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Six Essential Qualities of a Bio-Outsourcing Partner

What to look for in a Bio-CMO

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IMAGINE THIS SCENARIO: A company has a lyophilized drug on the market that's used in hospital emergency rooms. Suddenly, production cannot continue at the current manufacturing plant, and no other source supplies the molecule. Inventories are running low, and the company must quickly turn over production to another facility.

The company is fortunate to find a contract manufacturing organization (CMO) with the capacity and capability to handle production, and it gets several bonuses. While the original manufacturing process resulted in significant product losses, averaging about 10% per batch, the CMO designs a process that reduces lyophilization time by 42% and improves yield by 9% per batch. The CMO also helps accelerate the transfer of the process to the new plant, enabling the FDA to approve the manufacturing site in less than 10 months.

What could have been a disaster ends up working to the company's advantage, because manufacturing and operational improvements actually save \$4.7 million.

The message from this story is this: when selecting a CMO, choose wisely.

Whether one is moving production from one plant to another, looking to outsource fill-and-finish operations, or seeking a strategic partner for a compound in early stages of development, the choice of a bio-outsourcing partner is one of the most important decisions a biopharmaceutical company may make. Development of biologics is fraught with technical challenges related to the cost, unique size, structure, and stability profile of molecules, as well as the necessary regulatory hurdles that must be overcome. Therefore, companies should be careful to

partner with a CMO that has specific capabilities, skilled staff, specialized equipment, and dedicated manufacturing facilities.

In general, a company should consider whether a potential bio-outsourcing partner possesses six characteristics before signing on the dotted line.

1. Experience in Biotechnology

The most important quality of a good CMO for biologic drug makers is experience in biotechnology. While that would seem to be a basic consideration, it's not necessarily as common as might be expected. Although biotechnology has been around for approximately 50 years, the actual production of biologic drugs is a fairly new industry, one that requires a different skill set and larger investment in equipment relative to the manufacture of small-molecule therapeutics.

The first question to consider, therefore, is whether the CMO has experience developing a biologic product from early stages of development through regulatory review and to market availability. If the CMO has a successful track record in guiding biologics over technical and regulatory hurdles, then it is likely to possess the necessary equipment and essential experience for successful commercialization of a biologic drug. Moreover, a savvy bio-outsourcer will have implemented good manufacturing practices, aseptic processes, and quality-assurance systems

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throughout all divisions of the CMO.

Consequently, a CMO with biotech experience will be able to translate that knowledge and experience to other companies. For example, a knowledgeable CMO can help determine which molecules are sensitive to light, temperature, or may be damaged by materials in tubing and filters; can recommend processes that prevent loss of expensive active pharmaceutical ingredient (API); and can offer solutions to overcome parenteral drug solubility challenges.

2. Intellectual Property

When a biopharmaceutical company selects a bio-outsourcing partner, it is often concerned about its own intellectual property (IP). But the IP position of the CMO may be the more critical factor to consider when choosing a partner.

While biotechnology is not likely to become a commodity market overnight, there are at least three reasons why choosing a CMO with novel technology platforms and a strong IP position is essential for companies seeking a distinct point of differentiation for their product. First, it is common for multiple groups of researchers to be pursuing similar molecular targets, whether for genetically engineered proteins or monoclonal antibodies. Second, existing biotechnology drugs often are competing in crowded therapeutic categories and would benefit from novel technology as a means of product differentiation or to extend a biologic's life-cycle. Third, the arrival of generic biologics may be inevitable.¹

As a consequence, choosing bio-outsourcing partners with novel formulation strategies and drug delivery systems protected by international patents will help a biologic drug company to strengthen its own (perhaps tenuous) patent position.

A CMO's IP is a particular concern for drug companies looking to reformulate existing therapeutics. More than one-third of drug products launched by the top 50 drug manufacturers between 2002 and 2005 were reformulations.² Biologic drug companies looking to extend their products' lifecycles — and gain a competitive advantage — typically rely on novel formulation technologies. For example, almost 70% of biologics are delivered by subcutaneous injection.³ One popular area for reformulation is the

development of sustained-release versions of these injectable drugs, which not only help meet market demands for more convenient modes of administration but also help differentiate biologics in crowded categories or enable a company to reach parity with the competition.

3. Global Reach

An effective CMO also must have global experience in the development and manufacturing of biologics and with international regulatory authorities. Biotech drug companies — large and small — typically establish relationships with CMOs to avoid the expense of building their own manufacturing facilities.

Before choosing a CMO, however, biopharmaceutical companies should determine whether the CMO has a strong audit history with Japan, Canada, and Europe, in addition to the U.S. Finding a CMO with a successful and compliant regulatory track record is critical for smaller biotech companies with little or no experience submitting drug applications in different countries. An important consideration is whether the CMO's facilities are licensed with key regulatory authorities, such as the FDA; European Agency for the Evaluation of Medicinal Products (EMA); the Japanese Ministry of Health, Labor, and Welfare (MHLW); and Health Canada.

For companies looking to quickly bring enhanced packaging or drug-delivery technology to market for their existing biologic, a CMO's regulatory relationships and technology applications also are important. In the U.S., CMOs that have established their own drug master files (DMFs) with the FDA for drug delivery technology, or have similar documents with the EMA, will help accelerate the development and approval process.

4. Potential for Licensing Or Strategic Partnerships

When choosing a CMO, size does matter, regardless of the level of services a company is looking to outsource. The CMO needs to be large enough to handle the assignment, as well as to appreciate how its role inter-relates with the entire process of getting a biologic drug to market. Even more significant for biotech

companies, however, is whether the CMO can offer opportunities for licensing or strategic alliances. These companies especially need to consider the level of risk the CMO in question is willing to take with them, based on current products and their market potential.

