Creating a Successful Partnership with a Contract Manufacturer

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Increasingly, contract manufacturing organizations are being used to produce pharmaceutical products. The successes of virtual companies, plant closures, and heightened competition in time-to-market all have led to outsourcing being commonplace. The selection of the best contract manufacturer for a company and the development of a lasting partnership are crucial to successful outsourcing. This article examines the increasing use of contract manufacturers for scale-up and manufacture of final dosage forms, discusses criteria for selecting a contract manufacturer, and suggests recommendations for implementing a successful technology transfer program.

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In today's pharmaceutical environment, companies are facing increased competition in getting their products to market quickly. One result of the mergers of many pharmaceutical companies has been the formation of small drug development companies. Displaced pharmaceutical company employees are forming their own pharmaceutical companies that operate solely from an office setting. They outsource most activities, from preclinical drug development to the manufacture of supplies for clinical research programs. They also outsource their commercial manufacturing.

The increasing number and success of these virtual companies is forcing conventional pharmaceutical companies to use their resources (specifically time, personnel, and money) more efficiently. They are learning to focus their in-house resources toward a smaller number of projects and outsource others. Typically, projects are outsourced because

- they are of high priority with tight deadlines/timelines
- they are of low priority or are special one-time productions
- resources are not available in-house.

Traditional research and development (R&D) activities also are being outsourced, resulting in a multiple-partner relationship comprising the contract research organization (CRO), the pharmaceutical company, and the contract manufacturer (CM). Pharmaceutical companies select CROs instead of using their in-house research staff because of the CROs' apparent efficiency. This efficiency is born from a narrowing of their scope of supply. However, the narrower the scope of supply, the more times the pharmaceutical company has to be involved in managing a technology transfer.

At the other end of the spectrum lies the contract manufacturing firm. The perceived efficiencies of the CRO and the post-merger closure of manufacturing plants as part of consolidation also have led to an increase in the outsourcing of manufacturing. Traditionally, CMs were either pharmaceutical companies with excess capacity or companies specializing in a distinct processing expertise. This also is changing because the process-specific companies have begun to diversify to meet the CROs at a point within the development timetable. More often than not, this point is either shortly before or just after the manufacture of clinical supplies and ultimately involves scale-up (1).

One major pharmaceutical company has stated publicly that it will close down any of its manufacturing plants that are pro-

ducing at less than a certain percentage of their capacity. This is a sensible decision providing that the products produced in the facility can be outsourced for a lower total cost. Timing issues also must be considered — it is a considerable undertaking to transfer the technology to a CM. It is important to take the time to select the right outsourcing partner, ensuring that it is fluent with the technology and procedures needed to manufacture your products successfully for a long period of time.

Today, the trend is moving away from vertical integration and toward virtual integration, whereby each firm specializes in a few core competencies. Companies no longer need to have the total complement of competencies. The influence, power, and profitability of any firm within a virtual corporate network depend upon the uniqueness and relative importance of that firm's core competencies. However, some core competencies that uniquely define the company in the minds of customers and provide access to new markets must be kept in-house. Decisions on what to own and what to outsource must be aided by a proper understanding of what is and what isn't a core competence. Nevertheless, in no case should the idea of core competence provide a license for vertical integration into noncore activities (2).

Companies providing contract manufacturing must be competent and efficient by nature. Their very existence is based upon their ability to combine the manufacture of several products from different sources into an efficient use of their equipment's capacity. When the core competence is not unique and is available elsewhere, so that it may not warrant investment in space, processing equipment, or personnel for a product that would underutilize the available capacity, the use of a CM offers a competitive alternative (3).

Current trends also have dictated that if a product or process does not use at least 50% of the capacity of a piece of processing equipment, it is a candidate for outsourcing unless the manufacturing process is unique, and hence, a new core competence. This principle recently has been expanded to outsource products with gross sales of less than $100 million.

Most outsourcing arrangements specify an initial manufacturing term followed by annual or biannual renewals. This allows both parties ample time for strategic planning. If manufacturing is to be moved to the pharmaceutical company after the initial contract term, time is needed to meet any FDA requirements that may be prerequisite to the site change.

Selecting an outsourcing partner

Selecting the right outsourcing partner is the first critical step to achieving success. Regulatory and quality concerns always are important, but they become critical when manufacturing is relocated. The following are some points to consider when selecting a CM (4):

Selection committee. Define an internal team to properly handle the selection process. Quality auditors, engineers, scientists, purchasing agents, and business people may be among the resources necessary to make a proper selection.

Scope of services. Define what specific equipment and services are required to process a product. Are you able to supply the necessary equipment (for example, during a plant closure)? Are batch and equipment sizes fixed, or can they be modified to optimize throughput at your CM?

Mission statement. Define the stated mission of the CM. Is outsourcing a primary or secondary consideration? Does the CM have its own business that is more important than yours?

Proprietary technology. A major consideration is accessibility to a patented process or drug delivery system. Innovation and the ability to deliver that innovation to the market as quickly as possible will deliver a sustainable competitive advantage.

