



Biopharm Roundtable

1. What, in your opinion, is currently the single largest trend with respect to biopharmaceutical outsourcing and manufacture?

MA: The large companies with excess capacity are shedding that capacity and looking for right-sized manufacturing. Drug pipelines are inconsistent and it's expensive to maintain idle capacity for a pipeline that may or may not mature in the near term.

PS: From our vantage point there are several developments that are making preferred providers increasingly important to pharmaceutical and biotech companies, particularly in the area of development and manufacturing where companies are seeking out highly specialized strategic partners. Preferred partners must be capable of supporting them throughout the entire process from early-phase drug development to long-term market supply. This process is also being accelerated by the need for new compounds, which are getting more and more complex and are often sensitive to external conditions. Lyophilization is often required, along with subsequent reconstitution of the drug, which can be unwieldy. Systems with vial adapters in combination with prefilled diluent systems provide a more convenient alternative. Dual-chamber systems offer both patient safety and high convenience.

We also believe that combination products are becoming increasingly important, due to the growing home-healthcare sector. Development requires close collaboration between service providers and pharma/biotech companies throughout the entire supply chain.

Preferred providers bring expertise that helps pharmaceutical and biotech companies meet today's tough challenges.

JR: Due to recent overinvestment in mammalian cell culture capacity and improving titers there is a downward utilization trend in mammalian cell culture, leading to several effects:

- Several facilities are presently idle
- Originators enter and expand the CMO business with excess capacity
- Consolidation of industry (acquisition of CMOs by originators)
- Manufacturing alliances

SDJ: The largest trend is the increased use of small scale disposable bioreactors to produce clinical material. More CMOs are offering early stage biopharmaceutical manufacturing because it is cheaper and easier to set up a new facility that uses primarily disposable components.



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BN: As we think about the evolution of the pharma business model and the needs of the molecule pipeline, two trends stand out. First, relationships between pharma companies and their external suppliers have evolved from purely transactional, with many suppliers, to integrated alliances or collaborations, with fewer specialized providers. Pharma companies now manage suppliers as a virtual plant with standards and expectations similar to that of internal facilities. Secondly, the molecule pipeline is moving heavily toward biologics after three decades of R&D investment. These two trends indicate that, given the increasing complexity of the molecules being manufactured, CMO providers must be capable of offering sophisticated, fully integrated services and establishing close, collaborative relationships with pharma.

SW: Biopharmaceutical outsourcing is driven by the cost of infrastructure building, which pushes companies to look outside rather than build their own capacity, and by retrenchment among established firms, which frees up facilities and transfers contracts from in house operations to outside parties.

2. How, in your mind, has the landscape of biopharmaceutical outsourcing/manufacture shifted post-recession?

MA: Companies are looking for inexpensive single-use capacity for early phase manufacturing. Time and money are very important - especially to smaller organizations.

PS: As compared to other industries, the pharmaceutical and biotech industry is less affected by short-term economic fluctuations. Expiration of patents, globalization, cost pressures, increasing development costs and fewer products in the development pipeline impact the industry over the long term. For many companies, outsourcing to a preferred supplier is a pivotal measure to reduce costs, allowing them to better concentrate on their core competencies such as research and development of new drugs and their marketing. For small and medium-sized biotech companies, collaborating with specialized service providers can offer competitive advantages. The earlier a contract manufacturing organization (CMO) with development capabilities gets on board, the more the company can benefit from its expertise and experience.

JR: The financial crisis still impacts the outsourcing decisions in the biopharma industry, the main effects are cost consciousness, slowing down projects and/or strict prioritization.

SDJ: We have seen a resurgence of investment in biopharmaceutical companies and products, which is driving a greater demand for contract manufacturing. While we have not see capacity shortages in the contract manufacturing, current products are less likely to need the large installed stainless steel bioreactors that dominated the industry 10 years ago so there could be some local mismatch between the requirements of emerging biotechnology and the installed capacity of existing CMOs. Use of disposable equipment to bridge this gap is a growing trend that has increased post-recession.

BN: In addition to the impact of the Recession of 2008, the economics of the pharma industry are being changed by significant patent expiries, increasing regulation and extreme political pressure to control pricing. These factors - along with improved performance delivered from external partners - are influencing the "Make vs. Buy" decision. More and more we are seeing inclusion of external partners earlier in molecule commercialization decisions. This is changing the business case considerations for new product investments by lessening the negative impact on financial metrics like Return on Assets.

SW: I have not observed big changes as a result of the recession. Most of my clients are small biotech firms that are cost-conscious and looking for the best value. Some small firms did not weather the downturn and others have delayed projects. This has provided some increased flexibility in scheduling at some of the smaller CMOs, but has not appreciably changed the way these firms are doing business.

