A continuing debate for established, emerging, and virtual biopharmaceutical companies is whether or not to outsource production to a CMO. At its core, the issue is about brand protection. While outsourcing can minimize your capital and labor costs, it can be challenging to evaluate CMOs and determine which one will best serve your needs as a manufacturing partner.

Many factors influence the selection of a pharmaceutical contract manufacturing organization (CMO) beyond the price on the bid. This article discusses what to consider when choosing a CMO to manufacture your drug product.
You want to be confident that the CMO you choose will:

- Minimize the potential for negative consequences, including damage to your brand and loss of market share and revenue.
- Minimize product quality risks and ensure that the equipment, processes, and procedures used in manufacturing will maintain the intended strength, integrity, safety, purity, and quality of the pharmaceutical product.
- Do it all within budget.

While the right choice will be specific to each pharmaceutical company and its products and processes, this article will discuss some key factors to consider when selecting a CMO. Keeping these factors in line with your business goals will help you get your product to market in a safe, compliant, and cost-effective manner.

Make sure the CMO’s staff has training and experience with all the technologies your manufacturing process requires.

**Equipment and technology**

The CMO you choose must have the equipment and technology to successfully manufacture your drug product within specifications. You should evaluate the CMO’s technologies and capabilities during the technical and commercial due-diligence period and during the initial audit activities for quality compliance. As you consider the CMO’s capabilities, ask the following questions:

**Does your product have special handling or processing requirements?** To determine whether a CMO has the proper technology and expertise for the job, evaluate your product’s unique set of critical quality attributes (CQAs) and process parameters.

Consider the following:

- Does your drug product have special temperature requirements?
- Is it susceptible to foaming or clumping?
- Does it require some type of mixing or blending?
- Is it shear-sensitive?
- Is it sensitive to bio-decontamination or cleaning chemicals?
- Is it highly viscous or temperature-, light-, or oxygen-sensitive?
- Is it a controlled substance?

Your answers to these questions will help you determine whether the CMO’s equipment, technical competence, and resources are adequate to handle and process your product.

**Does the CMO have the right equipment?** Evaluate whether the CMO has the necessary quantity and type of equipment and level of automation to suit your needs. If not, determine the costs, in time and money, to modify the company’s equipment or purchase new equipment to meet your process requirements and successfully manufacture your product. Be sure to ask whether these expenses are included in the proposal cost. The CMO must prepare a proposal and present it to you. You need to assess the proposal as part of the bid tab or contract evaluation.

If the CMO does purchase new equipment, determine the equipment’s delivery lead time and when the equipment will be qualified. Ask for the findings of the most recent process simulation and whether the process experienced any problems.

**Can the CMO’s equipment accurately dose your material?** Ensure that the CMO’s equipment has adequate dose-accuracy control to meet your specifications. You have a legal and regulatory responsibility to meet all label claims, so you must verify that the drug product contains the dose stated on the label. Final product units with too much or too little API can potentially harm patients. Also, consistently adding more than the specified amount of API to the final product unit unnecessarily increases production costs.

**How does the CMO’s equipment handle rejects?** Ask whether the equipment is built to reduce rejects and what the rejection rate is for a given batch size to ensure that the rate is satisfactory. You’ll also want to know what controls are in place to prevent excursions and whether the bulk of a batch can be preserved if a machine failure occurs.

**Is the CMO’s equipment obsolete?** Manufacturing technology advances rapidly, especially in the area of microelectronic sensors, vision systems, and analytical instrumentation. The advancement occurs so fast, in fact, that equipment more than five years old is likely to be obsolete and may not have adequate sensors or instrumentation to detect critical defects in-line, which can lead to wasted product and lost revenue.

When touring a facility, ask how old the equipment is and ask to see it run. Inquire about the equipment manufacturer and any problems the CMO has had with the equipment. For example, you may find that, while the equipment has been in storage for just four years, the machines are actually 20 years old. Be sure to ask about the availability of spare parts and how the CMO will replace parts if needed. For example, are the machine controllers even available for purchase new or will the CMO have to shop at online bidding sites to try to find replacement parts?

