, sensitivity, reproducibility, and stability. The quality of an analytical method is normally assessed by the performance of standards and quality control samples (QCs). Current guidance recommends an acceptance criterion of 15% for accuracy, precision of all standards, and QCs, with the exception of the lower limit of quantitation (LLOQ), where the acceptance criterion is increased to a 20% deviation. However, standards and QCs may not adequately reflect the composition of study samples from dosed subjects (i.e., incurred samples). The limitation of using spiked control samples to assess 'real' samples is known, and there is general acceptance that confirmatory reanalysis of incurred samples can be used to assess the reproducibility of a method.

Method transfers are very common and, in fact, the majority of regulated bioanalysis is now performed at CROs. A method may be validated either in-house or at another CRO, and because of resource or quality constraints the sponsor might request that a new CRO use the previously validated method with minimal additional work. It is important to note that a regulator expects to be able to verify all aspects of the method validation during an inspection at the site performing regulated bioanalysis. If all raw data generated during method validation are available on-site for review, and the regulator can verify that the original method is being executed in the same validation manner, this would eliminate the need for repeating the method validation at a new CRO. Unfortunately, it is rare that all raw data are transferred to the receiving CRO, when what typically is provided is only the validation report. Moreover, it is difficult to assure a regulator that the method is being executed in exactly the same manner as might be documented in a validation report. The path of least resistance is to revalidate the method in its entirety to assure that all source records are available in the event of a regulatory audit.

A regulator will also typically require some assessment of comparability between methods, particularly if two or more methods are used within the same study. Comparability can be performed by using samples of known concentration (i.e., QCs and standards), and/or existing study samples. The acceptance criterion for comparability is commonly 20% relative error for small molecules and 30% for large molecules (e.g., protein therapeutics). **BP**

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CMOs Gear Up for Biologics Manufacturing Challenges

Contract manufacturers employ single-use facilities, screening technologies, and packaging systems to meet market demand.

THE EDITORS OF *BIOPHARM INTERNATIONAL*

Technologies, such as high-throughput screening and single-use systems, are facilitating the development and manufacture of large-molecule drugs. Representatives of contract service organizations discussed technology trends with *BioPharm International*. Roundtable panelists are Aileen Ruff, strategic director advanced delivery technologies, Catalent Pharma Solutions; John Sandles, business analyst, Fujifilm Diosynth Biotechnologies; Mark Pearson, director business development, Dr. Reddy's CPS; Wendy Saffell-Clemmer, director R&D, Baxter BioPharma Solutions; Peter Soelkner, general manager, Vetter Pharma International GmbH; and Andrew Strong, president and CEO, VP business development, Kalon Biotherapeutics.

BioPharm: What scientific or technical advances have positively or negatively impacted drug-development processes in the biologics market segment?

Sandles (Fujifilm Diosynth Biotechnologies): The introduction of high-throughput screening technologies across R&D means that it is much easier to demonstrate rapid and scalable process development. For instance, our recently purchased ambr250 (TAP Biosystems) aids in rapid selection of upstream fermentation conditions. This initial screening timeframe

The parenteral drug pipeline has continued to shift from small molecules to complex biologics.
— Wendy Saffell-Clemmer, Baxter BioPharma Solutions

reduction takes process development further off the critical path to human trials and consequently means the drug-development process is reduced with an increased data set to justify forward-working decisions and satisfy regulation.

Pearson (Dr. Reddy's CPS): Alternative technologies to extend the half-life of biologic drugs are being developed. This has positively impacted the drug-development process by giving more choice. However, the new technologies have yet to be approved by FDA for use in commercial drugs. A sponsor would have to license a new technology. PEGs [polyethylene glycol] are already approved and easy to use. A lot of the emerging technologies would require specialist expertise and be more complex to set up.