Ready capacity. How soon will the CM have an opening in its schedule? If it takes too long, cost and time advantages may no longer be applicable.

High use. Provided that this does not cause scheduling difficulties, a facility that is highly used allows wider spreading of overhead costs, which should result in cost advantages. Underutilized CMs may be available immediately, but they also may be less experienced and have higher costs.

Structure of the organization. Decide who will be the primary contact for your company. A project manager with people skills and a science background who has the ability to solve problems and sufficient time to do the job thoroughly is essential for success.

Depth of experience. High use and specialized focus should translate into a more experienced staff. Frequent training and employee turnover are key points to review.

Table I: Points to consider for each of the four Cs.

Credibility	Capability	Capacity	Cost
History and track record	Facilities	Equipment	Project
Operations	Equipment	Facility	Personnel
Personnel	Deliverables	Personnel	Benchmarking

Financial stability. It is important, before any money is spent, to ensure that the CM is a stable company with an established reputation.

Expandability. Determine whether the CM has the capacity to grow with your business.

Before selecting the outsourcing option, a company must evaluate how it wants to handle the relationship it has with a CM. This is particularly true when a technology transfer is involved. A pharmaceutical company that is prepared for outsourcing should have investigated thoroughly its own internal experiences. It will have determined what level of staffing is required. It also should decide how much autonomy it wishes to give to a contractor before enlisting one. It should determine its work system requirements and be willing to review them in detail with the CM. Finally, it must determine how accurate its timelines are. If the pharmaceutical company is using a CM to improve the time to market, it must not go into the relationship with unrealistic expectations at the outset.

CM selection may be based on a company that scores highly in the four Cs: credibility, capability, capacity, and cost. Using Table I and a point system (0 = poor, 1 = fair, 3 = good, 5 = excellent), a score can be calculated for three criteria under each of the four Cs. Contract manufacturing candidates that score

below 40 (for a particular process) should be avoided (for that process). Additional factors to consider are

- service excellence
- technical expertise
- product quality
- competitive pricing
- flexibility
- proactive partnership
- regulatory approvals
- confidentiality.

Factors for successful partnership

Communication. Good communication from the onset is crucial to implementing a successful transfer strategy. It is one of the most important elements of success, but it is often difficult to do well. However, efficient and successful scale-up and technology transfer can be achieved only by close cooperation between the development and manufacturing groups.

To ensure a future successful product launch, it is imperative that a complete transfer of the necessary technology is accomplished. The research and manufacturing groups must work closely together to complete a technology transfer program that trains and demonstrates proficiency in the skills necessary to efficiently manufacture and test product that meets all the appropriate specifications on a consistent basis (5). (The experience and documentation that come from this process provide invaluable tools for the continued support of the product throughout its normal life cycle.) For this to occur, it necessitates the input of both the research and the manufacturing groups early on in the product development cycle.

Before the initiation of the transfer, as many details as possible must be reviewed and addressed by all sides. This is particularly true when more than two parties are involved. Miscommunication, poor communication, and lack of communication are the most common sources of conflict during a technology transfer. Nothing can be left to interpretation or assumption without risking that the technology transfer will not proceed seamlessly.

Communication must be timely. The best mechanism for routine communication should be identified. Whether this is regularly scheduled calls, faxes, e-mails, or meetings, a backup plan also should be put in place. All oral communications should be expeditiously documented. The absence of clear and complete documentation of oral discussions can lead to misunderstanding and finger-pointing (6). Expectations should be clarified with respect to timeliness, compliance, protocols, and reports.

Additionally, technical contacts, besides the project manager, should be identified across all critical departments (such as R&D, manufacturing, quality, analytical). Having a designated technical contact identified by both parties is essential for solving technical problems within the project deadline.

Quality. Quality should be obvious in all work areas, and work must be conducted in compliance with FDA regulations. However, it should be understood that the standard operating procedures (SOPs) the CM follows might not match exactly those that are followed in-house. This is perfectly acceptable, providing the CM is willing to assume the same responsibilities for success and failure as your in-house units. Outside of process-specific requirements, it should not be expected that the CM should follow different SOPs for each of its clients.

Quality initially should be audited and continuously evaluated during ongoing site visits. Quality goes beyond technical expertise; it extends into the corporate culture. Whenever possible, in-process testing should be defined and performed to cease an out-of-control process before large amounts of material are wasted.

Timeliness. Timeliness is critical for the success of any project. To succeed in a technology transfer, expectations should be communicated, not assumed. Critical milestones should be clearly defined. It must be borne in mind that one of the fundamental reasons for choosing to outsource is to improve the time to market. Therefore, the sooner the CM knows the timetable, the easier it should be for it to meet deadlines.

Relationship. Successful outsourcing comes only from true partnership. This requires time and effort by both parties. Plant visits and meetings provide a forum for all parties to get to know one another. True partnerships occur only when both companies' goals are clearly defined and achieved. If the goals of one company do not meet the goals of the other, the partnership is doomed to fail. A good understanding of the other company's position will lend itself to a good partnership (7).