**Is the CMO’s staff experienced with your product and the required technology?** Suspension and high-viscosity products require different knowledge and experience compared to solution products. Highly potent and cytotoxic products require different skills and expertise to maintain a safe environment for equipment operators. Additionally, your process may require the use of specialized technology including vision systems, laser sensors, flow meters, gravimetric systems, decontamination sensors, and technology advances rapidly, especially in the area of microelectronic sensors, vision systems, and analytical instrumentation. The advancement occurs so fast, in fact, that equipment more than five years old is likely to be obsolete and may not have adequate sensors or instrumentation to detect critical defects in-line, which can lead to wasted product and lost revenue.

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systems, or analytical equipment such as an optical density meter to monitor homogeneity. Make sure the CMO's staff has training and experience with all the technologies your manufacturing process requires.

**Production capacity**

A CMO that already has clients may have a small window in which to produce your drug product. To determine a CMO's ability to fit you into its production schedule, ask the following questions:

**Does the CMO have the capacity to meet your production demands?** If the batch size and length of time required to produce your drug product on the CMO's machines increases your risk of not having the product when you need it, the CMO isn't a good fit. You can do a quick calculation by dividing the batch size by the machines' capacity (units per minute or hour) to determine the approximate amount of time needed to manufacture your drug product. Note that this calculation doesn't account for total production time, as a calculation of overall equipment effectiveness (OEE) would.

**Will you be a small fish in a large pond?** If the batch size and number of lots for your product are small, a large CMO might delay production of your product in order to satisfy a larger customer. If you're manufacturing for a specific period or for seasonal distribution and miss the production date, you could lose your market share. If you do choose a large CMO, you may need to dedicate resources at the CMO's site to advocate on your behalf or at least ensure that the CMO will notify you if a production delay occurs.

**Contamination prevention**

Because a CMO's equipment may be running one client's product one day and another client's product the next, preventing cross-contamination is critical. Make sure the CMO's cleaning procedures between products are sufficient. Determine whether the facility produces any highly hazardous compounds and, if so, how they're controlled and contained.

While each facility should have its own containment strategy, you may still want the CMO to use a separate set of equipment-format and product-contact parts exclusively for your product runs. Also, drug products created for specific high-risk populations may have additional containment requirements. Make sure the CMO can accommodate your needs.

**Training**

CFR Part 211 and various FDA Guidances require that pharmaceutical companies train staff members and document that training. Evaluate the CMO's training records as part of your initial quality compliance audit. Also, observe and assess the company's training practices as part of your technical evaluation during the due-diligence period.

The CMOs training should include general current good manufacturing practices (cGMP) training, identification and understanding of CQAs, proven acceptable ranges, critical process parameters, critical operational parameters, and other product specifications. Training should also include any knowledge related to your product, your standard operating procedures (SOPs), and your analytical methods. This will ensure that staff members understand why your procedures are written the way they are and that they can manufacture your product and determine whether it's acceptable for use.

**Regulatory observations**

Because pharmaceutical manufacturing facilities are built to protect the equipment operators, the drug products, and patients, quality systems and facility and equipment design are critical. Research the CMO's history with regulatory agencies, its documentation practices, and its process and testing procedures, including the company's responsiveness to problems and any previously documented corrective and preventive actions (CAPAs).

Search on the FDA's website for the CMO's previous inspection observation summaries [1]. When was the CMO's last inspection, and what were the findings? What were the CMO's responses to remediate the observations? Were the responses accepted and the corrective actions completed and verified?

**Personal interviews**

Finally, don't rely solely on a CMO's industry reputation and experience; conduct personal interviews with the company's executives, management, and current staff on site before signing a contract. Interview previous and existing customers and rely on vendors' feedback.

Ask what drug products the company has produced and if the staff has experience with drug products like yours. Ask the staff for examples of developmental or troubleshooting work they've successfully executed to determine whether they'll be able to handle any such needs for your drug product. Also, ask if the CMO has had any recalls, and, if so, what the root cause was and whether they've corrected the problem.

**References**

1. Available at [https://www.fda.gov/ICECI/Inspections/ucm250720.htm](https://www.fda.gov/ICECI/Inspections/ucm250720.htm).

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