Ruff (Catalent Pharma Solutions): The wider use of antibody drug conjugates (ADCs) and the introduction of improved, potentially safer ADCs in particular, will undoubtedly have a positive impact on this market. There are currently only two with FDA approval: Brentuximab vedotin for the treatment of Hodgkin's and anaplastic large cell lymphoma, and trastuzumab emtansine … for the treatment of HER2+ breast cancer. The current ADC pipeline is large, with more than 100 ADCs currently in clinical trials; this effort underscores the industry's belief that ADCs will help create safer, effective biotherapeutics.

SINGLE-USE TECHNOLOGIES, PEGs, AND ADCs

BioPharm: What emerging technologies or practices do drug sponsors expect your organization to provide?

Sandles (Fujifilm Diosynth Biotechnologies): For mammalian cell culture, there is an increasing demand for single-use technologies and is expected as the norm in this sector. The environmental and financial outcomes are favorable over stainless steel at smaller scales of production; however, at larger scale, stainless steel is still a very prominent option. Using single-use means up to 90% less water is needed for cleaning purposes per batch, meaning a reduced contamination risk and cost is incurred against stainless steel.

Pearson (Dr. Reddy's CPS): Drug sponsors have come to expect CMOs to offer the GMP manufacture of larger volumes of product at competitive prices. CPS has invested in a facility for the manufacture of mPEG alcohols in Mexico and a site at Mirfield, UK that can provide large-scale, multimetric ton GMP manufacture of activated mPEGs for biologic drugs. Increasingly, drugs being PEGylated are higher dose, which in turn requires larger-scale production of PEGs for half-life extension.

Strong (Kalon Biotherapeutics): Industry expectations of CMOs for technologies include disposable technologies and single-use systems. A broad, in-house analytical capability is also an expectation. In all cases, however, the bioprocessing technology needs to be scalable to commercial scale.

Ruff (Catalent Pharma Solutions): We have seen increasing demand for biologics and biosimilars development, where we have proven cell line technology and have recently launched new manufacturing facilities in Madison, WI. ADCs are also attracting much interest. Catalent is developing the oral delivery of vaccines to treat the flu, pneumonia, and HPV through our Zydis Bio technology platform. Further innovations for oral macromolecule delivery include our OptiGel Bio technology that may overcome the traditional hurdles by enhancing permeability combined with targeted delivery.

Saffell-Clemmer (Baxter BioPharma Solutions): The parenteral drug pipeline has continued to shift from small molecules to complex biologics such as monoclonal antibodies and ADCs. As the complexity of molecules increases, drug sponsors are requesting a broader array of analytical test methods for drug product release and stability. In particular, most biologics customers are now requesting capillary electrophoresis methods such as capillary isoelectric focusing (cIEF) or imaging capillary electrophoresis (ICE), in addition to more common chromatographic methods.

Soelkner (Vetter Pharma International): Sponsors expect state-of-the-art filling lines that both enhance quality and save costs, for example, fully automatic machines to optimize yield but also reduce risk of human contamination. To meet their products' specific needs, sponsors also demand from us high flexibility in equipment and processes. That means, for example, providing stainless steel and disposables; options in pumping and filtration systems; and the capability to handle new materials and injectable systems like polymer and pre-sterilized syringes.

CHALLENGES AHEAD

BioPharm: What pressing technical challenges have you seen in the biologics market segment? What actions has your company taken to resolve the challenge?

Sandles (Fujifilm Diosynth Biotechnologies): We are finding that customers are expecting material that represents scalability to be produced at much faster rates. Fujifilm has the technology to meet these demands with both microbial and mammalian cell culture expression systems. We have added extra HTS [high throughput screening] capability for upstream and downstream process development to further reduce time to clinic for our customers.

Pearson (Dr. Reddy's CPS): One challenge is the perception that PEGs can be expensive, potentially immunogenic, and may accumulate in the body. Producing PEGs in larger volumes brings costs down and there has been no evidence of adverse events in patients. Other technologies used for increasing half-life have not yet been FDA-approved. Therefore, PEGs remain the preferred half-life extension technology.

Strong (Kalon Biotherapeutics): The most pressing technical challenges are mostly on a case-by-case basis, and more often than not, related to the specific biological product in question. Having technologies that allow for solutions that will scale with the process to commercial scale, as part of the CMO toolbox, remains an important capability. Analytical resources and reliable analytical methods are key to any challenge and its solution.

