



Contract Manufacturing in India: Is the CMO Model a Viable Business?

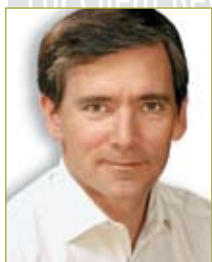
Indian biologics manufacturers can tap into the global biologics market by enhancing their quality image and maintaining cost competitiveness

Increased competition, patent expirations, and dwindling new-product offerings have put pressure on companies to offload risks by outsourcing. This trend has benefitted established contract manufacturing organizations (CMOs) globally. But for emerging India-based biopharmaceutical manufacturers, the short-term outlook remains a question. As we argue in our report, *Advances in Biopharmaceutical Technology in India*, the country is still widely perceived as having problems that may hinder future growth in outsourced biologics manufacturing.¹

Although the Indian biopharmaceutical industry has demonstrated its competence in several technical and manufacturing areas such as bioinformatics, small-molecule generics, R&D and drug discovery, and clinical research, industry observers question how India will position itself to offer CMO services. To be successful, CMOs must offer high quality technical know-how, process development competence, and lower cost manufacturing processes.

INDIA'S BIOPHARMACEUTICAL BACKGROUND

India's expertise in biopharmaceuticals dates back to 1925, when Haffkine Institute (Mumbai) began production of vaccines. Today, Haffkine's biopharmaceutical group ranks #37 in our *Top 60 Biopharmaceutical Manufacturers in India*.² Until recently, India has been highly dependent on foreign companies to meet the country's growing demand for basic medication. Biocron (#1 in our India biopharmaceutical ranking report), began to change that in 1978, when it became the first Indian company to manufacture and export enzymes to the US and Europe. India is now



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India is several years away from becoming a major destination for biopharmaceutical outsourcing.

the largest producer of recombinant Hepatitis B vaccine. Serum Institute (ranked #2) claims that one of every two children in the world is vaccinated by their vaccine. Although most major Indian biopharmaceutical companies today are focused on fermentation and vaccines, the domestic recombinant biopharmaceutical segment is beginning to make progress as well. Today, as they prove quality and cost effectiveness, these companies are beginning to tap into the global markets for a broader array of biologics. The current focus is on obtaining a share of the underdeveloped market and supplying to the World Health Organization (WHO) and other non-government organizations.

RISKY, BUT REWARDING

CMOs that make small-molecule products have definitely been enjoying a boom. From 2004 to 2005, the pharmaceutical contract manufacturing industry doubled, from about \$12 billion to \$25 billion.³ By 2006, it had expanded by another 50% to about \$35 billion.⁴

Biopharmaceutical contract manufacturing has tougher requirements for technology, human capital, and regulatory aptitude. In recent years, there have also been signs of adequate capacity, and would-be newcomers

to the business have faced significant barriers to dislodge existing players.^{5,6} The potentially expansive market for biosimilars has yet to take off because the US and Europe have been slow in issuing guidelines in this area.

Despite all this, growth of biopharmaceutical contract manufacturing has been fairly robust at about 25% annually.⁷ And as Figure 1 makes clear, there is going to be the need for outsourcing capacity to CMOs. Some of that may well be directed toward India.⁸

According to this year's survey data, outsourcing of at least some production in mammalian cell culture will be done by 60.4% of biotherapeutic developers by 2012. Microbial fermentation will be outsourced by 47.6% of biotherapeutic developers by 2012. The fact that manufacturers using mammalian systems have not significantly changed their five-year projection this year, suggests a relatively stable production environment.

INDIA'S RISK-ADDED PROPOSITION

India's challenges and weaknesses associated with biomanufacturing include weak infrastructure, quality management problems, intellectual property (IP) issues, inadequate financial support, and an unclear regulatory environment. While all these are receding, there are still lingering perceptions, and realities of technical insufficiency, quality problems, and foreign IP risk. Biomanufacturing is capital- and knowledge-intensive, rather than labor-intensive. As such, one of India's strengths, its relatively low-cost, talented labor pool, does not support this manufacturing segment. In biomanufacturing, any cost advantage can swiftly be wasted through technical or regulatory mistakes, loss of proprietary data, or supply problems associated with biotech-trained labor or logistics infrastructure.⁹

WEIGHING THE RISKS

Western biopharmaceutical executives have cited India's risky IP climate as one of the major reasons their companies have chosen not to offshore manufacturing to India. In addition, concerns exist over the ability of Asian manufacturers to be cGMP and FDA compliant, to have qualified management and a good track record, and in general to have the collective know-how to operate at Western standards. However, with narrowing developmental pipelines, looming patent expirations, and the failures of would-be blockbuster products, Big Pharma is looking to cut costs wherever it can.

