



20th Century Anniversary Special Feature

Outsourcing biologics manufacturing

This article reviews how today's contract biomanufacturing industry has developed to overcome the technical and commercial challenges of the past 20 years.

Biopharmaceuticals are the most rapidly growing segment of the pharmaceuticals market. Developing and marketing biopharmaceuticals are huge roles in almost every major pharmaceutical company's strategy. However, they are extremely complex molecules and are highly sensitive to the manufacturing processes used to produce them. These processes require exquisite control of living production systems, making, without a doubt, biopharmaceuticals one of the most challenging products of any type to manufacture.

This article reviews how today's contract biomanufacturing industry has developed to overcome the technical and commercial challenges of the past 20 years within the framework of capacity, capital, cost and capability (Figure 1). It also examines how the same forces will shape the industry through continued growth in future decades.

Capability

The first biopharmaceuticals on the market in the 1980s were manufactured by the companies that developed them. Because of the effort expended to overcome the technical challenges, the capability to manufacture these complex products became viewed as a core value driver for the companies that succeeded, and biomanufacturing quickly became viewed as a critical capability strategically important in its own right.

The importance of biomanufacturing capabilities has been demonstrated on many occasions during the past 20 years, both in terms of limits and advantages for individual companies, as well as impacting on the industry as a whole. One example is the development of biosimilar versions of off patent biopharmaceuticals, which has been severely hampered by the inability to easily reproduce the originator companies'

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manufacturing processes to deliver 'equivalent' products.

Capital

The growth of the contract manufacturing industry during the 1980s and early 1990s was restrained further by the regulatory framework within which biopharmaceuticals could be developed. The general regulatory approach was that "the manufacturing process defines the product", which made sense because the analytical methods used were insufficient to fully define and test the macromolecular structures of biopharmaceuticals. This made the transfer of manufacturing processes between companies far from straight forward, as there was no way to ensure products from different manufacturing sites were comparable.

Additionally, prior to 1996, companies were required by FDA to submit two licence applications to commercialize a new biologic product: a product licence application (PLA) and an establishment licence application (ELA; Figure 2). Regulations were specific about who held the PLA and ELA, the products to which the licence applications applied, and how and where the product was manufactured. Changes to any of these criteria necessitated submission of a new licence application and re-approval of the licence. Companies that didn't plan to manufacture their own biopharmaceuticals risked significant loss of product control because any change to a facility meant a reapproval for the license.

As a result, the late 1980s and early 1990s witnessed the development of fully integrated biopharma companies, such as Amgen, Genentech and Biogen, that were investing large amounts of capital to develop processes and build highly expensive manufacturing facilities. However, the need to spend huge amounts of money to commission and build facilities to make drugs long before they could be registered resulted in some huge losses. One high-profile example was the failure of Synergen's (CO, USA) Antril (anakinra), which failed to demonstrate efficacy in treating sepsis in a Phase III trial in 1994, after the company had made a major investment in a manufacturing facility. The resulting financial distress was one factor that led to the sale of Synergen to Amgen.¹

Capacity

Despite these obstacles to outsourcing, the late 1980s and early 1990s saw some early pioneers in the contract biomanufacturing arena. Companies such as Boehringer Ingelheim (Germany) and Celltech Biologics (UK) grew their initial capabilities in biopharmaceutical manufacture from the development of their internal pipelines, but made their capacity and capability available as a service. By the mid 1990s, there were sufficient contract manufacturing organizations (CMOs) for outsourcing biopharmaceutical development.

The contract biomanufacturing industry was boosted by the FDA Modernisation Act (FDAMA) in 1997. One of the most important changes was replacing the need for both a PLA and ELA with a single biologics licence application (BLA). This allowed biopharmaceutical development companies to retain greater control of their products while employing a CMO. Further guidance documents regarding biopharmaceutical development from FDA, European Agency for the Evaluation of Medicinal Products (EMA) and International Conference on Harmonization (ICH) also provided greater clarity on regulatory expectations for development.

