

# Top 10 Principles of Successful Manufacturing Partnerships

by Donna Williams

## 10 Principles

- 1 Articulate your strategy
- 2 Build relationships
- 3 Consider unique outsourcing strategies for novel molecules, administration routes, and formulations
- 4 Understand your CMO's operations teams
- 5 Know your CMO's regulatory track record and capabilities
- 6 Confirm scalability and sustainability
- 7 Assess a CMO's ability to deliver life cycle management
- 8 Confirm the CMO's technology track record
- 9 Compare organizational cultures
- 10 Create an environment that promotes mutual success

Outsourcing has become so commonplace in the pharmaceutical and biotechnology industries that the line often blurs between the contract manufacturing organization (CMO) and pharma/biotech partner—"us" and "them," if you will. Although outsourcing relationships are based on mutual goals and interests, the most productive outsourcing relationships are based on tried-and-true principles of business engagement, primarily communication, relationship-building, and maintaining a clear strategy and intent within the framework of sometimes very different corporate cultures. Like any close relationship, outsourcing exposes the parties to each other's good sides and bad sides, strengths and weaknesses, competencies and shortcomings. A successful outsourcing partnership should therefore maximize use of contractor competencies while retaining a big-picture view of all the technologies and services required to keep the project moving along.

### GENERAL CONSIDERATIONS

Making the wrong partnering/outsourcing decision can be costly. For example, switching from one CMO to another often entails direct costs related to tech transfer and new line validations, of \$500,000 to \$1,000,000.

As with any business relationship, due diligence is a key ingredient of success. Thoroughly researching a potential manufacturing partner to assure you make the right choice can mean the difference in whether or not

you reduce risks associated with supply and timing, improve yields, and even help extend the product's life cycle through novel formulations, delivery systems, routes of administration, combination products, and other strategies.

Communication is essential in any business agreement. Both parties need to articulate project plans clearly, identify criteria for success, and agree on appropriate metrics. Communicating each party's goals and responsibilities up front helps prevent future misunderstandings and sets the tone for a constructive working relationship.

Choosing a CMO is not only about the tactical outsourcing of a single molecule's manufacture or formulation, but also a decision about where to centralize expertise in your molecule and build agility between partnering organizations. The partnership should be structured in a way that leverages the participants' capabilities for both current and future needs.

### 1 ARTICULATE YOUR STRATEGY

Lack of clarity at the negotiation stage can be a source of significant problems in any business relationship, but especially for complex manufacturing partnerships. Sponsors should ensure that their outsourcing goals are clearly articulated, both internally and to outsourcing partners. This should be done in clear language, both in written form and through face-to-face meetings. Myriad reasons exist for outsourcing a particular molecule or a product at a particular stage of its life cycle. The sponsor must first clarify those motivations internally,

and then transmit them clearly to the manufacturing partner. A full understanding of intentions helps ensure proper selection of partners and structuring of the partnership.

According to data from the *Contract Pharma*, 2nd Annual Outsourcing Survey (May 2006), 53 percent of pharma/biotech companies consider outsourcing a long-term strategic activity, and 47 percent consider it more as a short-term, tactical solution to acquiring research, development, and manufacturing capabilities.

According to the same study, 43 percent of pharma/biotech companies outsource to focus on core competencies, 29 percent because of temporary lack of capacity, 3 percent for lifecycle management, and 25 percent are virtual companies that have decided not to pursue internal manufacturing capabilities. Core competencies may involve a specialized manufacturing operation or prefilled syringes versus vials, or lyophilized versus dissolved product. Specialized fill/finish operations are a common outsourced competency.

One area of increased specialization, and hence outsourcing, is parenteral drugs, represented increasingly by the emerging biologic pipeline. Although most drugs today are provided as oral solid dosage forms, only about 5 percent of small molecule drugs are parenterals. Biologics comprise approximately 30 percent of drug companies' current pipelines, and 90 percent of those products will be delivered by injection or infusion.

Another emerging trend is personalized medicine—products that treat smaller, targeted patient populations. Again, biologics are represented disproportionately in this group of new drug products. These tend to be manufactured in smaller batches than traditional small molecule or biologic drugs. Sponsors, reluctant to build fermentation, cell culture, and purification upstream capacity for small-volume products, will be likely to outsource such products.

## **2 BUILD RELATIONSHIPS**

Building a relationship between senior management of a pharma/biotech organization and their counterparts at the contract-manufacturing partner can pay serious dividends.

Rapport developed early on sets the tone for the duration of the partnership, and promotes an environment of ongoing cooperation and open communication. Such benefits assist in overcoming challenges as they arise, to mutual advantage.

Senior management need not necessarily be the highest-ranking officer from both companies. Often, when a mid- to large-sized CMO works with a very large pharmaceutical company, the top manager at the contractor will deal with a senior vice president at the pharmaceutical or biotech client. What is important is that the managers be roughly equivalent in terms of responsibility and authority. Relationships built at the top facilitate rapid problem solving because ultimate authority for problem resolution exists at this level.