Processing conditions. Generally, all of the development work is completed before bringing the larger-scale CM into the project. In these situations, scale-up will be successful only with a thorough technology transfer program developed jointly between the pharmaceutical company and the CM. The expertise of both parties must be respected — decisions should not be dictated by the pharmaceutical company. The latter can lead to undersized or oversized batches, scaling up before enough information is generated, documentation unfamiliar to the CM, and inadequately defined processes, for example.

All critical steps and equipment should be clearly documented during development. Changes in equipment can lead to disaster. For example, a piston pump substituted for a gear pump in a spray-coating operation may deliver the same rate per minute but not deliver the same average droplet size. Piston pumps can cause surging during spray and yield inconsistent spray patterns. If you are not sure what is or isn't a critical step, ask the developer of the process. Also, it pays to observe the process at all sites yourself. It eliminates a lot of guesswork during technology transfer.

Batch sizes should be well within the capacity of the equipment to be used. For example, it may be necessary to purchase an appropriate-size blender for your batch size rather than try to blend using one that is either over- or undercapacity. If the batch size has not been filed, perhaps it could be adjusted for optimum use of the equipment.

Operating parameters should define what can and cannot be changed. It is not wise to define a process within rigid limits so that slight raw materials variations cannot be compensated for. For example, granulation solution amounts, blending times, and tablet press rotational speed generally should not vary. However, in this same example, the spray rate and precompression forces may need some latitude within a defined operational range to help produce a better product.

Subtle processing techniques also can play a role. For example, in a high-shear granulation process the following should be ascertained:

- How was the end point measured (by power consumption, capacitance, torque, or visual determination)?
- After the end point, was the process stopped and manually discharged or allowed to granulate more during a rotational automatic discharge?
- If the product was transferred into a fluid-bed dryer, was it placed directly in the product container or vacuumed into a fluidizing air stream?
- Was the air preconditioned to the correct temperature, or did it start out lower?

These questions may or may not be answered in the documentation. Communication lines between the CRO and the pharmaceutical company must remain open during the technology transfer to the CM. Again, having a representative of your company attend trials at the different scales may help answer some of these questions.

Analytical and stability work. Analytical methods development and analytical methods transfer present their own series of potential problems during technology transfer. The problems most frequently encountered involve subtle differences in the equipment and techniques used by the research group and the CM. Because data obtained by the manufacturer after a technology transfer cannot be ignored or regenerated without sufficient reason, even if they do not match the data developed by the research group, it is imperative that representatives from both groups spend time discussing the methods before attempting the transfer.

The topics of this discussion should include equipment setup, calibration schedules, weighing and injection techniques, and sample preparation methods. In addition, it is highly recommended that analysts from the research group spend time at the manufacturer's site during the methods transfer, particularly if they were responsible for originally developing the analytical method. In fact, it is not uncommon for analytical methods to be transferred several times as the project moves from the preclinical to postapproval phases. At each transfer, the question arises as to the equivalence of data generated by the laboratory receiving the method transfer. During the final transfer to the manufacturing site, assurance of this equivalence becomes critical to the product from economic, compliance, and regulatory points of view (8).

The stability program should be designed with input from the research and manufacturing groups. Stability should be maintained at the research site for preclinical samples but at the manufacturing site for clinical samples and thereafter. Unless the stability program is poorly defined, it generally does not cause any problems that undermine success in technology transfer.

Conclusion

Mergers continue to consolidate the pharmaceutical industry into fewer companies. This consolidation largely is a result of the cost-conscious atmosphere in which the pharmaceutical industry must operate. Most pharmaceutical manufacturers now use contractors in the production and release of their products. This relationship between the CM and the pharmaceutical manufacturer is best when it approaches a true partnership. Because an original pharmaceutical product can cost as much as $350 million to research and develop and take 10–12 years to bring to market, companies must find ways to streamline the process and bring products to market more quickly and efficiently (9). As a result, pharmaceutical companies are creating closer partnerships between research and manufacturing operations. To be successful, effective and efficient technology transfer between functions is essential to support overall business objectives.

In the past, technology transfers were considered to be successful if ruggedness criteria were met — that is, the results obtained from the two locations were in close agreement. Today it is important that the technology to be transferred is robust (slight changes in operating parameters still yield comparable results) and rugged. The problem of subtle differences in processing equipment between the research and the manufacturing groups is the most overlooked cause of unexpected delays and failures during technology transfer.

Most processes will define the major pieces of equipment with the formulation considerations, but what may be neglected is defining the pumping systems, spraying systems, mixer or homogenizer types, and for a fluid bed application, the filter type and porosity. Minor changes in any of these can result in a technology transfer manufacturing series that does not achieve the expected results.

Therefore, when using a CM for scale-up and technology transfer, it is important to select partners that are proficient in, and focused on, the service that they are expected to perform. And for the maximum efficiency in a technology transfer, all parties should have a vested, long-term interest in the success of the scale-up process.

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