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Considerations for Choosing a CMO

Build criteria for the best outsourcing experience

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THE DEVELOPMENT OF A NEW DRUG is a complex venture that requires many evaluations and decisions prior to a commercial launch. Biotech and smaller pharmaceutical companies are increasingly choosing to outsource most, if not all of their drug manufacturing efforts throughout the development phase, including the clinical trials that lead up to commercial acceptance. Due to the low success rate of drug commercialization and the high cost of facility build out, validation, staffing and support needed to manufacture one product, the investment community does not support the building of manufacturing facilities to produce and fill a specialty drug until commercial acceptance is imminent. Many times, the investors of the drug, during the development phase, will not be the entity commercializing the product.

Large pharmaceutical companies are also beginning to outsource clinical (developmental) phase products in order to cut down overhead. For example, Pfizer announced in March 2007 that it had already increased outsourcing of its drug manufacturing to 17% of its requirements from less than 10% three years earlier. They see outsourcing as a way to improve asset management as well as gain access to emerging markets.¹

We will focus on elements to consider when choosing to outsource drug production. Considerations can vary from active pharmaceutical manufacturing, formulation development,

methods development, formulation and filling of the drug product, analytical development and testing, stability, packaging and distribution for clinical sites and storage of the finished product. Elements of the outsourcing process that should be considered when selecting a CMO are quality, timeliness, flexibility, technical expertise, facility/company size, confidentiality, facility compatibility, capacity, customer service and price. Since there are multiple CMO relationships that can be evaluated, this article will focus on choosing a formulation/filling CMO; the considerations presented can apply to other relationships, as well.

Assessing Product Needs

The first step in selecting a CMO is for a drug developer to conduct an assessment of its product(s) needs. There is considerable effort in the development of the active pharmaceutical ingredient (API). The safety, efficacy, dosing and other numerous tests and decisions that must go into this process

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are overwhelming. The evaluation of the formulation/filling CMO should be rigorous. How the product is “made” is presented to the FDA and if the documentation is not sufficient, approval can be delayed and even require more studies to be conducted prior to drug acceptance (or even clinical trial entry).

Evaluating the formulation/filling company to assist in your drug development process will consist of several items. Chart 1 (right) reviews the pertinent questions to be answered during the evaluation process to determine if the CMO has the necessary attributes.

The stage of development that a drug is in becomes an important factor in the decision-making process. For example, if the company is a small start-up then it might not have the ability to hire a CMO that requires a six-month lead time and has a very rigid structure to its production schedule. If the product is in a Phase I or II trial it may require and allow more flexibility than a product in Phase III or commercial where all aspects of development have already been determined. The filling equipment of a CMO can be a big issue if not evaluated correctly. For example, if a company has only a liter of product to fill and chooses a CMO that has only a commercial line that involves two liters of product (in hold up and line loss), then this is a poor match.

Assessing Company Needs

Companies need to consider their risk tolerance level; doing activities in parallel can create financial losses if there are manufacturing delays. How these delays impact your product and the CMO’s ability to accommodate changes in receiving the materials — such as the API — can make a big difference in early stage drug development. The cost to manufacture a product with a CMO is a critical consideration when it comes to selecting a CMO. However, this cost is significantly less than the cost of the clinical studies and the financial loss incurred in not achieving product goals.

Confidentiality

Confidentiality is rated a high priority amongst biotech and pharmaceutical companies when choosing a CMO. You need to evaluate how the potential CMO ensures confidentiality. The CMO should have a system in place that avoids the use of client names/initials, locks information in a secure area and sends the client separate passwords for electronic access to documents, under a separate cover. The issue of confidentiality can be critical when it comes to formulation development, because the formulation may provide a barrier to development. This issue is important for both the drug developer and the CMO. A drug developer would like to have a formulation/filling CMO with experience in handling drugs similar to the one they want manufactured; however, the CMO must also be diligent in maintaining confidentiality with any special/proprietary process. A Confidentiality Agreement is a must and it should, without question, be two-way. A CMO that signs only a one-way agreement is letting you know that it does not value its expertise.

Chart 1: Questions to answer

| CMO Attributes | Questions to Consider |
|-------------------------------|---|
| Technical Competence | Has the CMO had experience with your molecule’s class? |
| Compliance History | Has the CMO been audited by several companies and regulatory agencies? |
| Scheduling/Flexibility | Is there availability to formulate and fill when needed? |
| Personality | Does the CMO appear to be a group you can work with? |
| Representation | Do you find that the project management group is interested in your needs? |
| Engineering Expertise | Does the engineering department understand the validation and formulation requirements of your project? |
| Quality Department | Does the quality department appear actively involved or is there a rigid system in place that may not accommodate the product’s specific needs? |
| Confidentiality | How does the CMO protect your confidentiality? |
| Staffing | Is there sufficient staffing to allow for late-stage changes in your production plan? |
| Flexibility | Are systems in place that make it possible to change or modify a product once the production has begun? Is the CMO team willing to “think outside the box” to address and correct process issues that are identified? |
| Facility | Is the size of the facility able to accommodate the phase of your drug candidate and is there potential to scale-up as your product advances in trials? |
| Equipment | Does the CMO have the equipment necessary to perform the activity? |
| Validation | Do validations exist at the CMO to cover your needs or do you need to perform these? |
| Cost | Does the CMO fit into your budget? |