## **3 CONSIDER UNIQUE OUTSOURCING STRATEGIES FOR NOVEL MOLECULES, ADMINISTRATION ROUTES, AND FORMULATIONS**

Outsourcing strategies often differ for oral versus injectable molecules, or for small-molecule drugs versus proteins. Each molecular and dosage form category carries unique technical expertise and capability. For example, oral dosage forms tend to be outsourced globally, while skills for manufacturing more specialized products such as parenterals remain highly concentrated within a few U.S. and E.U. CMOs. Parenteral manufacturing uses more advanced unit operations, with significantly more rigorous requirements for sterility, unique process steps, and component experience such as syringes, vials, and stoppers.

Parenterals can often require cold-chain management, which raises the ante for this specialized competency in logistics, facility, and equipment. Developers of biologics should only consider CMOs with a proven record of mastering challenging manufacturing operations. Consider speaking to managers at companies with similar products about their experience with particular CMOs.

## **4 UNDERSTAND YOUR CMO'S OPERATIONS TEAMS**

The proficiencies of the supporting operations team are critical to outsourcing success. "Supporting team"

means the chemical, microbiology, research, analytical, packaging, process development, and general engineering/scientific capabilities that a potential CMO possesses in house. Researching a CMO's back-end capabilities should be part of your due diligence when investigating a potential manufacturing partner.

The importance of such competencies becomes evident when problems arise during manufacturing, for example the insolubility of an intermediate in a particular solvent, or a yield discrepancy during scaleup. Although these issues may be minor in the context of the larger manufacturing relationship, they can create unacceptable process bottlenecks. An adept support staff can work through "R&D" problems with minimal delay, assuring that a project is completed on time and within budget.

Recognizing the importance of support staff expertise, some CMOs are investing in their own pharmaceutical R&D departments. Such teams not only sit ready to solve day-to-day problems as they arise, but to develop process, analytical methods, formulation, and packaging improvements that can add value to their partner's molecule.

## **5 KNOW YOUR CMO'S REGULATORY TRACK RECORD AND CAPABILITIES**

A successful history of working with drug regulators in the United States and abroad, where appropriate, is a huge factor in favor of a manufacturing partner. Look for a CMO licensed to produce drug products for all applicable jurisdictions, with a clean history with respect to manufacturing-related recalls and a commitment to cooperating with regulators. The CMO should be capable of submitting its own regulatory filings, and transferring data to its pharmaceutical or biotech client for the latter's internal and FDA records, as appropriate.

Everyone recognizes the importance of FDA audits and regulatory filings, but companies researching a manufacturing partner often overlook OSHA and EPA regulatory history. Environmental and workplace safety issues can close down a manufacturing facility as surely as an FDA action, so be prepared to look into those issues as well.

## **6 CONFIRM SCALABILITY AND SUSTAINABILITY**

Pharma/biotech companies must ascertain their potential partner's ability to meet material needs for a product into the foreseeable future, especially if demand for the product increases substantially or unexpectedly. Switching CMOs entails numerous expenses related to research, due diligence, and validating the manufacturing process at the second location. When that occurs, CMO "acquisition" costs automatically double, as do attendant risks. Perhaps more important, considerable time and market opportunity are often lost unless the sponsor foresees the need to switch very early on.

Drug product developers need a clear understanding of potential CMOs' plant strategy—how the CMO is handling its growth (or decline) with respect to facility acquisition. Some CMOs have expanded too rapidly, leaving them with a dozen or more manufacturing sites operating at suboptimal capacity, thus straining their ability to maintain and operate each facility according to rigid industry standards.

Because the phase 3 manufacturing site is generally the one that produces postapproval material, focus on CMOs with the capacity and financial resources to serve your company's needs into the future. Look for manufacturing partners whose manufacturing capacity is relatively stable and unlikely to experience consolidation due to underutilization. The ideal CMO manages projects and workflow to maintain enough idle capacity to handle emergencies or unexpected demand. The flexibility to add or switch capacity to your product at the phase 3 production facility will assure that product introductions are not delayed because of capacity issues.

A top-tier manufacturing partner will resolve capacity issues before they become serious problems. For example, Amylin Pharmaceuticals and its partner, Eli Lilly and Company, experienced very high growth in demand for BYETTA, their drug for type 2 diabetes. The companies turned to an outsourcing provider, which supplied cartridges that hold BYETTA inside the injector pen delivery device to address the rapid

increase in demand and increasing manufacturing requirements.