These changes, coupled with the large investments of capital into biopharmaceutical development small- and medium-sized enterprises (SMEs) in the late 1990s, increased the demand for production capacity from CMOs. This was also driven by the product technologies themselves. The first products commercialized were, with the exception of insulin, potent microbial-produced products that required relatively modest quantities to meet demand; for example, < 10 kg

of erythropoietin (EPO), the world's largest selling biopharmaceutical, are required to meet global needs. This changed with the use of mammalian cell culture to produce products such as monoclonal antibodies (e.g., Rituxan, Enbrel and Remicade) that require > 500 kg/year to meet demand.²

In 2000, JP Morgan issued the first industry-wide report into mammalian cell culture capacity that infamously predicted "demand for manufacturing capacity will exceed current capacity by a factor of four by 2005".³ This acted as a clarion call to executives who needed justification to expand capacity. In the late 1990s and early 2000s, major international fine chemicals manufacturing businesses, such as Lonza, Akzo Nobel and DSM, entered or increased their market presence by acquiring smaller biologics manufacturers.

Figure 1 The CMO market environment.

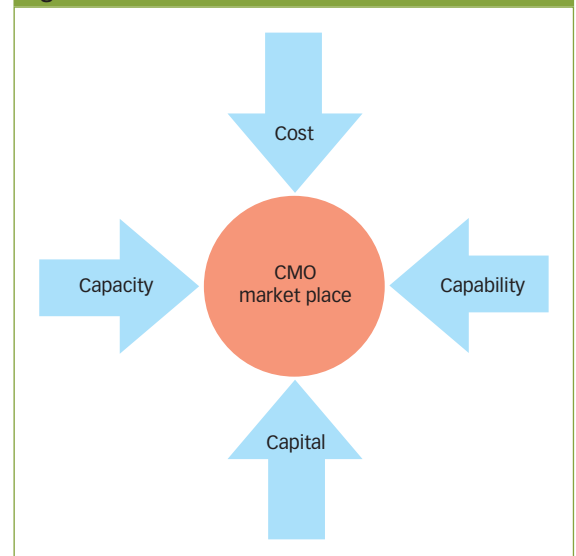
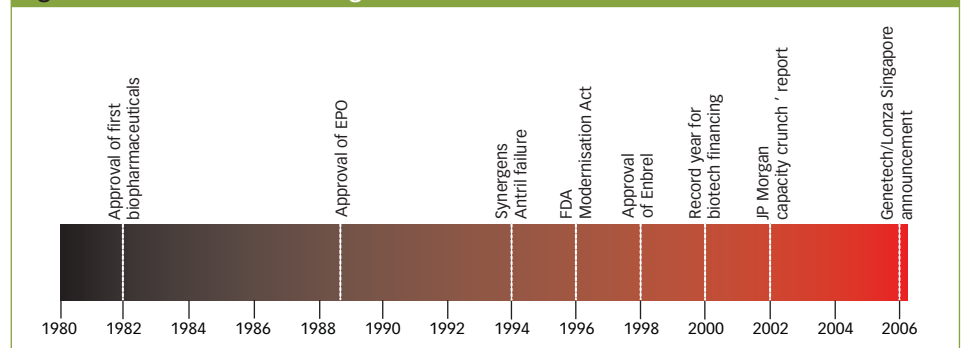


Figure 2 Contract manufacturing market time line.





One high-profile casualty of insufficient capacity was Immunex, which failed to construct (or contract) adequate capacity to manufacture Enbrel, one of the most successful biopharmaceutical products ever commercialized. Enbrel is produced by mammalian cell culture and requires hundreds of kilograms every year to meet demand. The situation led to product rationing, costing the company millions and leading to the eventual sale of the company to Amgen.⁴

Cost

Cost has been, and always will be, a driver for outsourcing. With the CMO industry maturing, and under the ever spiralling costs of biopharmaceutical development,⁵ companies face increasing pressure to reduce manufacturing costs. Diligence for product acquisition now includes a long, hard look at the cost of goods and market supply chain strategy. Previously, these aspects had often been overlooked in the haste to assess potential market size and share. Virtually all major biopharmaceutical companies have now rethought their positions on outsourcing the hitherto 'critical capability' of contract manufacturing. With the potential cost savings of outsourcing compared with the cost of building facilities, recruiting and training staff, and ensuring high-capacity utilization rates, there are now very few, if any, companies that do not use contract biomanufacturing as a component of their development and supply chain strategies.

The period 2003–2007 has seen consolidation, but also a steady growth in the contract biomanufacturing industry. Because of some late-phase product failures and the investment in new capacity, the crunch of 2005 never materialized. However, increased pricing pressures on pharma companies and the advent of biosimilars are causing more to focus on production costs.