3. What country/region, in your opinion, is currently leading the way in biopharmaceutical outsourcing/manufacture and why?

MA: US and Europe are leading the way with mature infrastructure for outsourcing. Other regions are still developing appropriate manufacturing systems and infrastructure that are acceptable to a broad base of Biopharmaceutical developers.

PS: The US continues to have a dominant role, with approximately two-thirds of new drugs still being developed in that country. And, of course, many big pharma and biotech companies are headquartered in North America. Europe, too, is an established market and will continue to experience moderate growth. The same growth was also expected in Japan in the coming years but the recent tragedy has made it difficult to predict how its market will react. For pharmaceutical and biotech companies, the greatest opportunity for growth remains in the pharmerging markets, where forecasts range as high as 20 percent. The industry is preparing now to meet demand in these markets.

JR: Microbial manufacturing: Europe (major suppliers/plants are located in Europe)
Mammalian Cell Culture: allocated between US, Europe, Singapore (in all those regions major production plants are located and/or under construction).

SDJ: For biopharmaceutical outsourcing and manufacturing, Europe and the USA remain the leaders for providing contract manufacturing to US and European companies. There is significant ongoing growth in Asia but these mostly serve the Asian market at the moment. The primary reason is that biopharmaceutical companies are more comfortable outsourcing to facilities that have already produced products for the clinic or market in the US and Europe, as well as the relative ease of overseeing contractors that are local.

BN: The most established pharmaceutical markets are clearly leading the way toward increased outsourcing. The industry buzzes about opportunity in emerging markets, but the growth in these markets is mostly from generics. For example, in the next decade, generic demand is expected to grow threefold in Asia and much of the new production capacity in the region is being devoted to fulfilling this trend. While emerging markets will have some branded molecule demand, the bulk of the commercial opportunity for highly sophisticated, branded molecules continues to be centered in North America and Europe. Given the value of these molecules, offshoring for cost advantage has not been an important driver of increased value. More important to ensuring branded molecules are a commercial success has been the technological know-how and performance from well established outsourcing partners located in the major markets of North America and Europe.

SW: Europe continues to lead the field of biopharmaceutical outsourcing. There are more firms that cover a broader range of technical capabilities and scales than in any other region. The top quality CMOs are primarily in Europe.

4. If things progress as they have the past five years, what can we expect in the next five years, with respect to biopharmaceutical outsourcing/manufacture?

MA: We can expect consolidation - there will be pressure to provide integrated solutions and you'll see a number of smaller drugs launched primarily out of contract facilities. Biosimilars will rely heavily on the infrastructure of CMOs in order to be successful.

PS: The outsourcing trend will continue intensifying, affording companies the latitude to concentrate more on research and development as well as the marketing of their products. From the perspective of "total cost of ownership", the outsourcing of development and commercial manufacturing is becoming increasingly attractive. For service providers, this means expanding their expertise in order to act effectively as a strategic partner, providing support in all phases of drug development and manufacturing. With the increase in significance of biologics this trend will continue and be an important factor for growth. Globalization will also be advancing, with established markets continuing to play an important role. The pharmerging markets should gain ground as well.

JR: Continuing need for production improvements and cost containment
Upstream titer improvements require more efficient and cost effective purification systems (e.g. innovative separation systems, highly automated facilities, debottlenecking of purification plants).

SDJ: More biopharmaceutical companies with robust pipelines will install their own small scale facilities to meet early stage clinical requirements, similar to Merrimack Pharmaceuticals or Acceleron Inc. Facilities will become smaller as cell culture titers increase and lower volume bioreactors will be able to meet clinical and even commercial requirements. Simultaneously, more companies will offer small scale manufacturing services. Some production will migrate to India and China, but more production will be brought in-house.

BN: As we have seen with many small molecules, therapeutic equivalence across molecules has been met in many cases through competing branded products with similar indications or through generic introductions. To renew their competitive edge in the market, pharma marketers have leveraged reformulation and enhanced delivery systems to differentiate their offering to customers. For small molecules, this trend is well established in the market.

With the introduction of biosimilars that will compete with branded biologic molecules, we see the same evolution of the market playing out, but with a twist. In the past, the paradigm of most pharma companies was to develop and build their own technology platforms to improve a molecule's benefits to customers. With the leaner investment profile required to compete in pharma, we see increased outsourcing of reformulation and enhanced delivery programs as turn-key solutions. By outsourcing to highly advanced turn-key systems providers, the pharma company does not have to divert scarce R&D resources away from other, higher priority programs for the company.