Biotech firms that are virtual companies without manufacturing capabilities need a CMO that can guide their molecule through the complete manufacturing process. Generally, the larger a CMO, the less a virtual company has to do. Bringing the CMO on board as a partner and consultant can enable a biotech firm to focus more of its resources on drug discovery.

5. Wide Range of Services

Biopharmaceutical companies may pull into a CMO full-service station and not need full service. Perhaps they want only fill-and-finish for a particular product. Or they are looking to reformulate an existing drug. Why, then, should that company care whether a particular CMO offers vector and cell-line development, bulk manufacturing sites, or fully staffed regulatory teams?

The answer can be as simple as going back to the original scenario that began this article. When large pharmaceutical companies and small biotech firms alike enter agreements with bio-outsourcers, it's important to consider not only what the CMO can do for them today, but also what they might need tomorrow.

In its 2nd Annual Contract Pharma Outsourcing Survey, the editors of this magazine reported that nearly 50% of companies use between one to five preferred CMO vendors.⁴ For those companies, limiting relationships to trusted outsourcers can simplify the process of getting molecules to market. Once a partnership with a particular CMO is established, a biopharmaceutical company will be familiar with that organization's level of quality, core competencies, pricing, and environment, thereby making it easier to outsource additional molecules or quickly address unexpected turns of events in getting a drug to market.

6. State-of-the-Art Equipment

The nitty gritty of whether a CMO is well qualified comes down to its formulation, filling, and finishing equipment. While a

CMO's manufacturing capacity is a significant consideration, the answers to three critically important questions will determine whether the CMO can protect sensitive biologics and overcome commercialization challenges with speed and efficiency.

Will the equipment be gentle on the molecule?

The processing of biologic drugs typically requires some degree of aeration. Yet high rates of mixing are known to cause foaming, denaturation, aggregation, viscosity, or oxidation of biologics. Consequently, a CMO with biotech experience should offer equipment that protects molecules from inadvertent shearing, breakage, or other damage. A critical factor is whether the CMO offers low-shear magnetic mixing tanks, such as those with bottom-mounted magnetic mixers, to reduce shear force compared with traditional mixed-motor processing.

Can equipment protect against environmental damage?

Large molecules can degrade in multiple and individually unique ways, so a CMO has to be fully equipped to ensure the integrity of biologic is maintained. Therefore, it is essential that the CMO's lyophilization and filling lines for vials, syringes, and cartridges be designed to handle these large, fragile molecules. On a more basic level, the CMO's machinery should be equipped with filling heads that have large apertures to avoid damaging the molecule as it flows through the tubing.

The CMO's equipment also must be designed to help address the more complex problems inherent to production of biologics. For molecules that are temperature sensitive, complex temperature-control systems throughout the production process are essential. CMOs that offer complete cold-chain filling can prevent temperature fluctuations during filling and lyophilization in order to maintain the quality of the API and minimize loss. In cold-chain filling systems, precise temperatures are maintained from filling tank to manifold, from filling head through accumulation table, and throughout the lyophilization load and unload process.

When molecules are to be lyophilized,

it's also best to choose a company whose lyophilization services are designed to handle organic solvents, which can be combustible. Lyophilization ovens that work with combustible organic solvents can prevent damage by averting sparking and exhausting fumes away from the fragile molecules.

Can the CMO reduce loss of API?

Choosing a CMO that has put in place a high-yield process design can directly influence a company's profitability, particularly for biotech drugs, which are priced from \$10 to \$2,000 per dose.⁵ There are a number of ways in which a CMO can prevent loss of valuable API, including:

- Improved homogeneity, using procedures such as a product recirculation guard to prevent product separation in vaccines and other suspensions.
- Fewer line stoppages by employing a vial-filling design that minimizes holding of product during the final manufacturing stages.
- Precise filling of syringes, cartridges, and vials, which significantly reduces overflow and unnecessary product loss.
- Non-destructive weight-checking systems, which ensure vial weight consistency without emptying random vials.

Growing Biotech Industry Turning to CMOs

The biotechnology industry is growing and evolving, and it pays to partner with a CMO whose technology and experience are on par with that of the industry. Nearly 30% of all therapeutic compounds under development are biologics⁶ to treat a range of diseases. The Biotechnology Industry Organization estimates that 300 biologic drugs and vaccines, currently in clinical trials, target more than 200 diseases, including cancer, Alzheimer's disease, diabetes, heart disease, multiple sclerosis, AIDS, and arthritis.⁷

When choosing a partner for bio-outsourcing, find out whether the CMO is

part of this growth. A successful bio-outsourcing relationship will require that the CMO has extensive experience in antibody and protein development and manufacturing, has the expertise and capacity for clinical and commercial scale projects, and is committed to growing with the biotechnology industry.

Consider, for example, whether the CMO has kept pace with new discoveries and technology. Is the CMO involved in the development of technology platforms or novel formulations that may improve the administration of biologics? How deeply committed is the CMO to hiring and retaining highly qualified staff to support these efforts? Is this an organization that will work with a biopharmaceutical company as a partner, understand the company's individual needs and molecule, and address the expected — and the unexpected — challenges quickly and efficiently?

A thorough evaluation of the CMO's experience, staff, and facilities can help a biopharmaceutical company make a wise choice and, thereby, directly influence the success of its molecule. ■

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