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# CMOS AND THE OUTSOURCING DILEMMA

**Eric S Langer, president of BioPlan Associates Inc, discusses the benefits and limitations of CMO services in biopharmaceutical outsourcing.**

**M**ost biopharmaceutical product developers prefer to manufacture products themselves because of the control and flexibility it provides. The value associated with outsourcing production to a contract manufacturing organisation (CMO) tends to depend on a number of factors, such as: how a product developer balances risk, if the company is early-stage or established, whether their product pipeline is full, and whether the company's primary core competency is as a product manufacturer or an R&D company and product developer.

Tracking comparative trends and changes over time can make it easier to anticipate changes. By identifying trends two and five years ahead, and allocating the proper resources, companies are better prepared to adapt and survive in a shifting landscape. Many of these trends have been tracked through the *3rd Annual Report and Survey on Biopharmaceutical Manufacturing and Production*. This study compares trends, capacity, outsourcing and changes in use of new technology over time. The most recent report provides insight into how organisations are shifting their outsourcing strategies, and the differences in how CMOs vs product developers are gearing up for upstream production, downstream purification improvements, and other changes, including outsourcing.

#### Why outsource?

Biopharmaceutical developers ultimately decide to outsource for a variety of reasons. Of course, the high capital costs of building a plant and the risk to investment

in a biopharmaceutical facility before product approval top the list. But the time involved in new construction and validation of a plant also plays a part. The challenges involved in building an experienced staff capable of working and managing under cGMP are substantial.

According to Dr Joanne Beck, director of biologics manufacturing, global pharmaceutical operations at Abbott Bioresearch Center in Worcester, USA: 'People thought it was more cost and time efficient if they owned a facility. This was true 15 to 20 years ago when biomanufacturing expertise was limited to very few companies. This is no longer true; many companies today have developed efficient and compliant biomanufacturing capabilities and outsourcing has become standard practice.'

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#### Risk reduction

Considering the benefits that in-house production provides, at first it might seem the right path. Why, given the wealth of benefits of producing their own products in-house, would a product developer want to outsource?

Risk reduction has historically been the premise on which the CMO industry has grown. The primary reason CMOs continue to provide benefits to biotherapeutic product developers is their ability to reduce risk. 'It costs \$200m to put up a biopharmaceutical manufacturing facility, and it needs to be done by phase 2 to have it ready for the pending commercialisation,' says Lonza's VP of marketing Michael Chaffee.

But not every company experiences risk the same. Depending on a company's financing situation, level of risk aversion, current pipeline, ability to weather a potential product failure, and many other factors, the balance has to be personalised and customised with weighted factors that make sense, and that are based on the company's current situation and their future strategy.

Small companies without the financing and production expertise must seek out the expertise. Mid-tier companies must weigh the risks of a product failure against the ability to survive a failure. Larger companies can re-purpose a facility in the event of a failed product. Some larger companies outsource to reduce costs of infrequent runs for clinical-phase products. The largest biopharmaceuticals see contract manufacturing as a way to reduce risk in their global manufacturing strategy.

Working with a CMO has its downside. The company loses a degree of control over the process, as well as control over daily decisions. Further, because quality decisions can be subjective, giving up control over the process tends to worry product development companies.

## The need to reduce costs is a natural progression as biopharmaceuticals mature

### Trends and benefits

Trends in the biopharmaceutical industry are a natural outgrowth of the industry's advancing technologies, mergers and growth. Pressures to drive down operational costs are increasing, and the need to reduce costs is a natural progression as biopharmaceuticals mature and competition increases. 'The industry is evolving from its old vertically integrated structure,' says Beck. 'Companies are seeing the value of focusing on what they are best at instead of trying to do everything themselves.'

Companies are also focusing on driving down costs in both process development and GMP manufacturing. Today, most activities centre on reducing costs incrementally.

### Disposables

The increased use of disposables in biopharmaceutical manufacturing is an ongoing trend. Bags, disposable tubing and assemblies, bioreactors, sampling systems, mixing units and other applications all add to the flexibility of a facility.

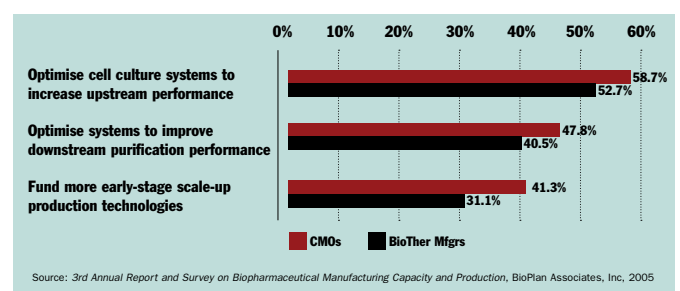
'The reach of disposables will extend even further over the next five years,' according to Michiel E Ultee, PhD senior director manufacturing and technical operations at Laureate Pharma. 'Conversion to disposables in manufacturing, switching away from stainless steel tanks, filter assemblies, reusable columns and carboys. This trend is driven by the need to reduce capital and cleaning costs, but for CMOs especially, the multi-product nature of their production will increase usage.'

### Bioreactor size

The effective size of bioreactors is likely to go down over the next five years. As titres improve and upstream production efficiencies continue to generate higher product yields, the need for the additional capacity is decreasing concurrently. 'Just a few years ago, people would laugh about a gramme per litre,' says Chaffee. 'That's pretty standard now. People are now talking about 10g. Even if it gets to 4g, a 20,000l reactor will go a long way.'