Ruff (Catalent Pharma Solutions): Technical challenges include 'big picture' ones, such as finding more efficient ways to purify protein and better ways to grow cells to obtain higher titers, cleaner starting material, etc., but also smaller, less exciting ones, such as standardization of single-use connectors and films that will also fundamentally effect the industry.

Saffell-Clemmer (Baxter BioPharma Solutions): There has been increasing awareness in subvisible particles resulting from the aggregation of therapeutic proteins. The size range of interest (2–10 µm) is not monitored by current compendia methods. Baxter BioPharma Solutions has invested in particle analysis systems such as micro-flow imaging and has conducted research in the area of protein aggregation during freeze-drying in cooperation with Fluid Imaging Technologies. Characterization and monitoring of subvisible particles throughout product development should be performed for large molecules.

Soelkner (Vetter Pharma International): Accuracy on the filling line is one of the industry's greater technical challenges. Precision is vital to product quality and patient safety. Combination products involving auto-injectors, safety features, and new primary packaging materials have to perform every time to prevent incomplete injection, glass breakage, and other failures. Continuous investment in technology and staff training helps us meet those challenges, as well as constant monitoring of the market and environment to keep up with new manufacturing regulations.

SPECIALIZED MANUFACTURING ADVANCES EXPECTED

BioPharm: What advances do you see in science or technology in this market segment in the next five years?

Sandles (Fujifilm Diosynth Biotechnologies): We expect to see more and wider deployment of single-use technology as the benefits become widely recognized.

Pearson (Dr. Reddy's CPS): There will be an increase in technologies able to prolong the half-life of biologic molecules. Companies who are looking for an appropriate half-life extension technology will screen several technologies to determine which is best. PEGs are likely to remain a significant technology but probably not the only one in regular use. There will be increasing development and use of mono-disperse PEGs and use of PEGs in new areas such as nanoparticles and niche formulations.

Ruff (Catalent Pharma Solutions): Look for breakthroughs in efficiency in manufacturing and for new technologies, such as ADCs with advanced linker technologies, to drive safer, better treatments. Many of these products will be more complex than current biologics, leading to more extensive characterization and testing.

We also expect to see more countries looking within their own borders for biologics manufacturing as they want to control manufacturing of these products due to concerns about supply chain of these products.

Strong (Kalon Biotherapeutics): Bioprocessing is becoming less of a unit operation and more continuous. Technologies that provide for continuous processing upstream and downstream are at the forefront for the next five years. Being able to process highly concentrated proteins without having to go through a lot of buffer exchange unit operations will impact time on plant, buffer-prep, and quality control resources and ultimately affect [cost of goods sold] COGS. BP

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Global Biopharma Industry Shifts Echoed in Real Estate and Facilities Clusters

Trends in real estate and facility clusters give insight into the state of the biopharmaceutical industry.

ROGER HUMPHREY

Biopharmaceutical companies large and small are seeking to balance costs while retaining—or gaining—access to talent, R&D resources, capital, and new markets. As tracked in JLL's annual *Global Life Sciences Cluster Report*, real estate and facilities strategies—how they are used, where they are located, and how they are managed—reflect the current state of the industry (1). They show how the industry is responding to the shift to biological medicines, the need for new products, the influence of healthcare reform in the United States, and other global pressures (see **Figure 1**).

Global trends are stimulating significant changes in the types and locations of biopharmaceutical facilities, and the rise and fall of cities and regions where life-sciences companies, jobs, talents, and resources are concentrated. Many large life-sciences companies have consolidated their operations and vacated major campuses in mature US and Western European areas—while expanding in developing countries with growing markets and lower operating costs.