Experience and Expertise

When evaluating formulation/filling CMOs, it is important to consider the following:

1. CMO compliance with the latest U.S. and European regulations
2. Equipment and facility status
3. Problem mitigation – knowledge and experience
4. Systems to transfer production, if required
5. Training, experience and personnel

When choosing a CMO the formulation complexities of the solution, filling, type of container (syringe, vial or other), final product processing (labeling, kitting, etc.), and volume required will dictate the size, experience and level of technical manufacturing expertise necessary. Consider the requirements of the product in regards to process scale-up, validation and/or stability testing, transfer issues, compound formulation, safety concerns and any regulatory implications. The regulatory and technical environment in CMO services is constantly changing. For example, many CMOs are utilizing disposable technology to reduce cleaning requirements and the potential for cross contamination, as they provide naive surfaces for every lot of production. Determine if the CMO is knowledgeable about and keeping up with the latest industry trends.

Facility Size

Matching your product to the facility size is important. Facility infrastructure typically increases along with facility size. Many think “bigger is better” but this is not always true in drug development and processing. In early phase trials the quantity of the drug product available is often very small. Matching the equipment and the handling experience with the product is essential in order to ensure a successful outcome. The phase you are in with a drug will dictate the capacity requirements of the formulation and fill. For larger, later stage production activities the output of the facility is critical to ensure success. It is important to evaluate the product’s requirements and determine the best fit.

The ideal CMO is one that can grow with a product’s success, but this is difficult — if not impossible — to find. CMOs that manufacture high volume commercial products typically lack the equipment and personnel to manage a developing product that requires low hold up volume, flexibility in scheduling and development in manufacturing. Companies that specialize in small volume early stage products will have sufficient staff to assist with the transitions that occur throughout the development cycle.

According to Frederik Defesche, President of CustoPharm, Inc. of Carlsbad, CA, “The difference in a fill/finish CMO is related to batch size capacity. Typically the CMO has a different mindset, which affects their suitability as a fill partner. Some partners will be accustomed to wearing many hats and be willing to accommodate changes, while others will be more rigid, with more well-defined roles and responsibilities. A smaller support staff generally has greater flexibility with regard to changes and timing. The lead time for changes at a smaller fill house should be less than for a CMO that is used to filling lots greater than 100,000 units per day. Larger CMOs have much larger capacity. They are more rigid and generally have defined

systems in place that are not easily changed. Scheduling is done well in advance (the lead time for scheduling or bringing a product in can be six months to a year) so the lead time for changes can be a factor.” Evaluating the structure that you require for your stage of production is an important aspect in choosing the CMO that will meet your current and potential future requirements.

Client Satisfaction/Project Management

A CMO committed to client satisfaction and quality provides an environment in which both parties can grow and develop. There needs to be a strong sense of partnership and a high level of commitment from the CMOs you are evaluating. Once the project begins the Project Manager is your in-house advocate. They are the liaison between you and other departments. Communication — early, often, and honest — is the only way to deal with these complex programs. The CMO should provide a contact person from project management who should be ready and able to answer all questions quickly and accurately. The client and CMO must realize that they are partners in the production, learn to trust each other and work with each other to overcome any and all hurdles.²

Many times the drug sponsor views the CMO as the expert with its product. A CMO may have expertise in a product class but each sponsor’s product is unique and should be treated as such. The sponsor needs to be the expert on its own. Every detail of the formulation and filling process known by the sponsor should be communicated clearly and in writing to the CMO. Having the CMO re-develop the path may lead to errors and many times result in additional work, incurring extra costs, and increasing the time to completion. It is best not to assume anything; when issues arise, keep an open line of communication to promote a successful completion of the project.

Compliance/Quality

“Good quality systems produce quality products. For that to happen you need to know that the staff is well-trained and the proper people are reviewing the documents. With a good quality system I can assure my boss and the board of directors that our product will be a quality product. We offer patients hope and promise of a higher quality of living a longer life, and a higher quality of life. We can only deliver on those promises if the product delivers what we said it would,” stated Don Holloran, Manager, Quality and Compliance of Novelos Therapeutics, Inc. of Newton, MA, during a recent interview.