Current market shape

The size of the market was estimated at \$2.5 billion (€1.64 billion) in 2006, and is predicted to increase at approximately 5% per annum until 2020.⁶

Contract biomanufacturing is a global business. The major territories active in contract manufacture are North America, Europe and the growing Asian market. According to a biologics CMO database maintained by Eden Biodesign (UK), out of 113 tracked companies, 61 are North American, 41 European and 11 Asian. Many of the larger players have operations in more than one of these territories, and a few, such as Lonza, have significant manufacturing assets in all three.

Research from Bioprocess Consultants estimates that 15–20% of the total cell culture manufacturing capacity (litres) for biopharmaceuticals is held by CMOs, and the remainder by biopharmaceutical companies.² The bulk of this (approximately 75%) is held by just three CMOs — Lonza, Boehringer Ingelheim and Celltrion — and there is more room for continued growth and diversification.

Contract biomanufacturing is one of the few segments of the biotech market in which Europe could be argued to be more successful than North America. Almost all of the major players to date, for instance, Boehringer Ingelheim, Lonza, DSM, Diosynth (Akzo Nobel) and Avecia are European, with most achieving the majority of their sales from North American clients. Eden Biodesign estimates that North America comprises approximately 80% of global demand for contract biomanufacturing services. This may be because cost has been a more serious issue than in North America given that capital has always been harder to come by in European biotech. This has limited the development of in-house capabilities, which in turn has led to greater demand for capacity outside of the biopharm companies themselves.

The framework of the CMO industry has developed, and will continue to develop, around the availabilities of capability, capital, capacity and cost. However, to better understand future trends it is worth looking at the impact of relationships, regulations and R&D.

Relationships

Currently, there are several different successful models of client–CMO relationships ranging from the straight forward 'fee for service' to more complex, integrated solutions.

Many CMOs offer clients access to proprietary production technologies, for example, mammalian expression systems or microbial strains, in return for licensing fees and downstream royalties. This trend is set to continue with more CMOs looking to benefit from stable, long-term revenue streams, and with clients prepared to accept additional royalty stacking if the technology allows them to differentiate their product or gain more secure patent protection.

Other CMOs are prepared to enter into risk-sharing deals that offset the up-front cost of development and manufacture by taking a revenue sharing strategy. The risk with this approach is that it is a relatively small transition from this point to becoming a product developer rather than a CMO. However, a small number of companies have proven that it is possible to have both proprietary products and build an excellent reputation for fee-for-service client work.

Recently, there has been a trend for CMOs to diversify their product offerings in an attempt to generate broader client relationships and more stable revenues. There are now several smaller CMOs that offer a broad range of product technologies whereas, traditionally, CMOs developed around a core skill set. Other CMOs offer additional services such as consultancy and training, vaccine development expertise and novel disposable

production technologies. This trend is set to continue.

There are several examples of CMOs and client companies using a shared cost approach, whereby a client provides capital or long-term manufacturing contracts to gain priority access to CMO capacity, without having to take on the responsibility of running a plant. Such deals were expected when capacity was in short supply, but current market pressures on pharma companies mean they are even more important today. Genentech (CA, USA) has more biologics production capacity than any other company,² and is well known for considering biomanufacturing as a core capability and value driver. However, in November 2006, Genentech and Lonza announced one of the largest CMO–client deals in the industry’s history.⁷ Lonza purchased Genentech’s manufacturing facility in Porriño (Spain) for \$150 million (€98.6 million). Concurrently, Genentech entered into a supply agreement for the manufacture of Avastin at Lonza’s facility, which is currently under construction in Singapore, with Genentech also receiving the right to exercise an exclusive option to purchase the Lonza Singapore facility.

As drug pricing pressures continue to squeeze margins, and as large biopharma companies agonise over what else will fill their 20000 L

fermenters when biosimilars begin to erode market demand, similar win–win deals will continue.

Regulations

Regulations, such as FDAMA and the European Clinical Trials Directive of 2004 (which requires all material destined for human clinical trials to be manufactured to cGMP standards), have had a major effect in strengthening the hand of CMOs. Future regulatory changes are likely to have a similar impact. Currently, these are difficult to predict with, to some extent, mixed messages coming from FDA and EMEA that includes significant tightening of the requirements for manufacturing processes and testing used to manufacture early phase clinical material.