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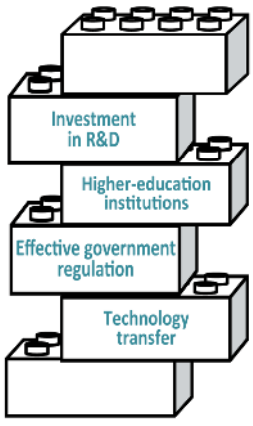
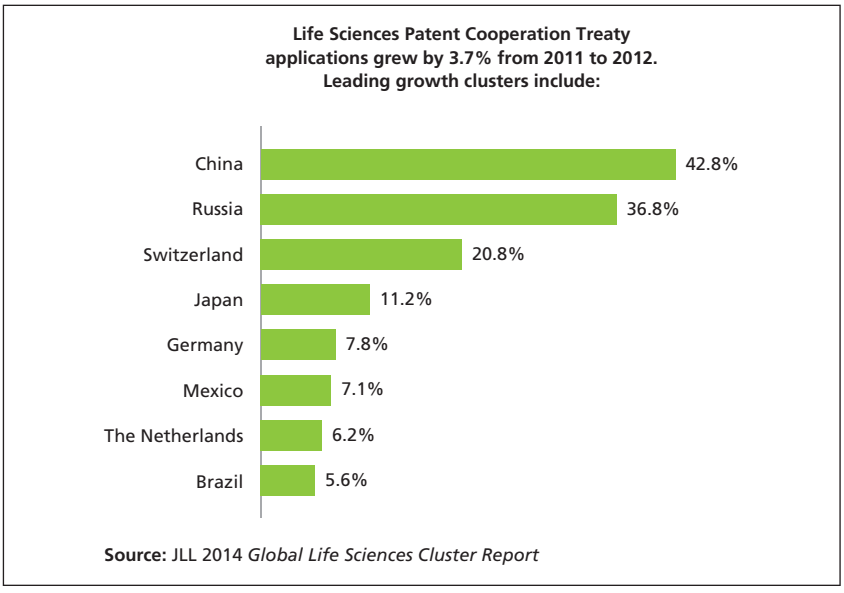
Figure 1: Building blocks of development.



Source: JLL 2014 *Global Life Sciences Cluster Report*

Figure 2: BRIC nations becoming R&D leaders.



Source: JLL 2014 *Global Life Sciences Cluster Report*

In 2013, for example, Germany-based Boehringer Ingelheim put up for sale its 190-acre, production campus in Petersburg, VA, in the southeast US. The company cited competition from low-cost generic medicines as a factor in the decision.

Another JLL report, *Global Corporate Real Estate Trends for the Life Sciences Sector*, reveals that more than one-third of life-sciences companies anticipate reducing or consolidating their real estate portfolios in European markets, while 63% and 48% plan to increase their portfolios in China and Brazil, respectively, and 35% in Russia (2).

SMALLER COMPANIES DRIVING REAL ESTATE AND FACILITIES DEMAND

Alongside the reshaping of global companies, 2013 brought new energy to the biopharmaceutical industry. A significant transition is underway, as start-ups, specialty firms, and mid-tier companies become the leading source of new product innovation, with initial public offerings at a volume not seen since the "dot.com" bubble of the 2000s.

These smaller players are spurring most of the new demand for office, R&D, and production facilities as they experience overnight growth and highly-variable needs. US clusters with a large percentage of start-up, mid-tier, and specialty companies flourished in 2013, with moderate increases in year-over-year employment and establishments. Conversely, clusters with large headquarter campuses and manufacturing sites generally experienced declining employment in 2013.

Greater San Diego is a prime example of a top US cluster where growth from large pharmaceutical and biotech companies was noticeably absent in 2013. Landlords have begun catering to San Diego's burgeoning small and mid-tier biotech companies, often transforming large vacant R&D facilities into modern multi-tenant alternatives designed to promote scientific advancement and collaboration, and to help companies recruit top talent.

GLOBAL SHIFTS IN INNOVATION

The significant shift underway in global innovation is a second major trend detailed in the *Global Life Sciences Cluster Report*. Developing countries, particularly those in Asia, are reporting impressive growth in patent applications, R&D funding, labor productivity, and science degrees. The US still leads the world in R&D funding, but Brazil, Russia, and India are experiencing the highest rates of growth in gross domestic expenditures on research and development (GERD).

