

# Managing Bio-Outsourcing Partnerships

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Bio-outsourcing has many benefits, but entrusting the quality of your company's products to a contractor also entails significant risk. Here's what you need to know to mitigate those risks and enjoy the rewards.

**O**utsourcing has long proved to be an effective strategy to improve operational efficiency and lower production costs for small-molecule manufacturing. Now a surge in approval rates for biotechnology products in the late 1990s, coupled with an urgent need to keep manufacturing costs low, has resulted in an increase in the number of biopharmaceutical companies outsourcing their biomanufacturing activities, commonly referred to as bio-outsourcing.

Bio-outsourcing has expanded rapidly during the past decade. Industry analysts estimate that bio-outsourcing grew at annual rate of 20% from 1996–2001, a period in which the biopharmaceutical industry brought an unprecedented number of products to market  $\approx 1$ . Recent surveys conducted by BioPlan Associates, Inc., a Maryland-based biomanufacturing consulting firm, indicated that in 2004, about 35% of biopharmaceutical companies outsourced some of their biomanufacturing activities; a number that is expected to grow to 47% by 2008  $\approx 2$ . The global market in 2003 was estimated to be \$1.3 billion and is likely to reach \$3.7 billion by 2010  $\approx 3$ .

This article discusses why to outsource, how to choose the right partner, and how to negotiate and manage outsourcing relationships.

## WHY OUTSIDE?

Biopharmaceutical manufacturing can be subdivided into three distinct activities:

- Bioprocess development
- Scale up for manufacture of clinical-trials materials
- Large-scale, commercial manufacturing.

In the past, many large biopharmaceutical companies (such as Amgen, Genentech, and Biogen/IDEC) chose to keep bioprocess development and clinical manufacturing in-house but outsourced commercial manufacturing. In recent years, many such companies built their own dedicated commercial manufacturing facilities, as well. In contrast, smaller biopharma companies, which lack the money, personnel, and in-house capacity for biomanufacturing, typically outsource everything from bioprocess development through commercial manufacturing.

The decision to outsource biomanufacturing is typically based on factors such as

- the financial status of a company
- corporate/business strategy
- in-house manufacturing capability
- phase of product development
- market size for the product.

Companies that choose outsourcing frequently cite the following reasons for their decision: reluctance to make a capital investment in biomanufacturing; lack of internal biomanufacturing expertise, experience, or personnel; and an urgent need to reduce time to market. Regardless of which factors prompt a company to outsource, the success or failure of a project is dependent on the quality of the relationship forged between a company and its partner.

## ENTRUSTING QUALITY

The reputation and commercial success of a company is inextricably linked to the quality of the product(s) it sells. When a company chooses to outsource manufacturing, it is largely ceding control of product quality—but not regulatory accountability—to its outsourcing partner  $\approx 4$ . Therefore, choosing an outsourcing partner is a critical business decision that must be taken seriously.

In contrast with typical customer-supplier relationships (which can be short-lived and largely impersonal), contract biomanufacturing involves long-term partnerships that require open communication, mutual respect, and inordinately high levels of trust. Therefore, a biopharma company must consider several critical factors when searching for an appropriate bio-outsourcing partner. (See “Choosing a CBMO.”)

**Type and Scale:** Management must determine the kind of outsourcing required—bioprocess development, clinical manufacturing, or commercial production. The core competencies of contract biomanufacturing organizations (CBMOs) are typically built around specific areas of expertise: Some CBMOs specialize in process development. Others manufacture only at small scales for clinical materials or only at large scales for commercial production. Still others manufacture at more than one scale or accept both manufacturing and process development work.

A subset of this consideration is the type of product and expression system. CBMOs tend to specialize in the types of products they manufacture and the production methods they use. Certain CBMOs have a long history of manufacturing monoclonal antibodies, and some specialize in other recombinant proteins. Furthermore, a CBMO that specializes in microbial fermentations might have little or no experience with mammalian cell culture.

Companies must consider the strength and depth of their pipelines. A company with some products in clinical development and others ready for commercial manufacturing may choose to use specialized vendors to manufacture products at

different scales. Or it might make sense—to ease product quality and project management concerns—to hire a single CBMO to manufacture all clinical and commercial materials.

**Compliance Matters:** In the past, cGMP manufacturing conditions were not legally required for experimental drugs used in phase 1–2 clinical trials in Europe and the United States, although they were strongly recommended. But effective May 2004, the European Medicines Agency (EMA) mandated that all therapeutics (small molecules and biopharmaceuticals) used in any phase of human clinical trials be manufactured under cGMP conditions  $\approx 5$ . The US Food and Drug Administration has yet to adopt similar guidance. Nevertheless, it is only a matter of time before that happens. Therefore, assessing a CBMO's standing with the relevant regulatory agencies is critical regardless of the type or scale of a project.