R&D

Biopharmaceuticals manufacturing has received an enormous boost in recent years with the launch and take up of new cell line and protein processing technologies. Any serious review is impossible within the constraints of this article, but as an example, mammalian cell culture productivity has increased by an order of magnitude during the past 10 years, with yields of >5g/L now reported.⁸ This will greatly reduce the volumetric requirements of

production plants for tomorrow’s approved antibodies.

Another development that has propelled biopharmaceutical processing by CMOs is the use of disposables in manufacturing, which have reduced the time and expense of cleaning validation to enable greater efficiencies within multiproduct facilities.

In terms of future development in process technologies, much research is now focused on improving purification throughputs and costs, as for many high yield processes, purification has become a bottleneck.

In addition to the hurdles overcome by the prodigious developments in processing technologies, there are several new challenges in terms of the novel product technologies now in clinical development. Today’s CMO industry has developed around manufacturing recombinant proteins, but new players such as Progenitor Cell Technology (CA, USA) are focusing on the new technologies of stem and other cell therapies. Gene therapies and RNAi represent other product types that may see a surge in requirements for contract manufacturing in coming years.

Conclusion

The continued growth of the biologics contract manufacturing industry seems

Biopharmaceutical production

Biopharmaceuticals represent the fastest growing segment of the pharmaceutical market. In 2007, the European Joint Research Centre, Bio4EU, study reported that the average growth rate of the European market is 23% per year during the past 10 years, more than double the growth of the pharmaceutical market as a whole.¹⁰ In 2005, the global market for biopharmaceuticals was reported as approximately \$48 billion (€31.5 billion).¹¹ More than 140 products have been launched and, on average, biopharm products account for 9% of all new product launches in Europe.¹⁰ In 2006, there were 23 blockbuster biopharmaceuticals (sales >\$1 billion (€657.2 million per annum globally), up from 6 in 2000. Biopharmaceuticals are now widely reported to account for more than a third of all products in preclinical and clinical development worldwide.

Biopharmaceuticals are complex macromolecules that rely on living systems as a means of production. Earlier recombinant protein pharmaceuticals such as Insulin and human growth hormone were produced using microbial production processes employing organisms such as *E. coli* and yeasts. More recently developed biopharmaceuticals, such as monoclonal antibodies, have been produced using

mammalian cell culture, which, although more expensive and technically challenging than microbial processes, is able to provide more complex protein structures, including oligosaccharide structures that can be critical for *in vivo* efficacy. Viral therapies and whole cell therapies are future biopharmaceutical classes. Of the 23 blockbusters in 2006, 8 were produced using microbial processes and 15 by mammalian. Eight were monoclonal antibodies.

A typical recombinant protein process begins with the thawing of a vial of cells or micro-organisms that have been genetically modified to produce the drug protein. The cells are then expanded to a sufficient mass to inoculate a bioreactor of suitable volume. In the controlled environment of the bioreactor, cells are cultured under precise conditions to synthesise the drug protein at high yields. The protein is then harvested from the bioreactor broth, clarified by centrifugation, concentrated through filtration and purified using column chromatography. The protein is provided in a suitable buffer as a low bioburden product, then formulated and filled under sterile conditions into a suitable container, such as a vial or pre-filled syringe. The vast majority of biopharmaceuticals are administered *via* a parenteral route.

assured. The product class continues to take market share and this is predicted to continue. Pharma companies previously resistant to the development of biopharm pipelines have reversed their strategies. For example, AstraZeneca, which prior to 2005 had no biopharmaceuticals in development, has since acquired Cambridge Antibody Technology (UK), MedImmune (MD, USA) executed a string of licensing deals and stated that their goal is to have biopharm representing 25% of their pipeline in the very near future.⁹

At the same time, a series of major pharma companies, including Pfizer, AstraZeneca and Amgen have recently cut back in-house manufacturing and publicly stated their intent to place greater reliance on outsourcing.

If growth in demand is almost certain and the cost pressure to use contract manufacturing is assured, it is hard to envisage any future capital investment into major manufacturing facilities in Western Europe and North America that does not consider alternative locations such as Asia. In the past, such offshoring was viewed primarily as a means to access cheap labour, but a more enlightened, strategic view of global contract manufacturing is now starting to emerge. Asian companies are acquiring US CMOs and, with skills and experience becoming proven in Asia and elsewhere, successful Western CMOs will leverage offshore talent to make gains in productivity, efficiency and quality. It is not so much about "how much we can save?" but "how — within the limitations of cost, capital, capabilities and capacity — can we continue to grow? "

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