Similarly, Asia's share of Patent Cooperation Treaty life-sciences applications grew to 26% in 2012 from approximately 5% in 1990, while North America's share shrank to 41% in 2012 from more than 50% in 1990. Other countries with significant year-over-year growth include: Russia, Switzerland, Japan, Germany, Mexico, the Netherlands, and Brazil.

Bringing new inventions to market, however, requires not

FIGURES COURTESY OF THE AUTHOR

only patents, but also a critical mass of talent, investment, laboratories, and production facilities. Governments in Asia and Latin America are making significant capital investments and improving public policies to become more competitive and to attract clinical-trial outsourcing opportunities. Massive research parks in these emerging global clusters are fuelling growth in R&D.

Singapore, for example, is best poised to increase its high-tech research sector because of its strong intellectual property laws, stable and industry-supportive political structures, and mature business environment. To date, 30 of the world's top pharmaceutical, biotechnology, and medical technology companies have located in Singapore's largest research park, Biopolis, and other research centers, creating an effective ecosystem that harnesses the benefits of economies of scale and knowledge transfer.

China, meanwhile, is quickly emerging as a top destination for life-sciences investment because of its large population, growing public healthcare expenditure, and relatively low-cost manufacturing resources (see **Figure 2**).

As reported in the 2011 *Global Life Sciences Cluster Report* (3), the Chinese government has invested massive amounts of capital to attract pharmaceutical R&D, including funding for research park developments. These investments are paying off with several big pharmaceutical players opening research operations in the country.

Global biopharmaceutical companies such as AstraZeneca, Boehringer-Ingelheim, Takeda, and GSK have established operations in the major manufacturing clusters in Taizhou China Medical City High-Tech Zone, Greater Hangzhou, Greater Tianjin, and the Yangtze River Delta, and the research facilities in Shanghai Clinical Research Center, the Zhangjiang Hi-Tech Park, and elsewhere. Beijing's Daxing District and government-developed Zhongguancum Life Science Park encompass R&D, manufacturing, sales, and distribution facilities. The newly-developed Suzhou Industrial Park's BioBay, in Jiangsu, offers innovation incubator and accelerator support, including capabilities for gene technology and nanotechnology.

INCREASED FACILITIES MANAGEMENT OUTSOURCING

Globally, the changes in life-sciences companies' real estate footprints have been among the most drastic of all industries. The need for strategic corporate real estate portfolio planning is at an all-time high as companies seek operating efficiencies. The cost pressures that began with the patent cliff will be exacerbated, as value-based product pricing becomes the new normal as a result of healthcare reform legislation.

Under these conditions, a nimble portfolio that offers the right facilities in the right places will drive value and productivity. Site selection is becoming more crucial, as companies seek vital access to multi-disciplinary research talent, new market opportunities, and cost-effective production facilities both at home and abroad to support narrow profit windows.

Global pharmaceutical companies have responded quickly to the patent cliff by consolidating, selling and decommissioning buildings, layoffs, and increasing the outsourcing of non-core services (1). With further overhead cost-cutting required to remain competitive, the prospect of outsourcing strategic facility functions is becoming more attractive.

The life-sciences sector is already the most active in facilities outsourcing, with 22% of companies fully outsourcing portfolio and facilities management functions, compared to 13% in other industries (2). Like the large companies, mid-sized firms are outsourcing more of their facilities' operations to real estate service providers.

Biopharmaceutical companies are increasingly outsourcing not only brokerage, site selection, and facilities management, but also management of hazardous waste and "beyond the yellow line" functions such as equipment maintenance, regulatory compliance, environmental and health safety, technology, critical environment, and other specialized functions. Outsourcing enables these organizations to devote more management attention to core businesses, reducing operating costs while improving facilities compliance, and production uptime.

An increased need for facilities management expertise in highly sensitive life-sciences office, R&D, and production environments, however, is coinciding with the nearing retirements of the most-seasoned facilities talent. For many companies, real estate outsourcing will be the fastest route to creating value through multi-generational facilities teams that can support regulatory compliance, hazardous waste management best practices, facilities safety, and other in-demand requirements.