Asia is certainly going to continue to be a major destination for much of the offshoring of small-molecule drug manufacturing in the short-term, and biologics in the longer term. India's perception in the West is evident from a decision by Wallace Pharmaceuticals, an established Indian maker of formulations and active pharmaceutical ingredients (APIs) in 2004, to purchase Florida-based Goodwin Biotechnology, an established biopharmaceutical CMO. Goodwin announced that it was in talks to provide its CMO services to Indian biopharmaceutical companies, chiefly because

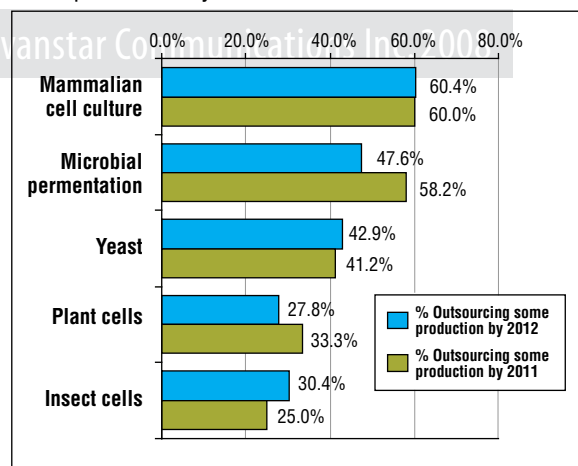
the intricacies of biopharmaceutical production require, "an intimate knowledge of what the US FDA expects, how to deal with the FDA, and ultimately, the flexibility to protect the drug sponsor's investment by continuously evolving the processes to the FDA's satisfaction. To do that successfully from India would prove extremely difficult."¹⁰

MODEST SUCCESSES

To date, about a dozen Indian biopharmaceutical companies have announced that they are equipped to make biologics for foreign clients. Success in attracting business has been modest, however, and has mostly included contracts for relatively simple APIs and intermediates, and vaccines in particular. Some noteworthy examples of homegrown Indian companies that have demonstrated or are buying world-class capability in biologics manufacturing include:

- Biocon, India's largest biopharmaceutical company that produces a humanized anti-EGFR monoclonal antibody for the treatment of head and neck cancer. Biocon also makes insulin products for US-based Bentley, Invitrogen, and BMS, and exports statins, which require some biotech-type manufacturing steps, through US distributors. For other clients, Biocon makes enzymes and biologic APIs for immunosuppressants.¹¹
- Serum Institute remains one of the world leaders in vaccine production. Its product line includes MMR, quadrivalent vaccine, rabies vaccine, and recombinant Hepatitis-B vaccine.

Figure 1. Five year projections: percentage of biotherapeutic developers planning to outsource at least some production by 2012 versus 2011.⁸



- Intas (ranked #12) provides through its Celestial Biologicals group manufacturing and marketing of plasma-derived products mainly albumin, immunoglobulin, and coagulation factors (factors VII, VII, IX, XI, and fibrinogen).
- Avesta Biotherapeutics and Research (ranked #50), a joint venture between Avesthagen and Cipla, purchased Swiss-based Siegfried Biologics, which is expected to be used by Avesta to manufacture its biopharmaceutical products.
- Bharat Biotech (ranked #6) makes a Haemophilus Influenza B conjugate vaccine for Wyeth Lederle, and a human lactoferrin product for Agenix, Inc.¹² Acambis Plc., a UK-based vaccine developer, has a manufacturing and marketing agreement with Bharat for a Japanese encephalitis vaccine.

Some major Indian pharmaceutical companies such as Dr. Reddy's and Wockhardt, are keenly involved in this developing segment. Dr. Reddy's currently markets two generic biologics that are versions of Roche's Rituxan and Amgen's Neupogen. Wockhardt has announced that it will introduce one biopharmaceutical product every year, with plans toward potential alliances with biotech companies in the US and the EU.

LOOKING AHEAD

India's actual and perceived shortcomings have together been detrimental to its ambitions in biologics manufacturing, even with respect to its main cost rival, China. These factors suggest that India is several years away from becoming a major destination for the outsourcing of biopharmaceutical manufacturing. In the long run, however, if Indian biologics manufacturers can establish a track record for recombinant products, enhance quality image,

maintain cost competitiveness, and demonstrate technology transfer and regulatory know-how, they are likely to be in the middle of the next boom in biologics manufacturing. ♦

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