**Check References:** A CBMO's commitment to product quality is an essential ingredient of any successful bio-outsourcing relationship. The best way to assess that commitment is to contact current and former clients for their opinions about the CBMO.

Other references to check include the contractor's record of cGMP compliance, its approval and inspection history with the relevant agencies, its vendor-certification processes, and the presence or absence of in-house training programs for its employees and customers  $\approx 6$ . You can also measure a CBMO's commitment to product quality by examining its adherence to product specifications, defect and rejection rates, any history of contamination problems, and materials tracking and documentation procedures.

You can easily determine the quality of a CBMO's customer service by assessing its responsiveness to customer queries, required order lead times, on-time product delivery, and willingness to provide clients with innovative technological solutions for their biomanufacturing problems  $\approx 6$ .

**Money Matters:** Pricing structures and manufacturing fees are other important factors to consider during the CBMO selection process.

## CHOOSING A CBMO

Stage of product development
CBMO's area of expertise
CBMO's commitment to quality
Costs and pricing structure
Customer service
Availability of capacity and trained personnel
Financial stability of CBMO

Pricing should always be competitive. Still, it is not prudent to outsource biomanufacturing projects to the lowest bidder—product quality is too important to sacrifice in favor of the cheapest price.

A critical factor frequently overlooked when choosing a CBMO is the potential partner's financial history and long-term financial stability. Adverse business conditions affecting a CBMO can have more catastrophic consequences for a client than any unanticipated regulatory or technical problems. The sudden and unexpected closure of a commercial manufacturing facility would have serious financial and regulatory consequences for a company that relied solely on that CBMO to manufacture its products.

Some measures of a CBMO's financial stability include its current and past earnings, present market share, and ongoing revenue and market trends in the industry  $\approx 6, 7$ . This type of financial information is usually available through corporate regulatory filings (if the CBMO is publicly traded), industry intelligence, financial analyst reports, and word of mouth.

## SIFTING PROPOSALS

To begin the CBMO selection process, a client company (sponsor) typically prepares a detailed, prioritized list of requirements for its biomanufacturing project. The list should be compiled (and reviewed) by all members of the sponsor's project team, which should include representatives from manufacturing, quality, and business.

Next, the project team prepares a detailed request for proposals (RFP). The RFP is usually sent to several CBMOs who have already been carefully vetted by project team members

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and represent good potential matches. The RFP should include as much information as possible, including the scope of the project, deliverables, and an explanation of the sponsor's experience with the product and corresponding manufacturing processes.

The sponsor should carefully review all proposals received, paying particular attention to each CBMO's responsiveness, cost structures, project lead times, and availability of capacity and personnel. Next, the project team should visit several finalists to

determine whether they can work well with one of them.

**Details, Details:** Once a sponsor and CBMO agree in principle to work together, the business and financial terms of the relationship are typically outlined in a *service contract agreement*. Although it outlines specific financial and business terms, it usually does not describe the work plan nor how the sponsor and contractor will interact on a project. To avoid any potential conflicts or problems, some sponsors also execute *joint service*

*agreements* (JSA) with their outsourcing partners. A JSA is a tool to manage ongoing contract manufacturing relationships by outlining day-to-day interactions between a sponsor and a CBMO ≈8. Unlike contracts, JSAs work best when they are simply written, easily amended, and not legally binding.

### MANAGED EXPECTATIONS

At the beginning of any outsourcing relationship, both parties must address several key issues. They must agree on the logistics of their working relationship: what will be accomplished, who is responsible for what, and how the project will be managed. The parties must also establish clear expectations of deliverables such as metrics for delivery performance, rejection rates, and product yield and reasonable timelines. Also, everyone needs to agree about the frequency and preferred methods of communication—telephone, email, regular face-to-face meetings—and how information flow and data will be managed ≈8. Individual project team members must clearly understand their roles and the project management reporting structure. Finally, it's prudent to agree at the beginning on a mechanism to resolve problems and conflicts as they arise.

**Technology Transfer:** After client and contractor have defined how they will work with one another, they are ready to tackle the next step in their relationship: technology transfer. It is during this pivotal step that all relevant product information—documents, product specifications, analytical and process development data, and so on—is given to the CBMO. Successful technology transfer ensures that a manufacturing process developed by the client can be duplicated at the contractor site.