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Weighing Clinical Trial Outsourcing Options

Evolving clinical trial research services give biopharmaceutical companies options for full and functional services.

BRYAN HAAS, DAVE AGRELLA, AND SCOTT MAISTO

Biopharmaceutical companies are facing increased research costs, along with the ongoing complexity of global regulations and market conditions. All of these variables create a diverse set of needs for biopharmaceutical research portfolios, which, in turn, create a wide range of needs in the outsourcing market. Adding to the complexity is the fact that biopharma companies have a multitude of choices in outsourcing partners and nearly as many options for contracting methods; there is truly no one-size-fits-all scenario for meeting their needs.

In some cases, the sponsor requires full-service outsourcing, in which the partner company takes full ownership of the trial deliverables. In other cases, sponsors are seeking enterprise scale on a functional level, while some simply need specific staffing solutions to meet global capacity requirements. The answer is an integrated outsourcing solution that encompasses the necessary legal, con-

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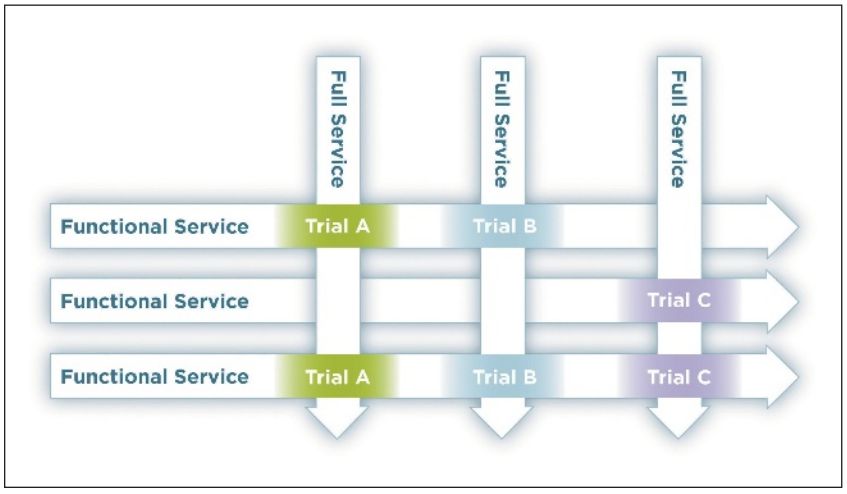
Figure 1: The two primary outsourcing types: full service and functional service.



tracting, and execution expertise that enable biopharma companies to successfully meet business objectives. In this article, the authors discuss how the successful integration of the appropriate expertise can help drug sponsors maximize the value of their research investments.

The Tufts Center for the Study of Drug Development reported in 2010 that spending on new drug development was growing at a rate of 9.1% while global spending on contract clinical services was growing almost at 13.4% (1). As drug development costs have continued to increase, there has been additional pressure placed on improving R&D performance. This improvement has been accomplished by focusing on drug development efficiency and/or by implementing new strategic partnerships and alliances (2). Both models are expected to experience continued growth (3).

As the marketplace has evolved, two primary outsourcing types have emerged (see **Figure 1**). The first is full-service outsourcing with an increasing trend toward alliances, in which a CRO typically is contracted to deliver all services required to execute a clinical trial and/or a portfolio of trials. The alliance model may be asset or therapeutically aligned. This method of engagement and, more importantly, contracting is focused at a trial, program, or asset level. This outsourcing method typically adheres to a unitized or milestone-based contract. However, the underlying construct is ultimately payment based upon the number of hours worked. This time-tested form of outsourcing has both advantages and disadvantages.