SW: There are a number of firms developing capability as CMOs in China and the number in India is expanding. However, firms in Asia that offer phase 1 and 2 clinical testing material manufacturing have had a difficulty attracting clients from the US and Europe. The lower cost of these facilities does not offset the risk and distance-related difficulties in the clients' evaluations. CMOs in Asia may well end up providing services primarily to Asian clients.

5. In your opinion, what research field currently benefits the most from biopharmaceutical outsourcing/manufacture and why?

MA: Developing novel compounds such as cytotoxics and conjugates, because many people don't want to spend the money to build the infrastructure to produce them, so there's potential synergy in using CMOs.

PS: Actually, there are several fields benefiting: Seasonal vaccines is one such example. Because the development of vaccines is always short-term, large amounts have to be filled within a short period. By outsourcing, companies don't need to build in extra capacity that would be underutilized for much of the year. Another is that of orphan drugs, which often cannot be filled cost-effectively in-house because their low volume makes them cost-prohibitive. Therefore, collaborating with CMOs offers flexibility and an economical alternative. Therapies for metabolic illnesses like diabetes also benefit because the obstacles to approval of such compounds are very large. By outsourcing development and manufacturing, companies can avoid investing prematurely in internal infrastructure, and can thus reduce their risk. Finally, the development of biologics overall, particularly by small and less experienced biotech firms, will benefit from the experience and skills of specialized CMOs.

JR: Small biotech companies benefit from established CMOs with respect to cGMP systems and experience in late stage development, process characterization, and process validation know how.

SDJ: Any disease area that can potentially be treated with a monoclonal antibody benefits from the extensive array of antibody manufacturing platform service offerings, the relative ease of antibody manufacturing compared to new biologic entities that are not Mabs, and the infrastructure that the industry had built to support Mabs. Oncology and inflammation are definitely able to benefit by bringing more products to the clinic quickly.

BN: Clearly, formulation development and delivery technology benefit from outsourcing. As pharma companies have fewer new molecules to launch, they need to get more commercial results from their existing molecule assets. The formulation development and enhanced delivery capabilities of premier outsourcing providers can offer the solutions needed to deliver on increased returns from existing molecule assets.

SW: It seems that more therapeutics are being outsourced than vaccines, and among the therapeutics, monoclonal antibodies dominate. But this is more likely the result of the dominance of Mabs in the development pipelines than of any characteristic of CMOs.

6. What recent improvements/methods have been implemented to make biopharmaceutical outsourcing/manufacture a viable option?

MA: Disposables - the changeover is so fast now and you can turn around projects much faster, which really helps to move clients through the facility.

PS: CMOs today focus on challenges in the development and manufacturing of complex compounds and large molecules. In previous years pharmaceutical companies would engage CMOs either at the end of phase II or during phase III of development. Today, CMO

support often begins much earlier, in large part due to the complexity of biologic research and development. That is why some CMOs have expanded their development capacity and expertise to become true contract development and manufacturing organizations (CDMOs). Vetter, for example, has been supporting early development work for many years now through Vetter Development Service. We recently expanded that expertise to our new facility in Chicago, which supports preclinical through phase II projects. At phase III, projects are sent to our European facilities for further development and seamless transfer to Vetter's commercial manufacturing services.

To offer the best possible support in the early development phase, some CMOs have significantly expanded their project management capacity in the past few years. They offer specialized expertise and tools to provide support for large and small companies in all phases of drug development. In addition, CMOs have refocused their supply chain management on processes and requirements that are becoming increasingly complex. They allow close collaboration with all parties concerned, including individual customer divisions and suppliers.

JR. In general biopharma customers expect and established CMOs have established a full set of services („one stop shop“) including e.g. access to expression systems, process transfer, process development, process characterization and process validation activities.

SDJ: Outsourcing biopharmaceutical manufacturing has been a viable option for more than 15 years. Improvements in process development, process and product understanding, quality by design, analytical methods, and risk assessment during process development have led to more robust manufacturing processes and better characterization of the products that are manufactured, either by outsourcing or in-house.

BN: Outsourcing vendors have recognized the need to provide broader lifecycle management solutions for pharma client molecules. This has required the strengthening of formulation and enhanced delivery capabilities to maximize the value of the molecule to the client.

SW: The increase in the number of CMOs is driven by demand, not by supply. A greater proportion of startups are not building infrastructure but instead are relying on outside support for most of their development and manufacturing needs, which provides incentives for companies to offer manufacturing and development services. In addition, established companies are rationalizing their manufacturing organizations, which frees up amortized facilities to be converted, often with accompanying contracts that make the new CMO profitable from the beginning.

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