

10 Steps for Choosing a Contract Manufacturer

by Leah Choi and Scott Rudge

For many young companies, choosing a contract manufacturing organization (CMO) for their lead pharmaceutical candidate is critical. Choose the wrong contractor, and you could be faced with delays and cost overruns — and little sympathy from investors or patients. With so much on the line, how should you make this important decision? It doesn't need to be based on instinct alone or on overanalysis. With the right set of tools, selecting a CMO doesn't require endless investigation, and the process can be well documented. Although there is no guarantee that companies will always make the right decisions, some tools can help you make a thoughtful, meaningful, and objective choice through an organized procedure.

Much has been written about the selection of contract manufacturers, including case studies (1), assorted tips (2), management issues during the selection process (3), regulatory implications of outsourcing (4), FDA guidance (5), and survey results (6) highlighting the importance of outsourcing as a strategy for producing biopharmaceuticals. The three definitive phases of outsourcing a drug development and commercialization function are the decision to outsource (“make or buy”), selection of an outsourcing partner, and subsequent oversight of that partner.

Here we describe a systematic approach to selecting an appropriate

contract manufacturer for a given project. Because all projects are different, it is important to follow these steps each time an outsourcing decision is made. We have found this approach to be very helpful for project management.

Start-up companies in particular can benefit from a systematic approach such as this. It is a rare project that proceeds without a hiccup, and periodically revisiting a documented selection process is very useful for preventing “outcome bias” (3). This can be very important, for example, in tense management meetings when problems are encountered. Choosing a manufacturing partner is frequently the largest early partnership into which a start-up biotech company enters. Potential investors want to know how you select your partners. Having a documented, rational methodology to present during due diligence reflects very positively upon you.

STEP ONE: MAKE A LIST

List all possible suppliers of the service you need. Such lists may be purchased (from companies such as HighTech Business Decisions, Inc., www.hightechdecisions.com/index.html), but they are also easily assembled through Internet searches, publications, and personal recommendations. Create a list of CMOs that fit your business. For instance, if you're working on a biomolecule, you should begin with biologics manufacturers. If you're



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working on a small molecule, you should be looking at specialty chemical manufacturers.

Prescreen potential CMOs by conducting your own survey. Before calling anybody, screen the list by considering your key capabilities and requirements: Does the CMO have the necessary facilities and available time to manufacture your product? Does it have experience manufacturing a similar product? What kind of reputation (if any) does the CMO have with regulatory agencies?

STEP TWO: GET ON THE PHONE

Screen potential suppliers on the telephone. Don't reveal too many details about your project; do be prepared mostly to listen. Look for three or four key capabilities or

proficiencies in all potential vendors. If possible, try to rule out those that do not meet your business-enabling requirements at this stage.

A “show-stopper” list of those requirements is critical and may extend beyond those key capabilities and proficiencies. Most valuable attributes may include total cost, timeline, location, royalty and licensing fees, intellectual property stipulations, and the potential to be a one-stop-shop. Other factors to consider may be payment schedule, reputation, and methods. Be careful with the relative value you place on your timeline. Most projects run on an “as soon as possible” mission, but your desired timeline may not be reasonable. Some contractors will agree to a timeline, then look for reasons to blame their clients when they fall behind.

Make sure your timeline is reasonable and that your project execution includes a budget for contingencies. When a CMO proposes a timeline, it needs to be thoroughly vetted by your operations staff. If long lead items aren’t accounted for, or if critical data required to take a next step will not be available on time, then a timeline can be at considerable risk. Time is money, and success is defined by a releasable batch. So make sure that your timeline is detailed, that the critical path is constantly identified, and that you allow for margins of error and delay.

STEP THREE: AN INFO MATRIX

Keep a matrix recording the date you first contact each vendor, when that company responds to your initial contact, and the status of all

confidentiality agreements — as well as all the contact information you can gather (email addresses, cell phone numbers, main switchboards, and extension numbers). Also note the initial responses from each contact relative to your three or four show-stopper criteria.