The second type, functional service provider (FSP)-based outsourcing, is not a new method of outsourcing, but it does not carry the same level of maturity and understanding within the broader market when compared to full service outsourcing. In many cases, FSP contracting includes large-scale contracts focused on a given functional service, such as data management, biostatistics, programming, and even monitoring. In this model, teams work across clinical trials in an effort to maintain functional consistency—both from a process and resource standpoint—to ultimately reduce the cost of delivery. Contractual structures for FSPs span from full-time equivalent (FTE) and dedicated capacity models to service-oriented, outputs-based contracting. It is here, in this evolving focus on outputs-based contracting, that will prove a significant value to the industry in driving increased innovation and aligning shared goals.

Several trends are emerging within both models:

- General interest in moving away from FTE-based contracting to an FSP outputs-based model in which companies pay for a result and not a resource.
- Consistent with trends noted by Tufts CSDD, FSP and full-service outsourcing are being integrated to offer efficiencies in oversight and cost flexibility. Industry Standard Research has provided examples of the top selection drivers for these models, including the combination that provides increased resource flexibility, access to expertise, greater efficiency, reduction in development costs, lower administration burden, and improved service relationships (3).

Although it is difficult to determine the future outlook, this article addresses a potential outsourcing model that integrates FSP and full-service outsourcing, while depending less and less on FTE models. The rationale to send trials to a full-service or functional-service provider may differ from company to company based on internal needs and core competencies. However, by leveraging both models, companies are able to maximize spend, time, and quality across a given portfolio.

FIGURES COURTESY OF THE AUTHORS

BENEFITS AND CHALLENGES IN EACH MODEL

Full- and functional-service models both carry unique sets of benefits and challenges that must be considered when a company pursues an FSP relationship. These benefits and challenges include the main drivers to the supply; management of resources; alignment to the core vision; accountability; and agreed standards, processes, and technology (4). These specific advantages and limitations are cornerstone to the belief that the model carrying the greatest benefit is a fully intertwined combination of the two.

As an advantage, full-service outsourcing is mature, well understood, easily deployable, and simple to contract. Most pharmaceutical companies and CROs enjoy a thorough understanding of contract terms and approach to the financials. Many, if not all, full-service models are built on an hours-/role-based assessment of what it will take to complete a trial. Another important benefit of this model is that it often allows the CRO to leverage its own systems and processes to execute the trial in an expedited fashion. The more services a CRO can execute, the more streamlined its internal operations. If the CRO is performing all services in a clinical trial, it can align its staff, processes, and technologies to more efficiently execute the trial.

This full-service model offers lower risks from a contracting perspective, but it presents challenges with how bio/pharmaceutical companies perceive oversight and execution risk management. Another challenge with the full-service model is significant inefficiencies within the execution of a trial may occur due to a duplication of roles (i.e., both parties are providing oversight and direction when only one should). This lack of definition within the model often proves to be a significant challenge. Additionally, defining scope and ownership tend to be a challenge. That challenge can be due to a lack of understanding between parties or simply based on the nature of executing a complicated global trial. These scope variations ultimately may drive contract modifications and costs overruns.

A functional-service model may offer significant cost and efficiency opportunities by connecting a single functional contract to a high volume of work. Simply put, companies provide vendors an opportunity to streamline and innovate around a core set of tasks. These models also can offer contracting terms aligning delivery with the service and not to time or effort. Essentially, the company pays for the functional output and is not concerned with the hours or tasks necessary to reach that goal. Although subtle, this shift in contracting is crucial for CROs that continue to seek new and innovative ways to execute trials with increased efficiency and quality at a reduced cost to clients. One challenge in this environment is the potential for an increase in oversight requirements. Based on the structure of the contract, the added oversight sometimes can offset the potential savings. Additionally, expectations aligned with full-service oversight in an FSP environment can prove to be the limiting factor in the success of an FSP deployment. The functional model requires a full understanding of the scope and roles by both parties prior to contractual execution.