That task is long, tedious, and labor-intensive. Successful technology transfer frequently takes much longer than sponsor companies expect, which can place an unnecessary strain on the client–contractor relationship ≈9. As a general rule, do not rush technology transfer. Furthermore, clients must also realize that not everything will work correctly the first time a process is run at a new site.

## WHO IS RESPONSIBLE?

PROBLEM OR DEFECT	CLIENT	CONTRACTOR
Instability or poor performance of cell lines	X	
Nonvalidated process or suitable process not possible	X	
No assignable cause; act of God	X	
Contamination of master cell line; faulty precursors to process	X	
Contamination of run		X
Product does not meet specifications		X
Operator error		X
Lack of cGMP compliance		X
System control problems		X
Power outages, fire, and floods		X

Assignment of problems or defects in a bio-outsourcing relationship adapted from Wong H, Sopchak L, Farr-Jones S. *BioManufacturing Responsibilities: Who Is Responsible When Something Goes Wrong in a BioManufacturing Partnership*. *Contract Pharma* March 2003: [www.contractpharma.com/march031.htm](http://www.contractpharma.com/march031.htm).

The first step is the transfer of all relevant product information from the client to the contractor. Once information transfer is completed, the next step is to develop a process design or scale-up plan—a detailed technical document that outlines the methods to be used to move the transferred process from its current scale to whatever is needed for the outsourced project. Jointly developed by the client and contractor project teams, this plan includes details about project scale size, the equipment that will be needed for scale up, the source and quantity of raw materials, storage requirements, sampling and testing arrangements, and project lead times ≈10.

After they develop a scale-up plan, project team members must formulate a production plan, the way the product will be manufactured during an actual production campaign. This plan usually contains a detailed list of required equipment, quantities of supplies

and chemicals, number of personnel involved in the campaign, assays to be used, and a document preparation and review plan with SOPs, batch records, quality assurance forms, and so on ≈10. The production plan should first be implemented as a series of trial or training manufacturing runs. Such runs are typically scaled down versions of the production plan and can be performed at minimal cost with little impact on project timelines.

Trial runs allow production personnel to review the process in action and to consider and evaluate potential improvements. They also permit production personnel to anticipate potential scale-up issues, provide hands-on training for manufacturing and quality control personnel, and generate material for preliminary product characterization to validate the production process ≈10.

In recent years, it has become accepted practice in the biomanufacturing industry to perform engineering runs before actual production campaigns begin at CBMOs ≈10. Companies typically perform engineering runs at production scale to identify and resolve process and equipment issues. Like training runs, they provide valuable hands-on training for personnel. They also permit a review of cGMP documentation. Process modifications occur as necessary during engineering runs with the intention of making them permanent in the master production record. At least one problem-free engineering run should be completed before initiating a production campaign. Technology transfer can be considered complete when several production runs are done and the resulting product(s) meets specifications.

### FUTURE IMPERFECT

In the biomanufacturing world, few projects are devoid of problems, unanticipated changes, or surprises. The best way to deal with problems is to agree at the outset who is responsible—client or contractor—when things go wrong. Without such agreements in place, lengthy production delays are likely to happen as the client and contractor argue over responsibility for problems.

There is general agreement in the bio-outsourcing industry regarding assignment of responsibility ≈11. (See “Who Is Responsible?”) If a problem can be clearly traced back to the client company—contaminated master cell bank, poorly performing cell line—then it is financially responsible to correct the problem. However, if the situation involves contamination, lack of cGMP compliance, or contractor operator error, the contractor is responsible.

Nevertheless, there are always circumstances in which the assignment of responsibility is not clear cut. In rare circumstances, arbitrators have been brought in to resolve conflicts between clients and contractors who are deadlocked over responsibility for problems or defects. But in the spirit of good working relationships and keeping production costs down, all parties are better off if they can work out their differences without spending money on legal remedies.

To that end, some clients agree to no-fault clauses in their contracts with CBMOs. In such cases, the client and contractor agree to split financial responsibility equally for problems or defects without any assignment of blame ≈11. These agreements foster a team relationship and encourage the client and contractor to work together to correct problems as quickly as possible.

### TRUST IS VALUE

The bio-outsourcing industry is continuing to expand as more biopharmaceutical companies realize the benefits of outsourcing manufacturing projects. Finding the right CBMO can be a long and daunting process for any biopharmaceutical company, but the benefits of a good outsourcing relationship outweigh the costs of creating it. The success of a bio-outsourcing partnership depends on open communication, trust, and teamwork between a sponsor company and its outsourcing partner. ∞

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