Such an information matrix saves a tremendous amount of time by organizing details of initial conversations into a format that will easily separate CMOs worth pursuing from those that aren’t worth pursuing for the project. Table 1 is an example of such a matrix, in which each vendor has some question marks that the project team would need to discuss.

STEP FOUR: NARROW THE FIELD

Meet with your team, and select three to five potential vendors from which your company can request a proposal. We don’t recommend more than five because getting good, comparable proposals takes a lot of work. Some of that work involves ensuring that all proposers understand your provided information, make similar assumptions where there is none, and reply to you promptly with enough information to make quantitative comparisons. Try not to have too many organizations competing for your business at this point. Your project team should be able to pick the top few front runners from the initial screening process.

CMOs also spend time and money to read your request for proposal (RFP) and prepare their response. The business development contact will get input from his or

her operations, manufacturing, process development, quality control, quality assurance, purchasing, and finance groups (at least) to respond to your RFP. Some of those people may want to visit you (and/or you to visit them) and conduct one or more conference calls to clarify information. A good contract manufacturer will spend well over a hundred labor hours and several thousand dollars just responding to your RFP — and of course, yours isn’t the only one. This is a cost of doing business for contractors, but it doesn’t represent an unlimited resource.

Your three or four show-stopper criteria should help you limit the number of proposals, but if necessary, you can also narrow down your list based on “nice-to-have” criteria. You may also choose to look at a range of vendors that represent different strengths and weaknesses. For example, do you prefer a “one-stop shop” that is convenient (but maybe not the best at everything) or a “specialty” vendor that provides higher levels of expertise (but ultimately will require you to select and manage multiple vendors)?

If you can’t narrow down the field to fewer than six, you may want to add screening criteria or skip ahead to step six (see below) and perform a preliminary scoring to identify CMOs that are most likely to be the best match. You then may decide to solicit proposals from a subset of those passing the screen. As more information comes to light, you can then drop those organizations identified as poor fits and replace them with others from your passing list. Your decision timeline will be

Table 1: Example CMO matrix for tracking initial contacts and initial screening responses

CMO	Contact Name, Phone, Email	First Contact	CDA Sent, Signed	RFP Sent, Proposal Received	Can Commit to Timeline?	Experience with Our Cells?	Fill-Finish Affiliate?
#1: Location 1	Joe Casebolt, 555-5555, jcase@gmpcmo.com	1/1/10	1/3/10, 1/10/10	1/14/10, 2/17/10	Yes	Yes	No
#2: Location 2	Avery Jackson, 666-6666, aj@apisynth.com	1/2/10	1/3/10, 1/5/10	1/14/10, 2/17/10	Has questions	Yes	Yes
#3: Location 3	Charlie Parker, 777-7777, cparker@birdpharma.com	1/1/10	1/3/10, 1/17/10	1/21/10, 3/5/10	Yes (?)	Yes	Yes

ELEMENTS OF A REQUEST FOR PROPOSAL

Background and Objective

Provide a high-level description of the molecule and its manufacturing process. Include information on your cell substrate, process steps, and all requirements that require capital investment (e.g., nonambient temperatures or personnel isolation).

Scope of Services for Proposal and Quotation

Scope of Work: This is the most important part of an RFP. Be very clear about the services to be quoted. If possible, project scale, number of batches, process development and technical transfer batches, engineering batches (if required), quality assurance and regulatory support, project management, and the expected number of meetings and visits expected. This is all very helpful not only to the CMO, but also for you to compare quotes once received.

Working Assumptions: Here you should list everything you expect (but not necessarily demonstrated) about your process and product. For example, if the process has not been run at a particular scale, your working assumption might be that it will scale linearly to the project scale and perform perfectly the first time — or the third time, depending on your appetite for risk. You may also want to make assumptions on the performance of release assays, process yields, availability of materials, product stability, regulatory filings and outcomes, and a number of future events that cannot be known at the time of the proposal.