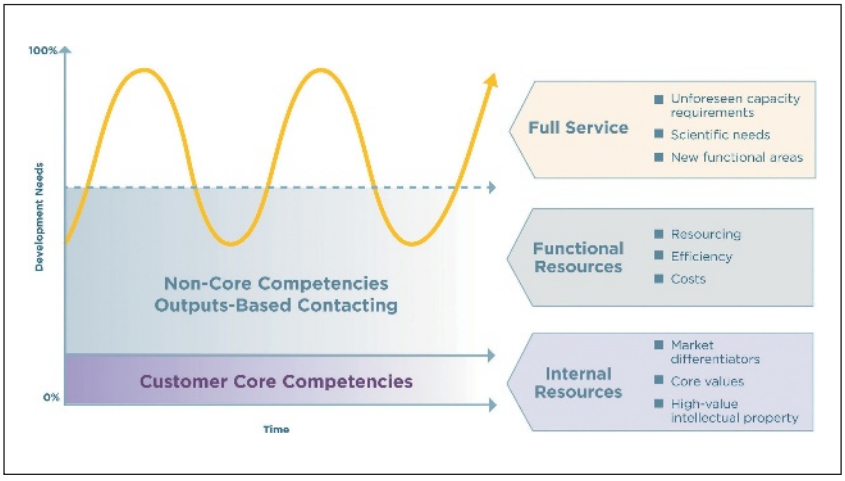
CONTRACTING

In the two models, a key consideration is contracting and how to leverage that vehicle to improve efficiencies and drive innovation. In either case, we see the separation of hours and services delivered as a key component to driving the biopharmaceutical industry forward. In termed incentive-based contracting, the alignment of each contracting party's goals through the contract payment vehicle is a significant move. Essentially, the industry needs to transition from focusing on hours and tasks to emphasizing the more important factors of cost and value.

For example, when using a simplistic contract unit for payment that encourages productivity and quality, both parties can build the structure of their relationship around common goals and shared incentives. When executed correctly, these units are more easily managed and operationalized, and they eliminate the need for a risk/reward component, as it is inherently built into the currency of the unit.

An example of this would be a study start-up FSP contract that establishes payments will be made to the vendor when a site is ready to receive the investigational product (IP). The currency in this case would be a site status of IP shipment eligible (IPSE), which would require all essential regulatory documents to be properly collected; ethics committee/ministry of health approvals in place; and a contract executed with the site. Productivity and quality are encouraged in this model since the CRO's profitability hinges on its ability to perform efficiently, with no need for rework due to quality issues. If start up is protracted, then the

Figure 2: Successful outsourcing strategies leverage both full-service and functional-service models.



CRO's profitability suffers due to extended timelines, additional efforts and over-burn. For the biopharmaceutical company, this represents a simplistic, single-payment option based on the status of when the site is ready to participate in the trial. Plus, it incentivizes process optimization and quality performance by the CRO.

WHAT IS THE OPTIMAL MODEL?

Often, in interactions with biopharmaceutical companies, there is a primary focus on one model or the other. Essentially, company X deploys a full-service outsourcing strategy and company Y capitalizes on functional services. As depicted by **Figure 2**, the most successful outsourcing strategies leverage both models to help manage the diverse needs of their trial portfolios.

There are several clear advantages to this combined strategy. Centralized governance saves time and oversight hours. These models also benefit from a single view across a portfolio and allow companies to adjust accordingly.

FSP can offer a cost savings when the oversight and blend of resourcing is correct, while full service can deliver critical compounds more efficiently. Combined, a company can maximize investments in both time and operations based on the needs of the portfolio. This includes strategies that take advantage of the global marketplace to hire and retain talented workers. The availability of global talent has improved as clinical trials have moved into new and emerging marketplaces over the past decade (5).

One size simply does not fit all. Successful companies employ a flexible strategy and engage vendors who can offer a blend of solutions.

CONCLUSION

So, is FSP or full service the best contracting method for a biopharma company's needs? The answer may very well be both. Each model has its own unique advantages and challenges. When executed correctly, a combined outsourcing strategy that deploys both can yield the best of each. The most successful companies focus on internal core competencies and retain internal expertise for those competencies. From there, they identify the service(s) that would benefit most from large-scale functional outsourcing and those that would benefit from full service. The answers will vary based on the core competencies and capacity needs of each organization. Once a decision tree is built, the company can work within a network of vendors that offers the flexibility to maximize returns both financially and operationally.

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