



Outsourcing Insights: Ferment in Biomanufacturing

Small-scale biomanufacturers attract capital, while large CMOs build competitive barriers

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The contract biomanufacturing business has never been for the faint-hearted, but for companies that have stuck out the difficult years, patience and commitment are paying off. The burgeoning biopharmaceutical pipeline and looming commercial capacity shortages are creating new opportunities for growth. They are also creating a supply base divided between large-scale and clinical-scale biomanufacturers with very different competitive dynamics in each segment.



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According to a recent analysis by BioProcess Technology Consultants (Acton, MA), the industry will require nearly 3.3 million liters of cell culture capacity by 2010, thanks to the growth of currently marketed MAb and recombinant protein products, as well as expected approvals over the next three years. However, only 3.0 million liters of capacity (captive and contract) is forecast to be available by 2010; that's a 10% capacity shortfall. The capacity deficit is likely to be exacerbated because that capacity is not where it is needed, i.e., there may be not only a more extreme shortage of contract capacity but also unused captive capacity at the major biopharma companies.

The capacity shortage puts the commercial-scale contract manufacturing organizations (CMOs) who are still in the game—notably Lonza, Boehringer Ingelheim, and Celltrion—in the driver's seat. Having survived an industry turndown in which key competitors, including DSM, Dow Chemical, and Cardinal Health, closed down facilities or scaled back investment plans, survivors are now seeking to secure their market shares and raise the barriers to entry for potential new entrants.

A central strategy for the market leaders is simply to have more capacity available than potential new entrants. Large capacity means economies of scale, accumulated experience, and availability that new entrants cannot match. The three largest players have accumulated, or are in the process of accumulating, nearly a million liters of capacity between them, and have scared off most potential competitors.

The moves by Lonza have had the highest profile. In February, Lonza completed its acquisition of Cambrex's biomanufacturing business and late last year it announced a major deal to acquire Genentech's facility in Porriño, Spain, while building a new large-scale facility for Genentech in Singapore. Those transactions combined with expansions at facilities it already owns in Portsmouth, NH; Visp, Switzerland; and Slough, UK, give Lonza 350,000 L of biomanufacturing capacity, the most any CMO has.

Celltrion broke ground last year on a massive 180,000-L expansion expected to cost over \$400 million, which will make Celltrion the second largest biomanufacturing player based on capacity. The company completed the construction of its initial four 12,500 L cell culture bioreactor trains in 2005. The expansion was undertaken after Celltrion signed a second supply agreement with Bristol-Myers Squibb (BMS), which will lock up 60,000 L of capacity. In 2005, BMS and Celltrion signed an agreement for 50,000 L of capacity to produce Orencia, BMS' rheumatoid arthritis drug approved in late 2005.

Another key strategy for the market leaders has been to offer early development services in order to build potential commercial relationships at an early stage. Their combined clinical and commercial solution is something that smaller competitors cannot offer.

To that end, Boehringer-Ingelheim Biopharmaceuticals (Biberach, Germany), with over 180,000 L of cell culture

capacity and 12,000 L of fermentation capacity, recently formed a development collaboration with Laureate Pharma (Princeton, NJ). Under the agreement, Laureate will offer its clients access to BI's HEX expression system and large-scale manufacturing capabilities at BI's Biberach facility. Lonza has development capabilities in the UK and the Cambrex acquisition added a North American presence. Celltrion currently lacks development capabilities outside of Korea.

CROWDED CLINICAL SEGMENT

While the few commercial biomanufacturers are consolidating their positions, clinical-scale biomanufacturers are battling it out in a crowded arena. The PharmSource Advantage database lists over 70 contract biomanufacturers worldwide with GMP capacity of at least 100 L. The supplier base includes 39 companies in North America, 28 in Europe, and a small but growing number of players in the Asia-Pacific region.

Smaller biomanufacturing CMOs see themselves as catering to underserved niches in the market. The market for their services is highly segmented, with client needs varying widely across dimensions like manufacturing technology (cell culture versus fermentation), nature of the substance (e.g., glycoproteins or vaccines), need for expression or host system improvement, breadth of support services required, and geography. These wide variations in the needs of biopharmaceutical companies have probably kept price wars from breaking out despite the large number of competitors.

The clinical biomanufacturing segment continues to attract new players, especially at intermediate scale (500 L–2,500 L). Industry veterans like Laureate Pharma, Goodwin Biotechnology (Plantation, FL), and Rentschler Biotechnologie (Laupheim, Germany) are expanding; while new players like Cytovance (Oklahoma City, OK), Cook Pharmica (Bloomington, IN), and InnoBio (Selangor, Malaysia), are entering the business.

The capacity expansion is supported by real top-line growth. Most clinical-scale biomanufacturers are reporting robust top-line growth, generally in the mid-to-high double digits. For instance, Danish biomanufacturer CMC Biopharmaceuticals reported its revenues grew 50% in 2006, and Laureate Pharma saw its volume jump over 200% for the year. However, most of the growth has been off a relatively small base (revenues in the low tens of millions at best) and most companies have yet to reach a volume sufficient to generate profits.

In fact, the quest for profitability is a major objective for increasing capacity. Limited batch size and project capacity make it difficult for clinical scale biomanufacturers to grow their client base and retain existing customers as their requirements increase. More and larger capacity enables biomanufacturers to leverage the fixed costs of operating their facilities and developing new business. It also helps companies to hold on to clients as their needs graduate to pilot-and launch-scale quantities. Improved titers and yields are making intermediate-scale bioreactors feasible for commercial supply.

ATTRACTING CAPITAL

The dramatic growth and perceived opportunities for clinical manufacturers is attracting badly-needed capital into the industry. Venture capitalists have made substantial investments in Xcellerex (\$20 million) and Althea Technologies (\$23 million). Laureate Pharma gained access to capital thanks to its acquisition in 2005 by Safeguard Scientifics, a publicly-traded holding company.

Private investors are actively looking for more opportunities in the industry, and are likely to finance more deals in coming months. We are aware of at least one small CMO that is actively looking to be acquired, and it is expected that the ICOS manufacturing facility, which has been doing a lot of contract work and which Lilly declared redundant following its acquisition of ICOS, will be sold this year. There is speculation that VaxGen could sell its South San Francisco biomanufacturing facility as part of its restructuring following the cancellation of its vaccine contract with the US government.

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