A comparison was made about how CMOs and in-house biopharmaceutical manufacturers address issues of upstream performance. According to research from the 3rd Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, a larger percentage of CMOs are concerned about optimising upstream performance, 59 per cent of CMOs feel optimising cell culture systems upstream is a key to avoiding capacity constraints, compared with 53 per cent of biopharmaceutical product development companies (Table 1).

**Table 1. Key areas to address to avoid capacity constraints 2010**



### Downstream purification

Greater interest in improving downstream purification and separation technologies has sparked demand for new research into the downstream side of production. Low investment in this area in the past may have been due to an industry-wide focus on improving yields and expression levels on the upstream side.

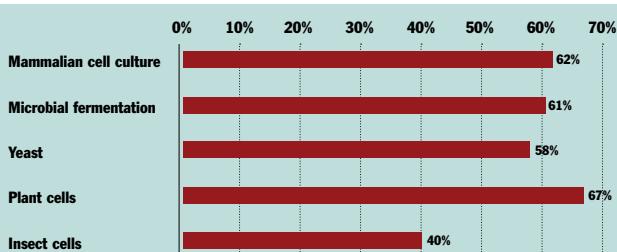
Today, more progress needs to be made on the downstream side because, as titres continue to increase, there will be a tremendous pressure to find more efficient systems. Most suppliers and users predict that there will be incremental improvements.

### Increased outsourcing

Many companies are beginning to recognise that in-house production is not even an option. As more companies evaluate what might or should be outsourced, the trend appears to be to consider what, and how much to outsource. By 2010, 62 per cent of biopharmaceutical product developers in mammalian cell culture plan to have outsourced at least some of their production (Table 2).

‘Many more biopharmaceutical developers are outsourcing now than even five years ago,’ says Beck. ‘It’s not just the risk of making a huge capital investment: companies are realising that staffing and maintaining a cGMP-compliant facility are daunting tasks. Outsourcing process development and GMP manufacturing will likely expand as biopharmaceutical product developers focus on discovery.’

**Table 2. Percentage of biotherapeutic developers planning to outsource at least some production by 2010, by system**



Source: 3rd Annual Report and Survey on Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc., 2005

## Biopharmaceutical R&D will continue to feed the growing demand for CMOs

### Customisation and flexibility

Product developers use CMO services in different ways, and they expect more customisation and flexibility to meet individual company needs. For smaller companies, outsourcing shortens timelines from development to the clinic and to preserve capital. Mid-tier companies may require management of multiple projects to spread risk and minimise internal capital outlay. Larger biotechs at the development level expect CMOs to keep multiple projects moving quickly and provide access to outside technologies.

Commercially, companies may expect CMOs to create a bridging strategy until market potential becomes clear enough to warrant building the proper size facility or to offer a secondary production source in the event of problems at the primary facility.

### Capacity situation

Capacity utilisation becomes a scheduling and pipeline balancing act. CMOs must always try to maximise their use, yet still have capacity available to feed the CMOs’ production pipeline.

The Achilles heel of the CMO industry is the need for a certain level of costly excess capacity. Overall, worldwide

biopharmaceutical manufacturing today is running at 70 per cent of capacity, compared with 79 per cent in 2003. This is likely a reflection of the industry expansion, improvements in expression levels and productivity, and some failed products. Despite the excess capacity today, nearly half (48 per cent) expect their organisation to experience capacity constraints by 2010. For both mammalian cell culture and microbial fermentation capacities, biopharmaceutical product developers own around 75 per cent of the industry capacity. CMOs retain the remainder.

The microbial market has had plenty of capacity over the past few years. This has driven pricing down significantly. The pricing pressures have focused efforts at CMOs to improve production efficiencies. The biopharmaceutical CMOs during this period of excess capacity have focused on optimising their systems, which will ultimately help ensure overall costs in the biomanufacturing segment are reduced; another sign that this business is maturing.

### Differences between CMOs and product developers

According to the *BioPlan Annual Biopharmaceutical Manufacturing Report*, 22 per cent of CMOs are experiencing significant capacity issues, compared with 42 per cent of biopharmaceutical product developers experiencing cap issues.

Overall capacity utilisation by biopharmaceutical developers and contract manufacturers has decreased. This is a result of continued industry expansion, and improvements in yield at existing facilities. Capacity utilisation for all biomanufacturers using mammalian cell culture systems is currently 68.8 per cent. Capacity utilisation for microbial fermentation is 60.5% (as a comparison, the US Federal Reserve Statistical Release showed that capacity utilisation for all US industries in July 2005 was 79.7 per cent).

Comparing CMOs with biopharmaceutical product developers, though, shows capacity utilisation at CMOs 10–20 per cent lower than utilisation at product developers. This may be partly because a CMO needs additional capacity to assure it is not constrained on individual contracts.

There is a lot more equipment turnaround at a CMO than at a product development company. Product development equipment may also stay online longer. Lonza’s Chaffee takes it a step further, and notes that: ‘If you have 100 per cent capacity utilisation, you have 100 per cent pipeline constriction.’

Biopharmaceutical R&D and discovery will continue to feed the growing demand for CMOs manufacturing capacities. Drug manufacturers look to contract manufacturing as an asset to drive strategic manufacturing decisions. In the future, increased risk sharing and partnerships are likely. **END**