Most companies need a CMO that can operate under a variety of regulations. The CMO should have an understanding of the regulatory environment in which a product will be evaluated. If a product is being developed or manufactured by a CMO that is not aware of the regulations needed for the agency (FDA, EMEA) filing then there is a risk that they will not prepare adequate documentation for submission. This could lead to delays in approval and/or the request for additional studies.

In the early stages of drug or device development, parameters will be adjusted to meet efficacy targets better and/or overcome processing hurdles. The CMO making these adjustments should have a formal change control system that allows the client to present this documentation to the FDA (or other agency) during later stage filings. Gauging a CMO’s ability to make changes in an efficient and compliant manner is essential to the selection process.

Getting the List

Finding a CMO is simple — Google them. Ask some industry colleagues who they have used and you have an ideal way to create your “short list” of CMOs to consider. Word-of-mouth is one of the most credible forms of advertising because people put their reputations on the line every time they make recommendations, but have nothing to gain except the appreciation of those who are listening.³ Learning from the experience of others can save time, money and bring your product to market on schedule. Contact the CMO and be prepared to fill out a survey or send an RFP that relays all relevant information about the product.

The Site Visit

A drug sponsor should *always* visit the CMO’s site during the evaluation process. This visit gives the drug developer a good overview of how the CMO works. Touring the facility shows if it is a clean and functioning facility. This is the time to explore many of the considerations listed above. Evaluate, among other things, whether the staff grasps the scope of your project, quickly, and determine whether the engineers and chemists have familiarity with the product class. Drawing on a CMO’s experience can save time and potentially deliver a better outcome. For instance, drug or device sponsors believe that filling their product in a vial is the best administration method for a clinical setting. However, this practice can lead to errors in dosing and loss of extremely scarce product, consequently determining the path forward in container stability. Being open to advice from a CMO on which container to fill your product in might save you time, cost and perhaps improve the clinical outcome. There are always some engineering challenges.⁴ It is important to develop confidence in the competency level of the CMO. Devoting a minimum of four hours to the site visit will provide the opportunity to visit with most relevant departments such as Project Management, Engineering, Quality, Sales and Corporate. If you leave a site visit with confidence then the next step would be to conduct an in-depth audit.

The Audit

Auditing potential CMOs will provide answers to many of the questions posed in this article. Evaluating three CMOs is recommended and spending two days at the site is ideal. Being prepared for the audit will guarantee a better result. The more a drug developer knows about its product and the GMP regulations the more prepared it is to make a wise choice.

During the audit you will review documentation systems and discuss the project in more depth. All information and discussions should be viewed from a quality standpoint. First, learn about the company’s history, size, services, financial stability, future plans for growth and technological innovations. Then determine the training of personnel and the expertise level of the staff. Find out about the Quality Assurance and Quality Control systems, manuals, reviews and methodology; also determine certifications, document management, procedures and problem solution systems, and equipment maintenance and calibrations.

Also, look at measurements/metrics for monitoring and controls, deviations (the number and significance of them), technical transfer controls, capabilities, test methods and validations, material controls and inspections, supplier and material qualifications, purchasing controls, and laboratory controls. Determine the GMP compliance history, and SOP

(Standard Operating Procedures) records. From this review a drug developer will be able to determine if a CMO has the technological knowledge, compliance record, and experience to provide solutions to problems and be able to complete documentation in a timely fashion.

The Contract

In a recent conversation with a drug developer, we heard the following (paraphrased) statement, which summarized succinctly how many pharmaceutical and biotech companies think about selecting a CMO:

“In choosing a CMO we looked at various factors that were relevant to the phase we are now in with developing our therapeutic. One of the most important factors was the regulatory aspect. We needed a CMO that had the specific capabilities, experience and production environment to meet our product’s specific requirements. We needed a CMO that had the staff on hand to support our product from an analytical perspective. The inherent nature of our drug made it difficult to work with. It was important to have a CMO that uses its equipment on a regular basis and that if a piece of equipment needed maintenance then in-house personnel could repair it vs. waiting a week to have an outside vendor repair it. We also needed a CMO that had the analytical and lab support on-site. Finally, price was an important factor. The first three considerations were the most important and once the CMO was able to meet those then we looked at price. It is important to factor in the cost of the tech transfer, which varies from CMO to CMO. Initially, we looked at 20 different CMOs and then were able to pare this group down to a short list of realistic contenders. The CMO we finally selected and contracted with worked with us on all aspects of the manufacturing project.”

Making the final decision on which CMO to select to manufacture a drug has two main aspects. First, evaluate a CMO for compliance, facility, experience, and capabilities. If these attributes of a CMO are positive then the second aspect to consider is the “personality” factor. Relationships vary between sponsors and CMOs. If you have a complicated product you will need to rely on the experience and expertise of the CMO to overcome the challenges and being able to work together in this process is crucial. Consideration of all the elements presented above will lead to choosing the best CMO amongst all that are being evaluated. ■

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