## **7 ASSESS A CMO'S ABILITY TO DELIVER LIFE CYCLE MANAGEMENT**

The pharma/biotech industry's need to optimize each molecule's value through life cycle management has never been greater. A manufacturing partner should be up to the task. A case in point: most biotech products are distributed initially in vials, either as solutions or lyophilized solids. Those forms are often the quickest to bring to market, but not the most desirable because of convenience, active pharmaceutical ingredient use, or patient safety issues. At some point, the original developer will see the need to differentiate the product through reformulation, supplying it in a prefilled syringe, or packaging it in a kit for self-administration. CMOs that assist in managing that type of life cycle management provide the most value. Partners with deep, thorough knowledge of a biologic can leverage that experience by assisting the developer in transferring the product to a syringe or cartridge, or by offering additional value-added services such as preapproved diluent syringes or expertise in developing kits.

The secret is to "think life cycle" by building on the molecular expertise already acquired and applying that through novel formulations and delivery mechanisms. A best-in-class contract manufacturer will evolve and apply its expertise to serve not just today's immediate tactical needs, but tomorrow's strategic developments as well.

## **8 CONFIRM THE CMO'S TECHNOLOGY TRACK RECORD**

A CMO's technology savvy is as important as its financial history and record of regulatory compliance. Technology means not just the latest science, but also a CMO's plans for maintaining and upgrading plant and equipment. This is especially critical for biologics, which require specialized treatment at every level (manufacturing, formulation, fill/finish, and packaging).

Top-tier CMOs maintain an active intellectual atmosphere, continuously seeking out the latest manufacturing and analytic technology to assure the

highest possible yield at the best quality level. A good sign of this is when a CMO sends its scientists to professional and scientific meetings to keep up with the latest trends in manufacturing management and practice (for example, lean/six sigma methods). Contract manufacturers with ongoing relationships with academic and government labs demonstrate that they respect, and are willing to look outside, their in-house expertise—not as a mere scientific exercise, but to serve their clients better.

As part of your technology checklist, consider the age of a manufacturer's equipment and facilities, their recent investment in analytic and production equipment, and their willingness to retool to adapt to the ongoing demands for biologic drugs and combination products.

Seeking such forward-looking capabilities helps drug developers identify contract manufacturers who are most likely to acquire, maintain, and draw on knowledge of your molecule, and leverage those capabilities in a way that best addresses your current and future needs. No discussion of manufacturing technology would be complete without mentioning FDA's Process Analytic Technology (PAT) initiative. Through PAT, FDA is encouraging biologics and drug manufacturers to monitor product and process more regularly, closely, and intimately, with the goal of improving quality. PAT implementations are further along for oral drug manufacture than for parenterals, but parenterals are catching up. Ideally, FDA hopes that through sophisticated in-line, at-line, and off-line analysis methods, manufacturers can design quality into their processes, rather than testing for quality after the fact. A CMO with the capability for, interest in, and knowledge of PAT, as well as a plan for implementing it into future projects, will be an ideal partner.

## **9 COMPARE ORGANIZATIONAL CULTURES**

A good deal has been written about "organizational culture" within collaborative business environments. What is important here are not superficial differences—for example, in dress codes or work hours—but a mutual commit-

ment to ideals that matter most to a longstanding business relationship.

Both organizations must mutually respect the other's mission, and be committed to complete accountability, open communication, and a team-oriented approach to problem solving. Furthermore, the partners must operate transparently and with respect to their goals and missions.

Finally, because pharmaceuticals are products of some of the highest-level technology, the organizations should share a dedication to scientific and engineering rigor within a framework of innovation and compliance.

## **10** CREATE AN ENVIRONMENT THAT PROMOTES MUTUAL SUCCESS

Contract manufacturing is about producing product, which is why product yield is so important in a developer-CMO relationship. The arithmetic of yield is straightforward enough: the higher it goes, the fewer manufacturing runs will be needed to keep product on the shelves. Yield is especially critical for high-value biologics, where doses range from micrograms to a few hundred milligrams and cost hundreds or thousands of dollars.

Pharma/biotech company partners should therefore institute incentives and initiatives up front for achieving yield and productivity targets. Depending on the product, contracts should explicitly enumerate dollar incentives for improvements in yield or throughput as small as fractions of a percent. Incentives are obviously easier to implement for development-stage products, where improvements in unit operations or analytics are still possible without incurring a heavy regulatory burden. But even for approved biologics processes, which are set in stone and regulated most closely, a CMO can do much more to improve yield and reduce waste.

Similarly, incentives (and penalties) can be employed for batch release times or any other mutually approved performance metric.

### **A BENEFICIAL CHOICE**

Engaging a contract manufacturer for pharmaceutical or biologic products can be one of the most beneficial choices your company makes. Finding the right CMO is a relatively

straightforward exercise in business relationship building, provided that drug developers apply these ten basic principles, and understand the nuances of producing high-value products in a highly regulated environment. Your ultimate goal in developing a relationship with a CMO is to obtain a safe, reliable source of material from a business partner who shares not only your quality objectives and commitment to excellence, but who can apply their expertise to add value to your molecule throughout its life cycle. Although price is certainly an issue when choosing a contract-manufacturing partner, managers should focus on value, which depends as much on a CMO's track record, timeliness, and commitment to your product as on price per unit of finished product.

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