Transfer Materials and Equipment: List materials available for transfer to the CMO. For the manufacture of a biologic these materials typically might include master, working, and research cell banks; plasmids containing DNA coding for the protein of interest; reference standard(s); detection antibodies; bioassay materials; historical in-process samples and others for use in method transfer; columns; specialized or dedicated equipment; and resins, membranes, or other durable consumables. You are not likely to transfer every item listed here. Possession of a working cell bank, for example, indicates that a project has moved beyond the need to transfer a research cell bank or coding DNA. Transfer and sharing of equipment is also relatively rare.

You should have a number of reports available for review by the CMO. You need not list these in the RFP; this information is a basic expectation. However, without good documentation at

your disposal (or if you cannot share it with a CMO because it was developed by another CMO and you failed to secure the full rights), you should probably disclose this.

Standard Methods

You may or may not want your CMO to be a release laboratory. It is likely that the contractor will perform in-process testing — and also likely that it will perform some basic release testing (e.g., bioburden and endotoxin testing) because they relate to the cleanliness of processing. You don't need to include test methods in your RFP, but you do need to list whatever methods you have, indicate their state of validation, and indicate the testing you will require to demonstrate method transfer.

Deliverables

The ultimate manufacturing deliverable is obvious: one or more released batches. But this should be spelled out, anyway. If you are expecting reports, campaign summaries, and/or certificates of analysis, then those items also should be listed. Details of expected release documents can be left for a quality agreement, which will be negotiated with the CMO you select (2, 4, 5). Some CMOs expect to ship drug substance within a defined time frame; if you need storage beyond 90 days, you should specify that in your RFP.

Submission of Proposals

Instructions for submission of proposals are helpful. Most proposals come by email, but if you require a hard copy or original signature, you should make this clear. If you are not getting an electronic proposal, you may want to insist on a number of copies. You may also want to specify a format for proposals. You may want a summary of proposed costs right from the start, then a timeline second and supporting material third. You may or may not want company background included. Ask for references along with the proposals. The contact for these references should be tracked on the matrix mentioned in step three.

Attachments

If you have referred to detailed process flow diagrams, bills of materials, materials required for analytical methods, or any other reference information, it belongs here as well.

longer, and you may end up leaving a good fit behind if your preliminary scoring was inaccurate. If you decide to select a contractor before receiving proposals from all candidates, that one should be a good enough fit to make further screening unnecessary.

If, on the other hand, you have trouble finding even one potential outsourcing partner, then you should assess the reasons for that. Which of your “show stoppers” disqualified the most potential proposers? Your internal project team may have to discuss relaxing that criterion. Such teams seldom want to loosen

requirements, so you need to be well informed as to why the criterion can't be met. What would be a more reasonable criterion, and if you relax this one, how many proposals are you then likely to get? If you find only one feasible contractor, you should go back through the same exercise. If your major disqualifying criterion is timeline, and the one proposer is suitable, then this may not be such a big issue because you can get back-up suppliers on another timeline. But if the disqualifying criterion is technological, then you may assess whether resources should be spent developing a back-up

strategy either by developing some internal capability or helping (or encouraging) another contractor to develop the technology needed for your process.

STEP FIVE: GET PROPOSALS

It's time to solicit proposals. The RFP process of most CMO seekers includes an RFP document. Such documents vary from one-page requirements descriptions to lengthy, detailed documents. Do what is comfortable for your organization. You need to provide enough information that the vendor can respond with a meaningful proposal.

There is some legal risk, particularly with intellectual property, so it's a good idea to get the RFP reviewed by legal counsel. You should send your RFP to a vendor only after it has signed a confidentiality agreement. Having a mutual agreement in place allows a free exchange of information between both parties.

Remember that confidential information is not the same as intellectual property. Be clear that an RFP process is not a brainstorming session or a process development activity. You must be free to operate and innovate both internally and with your selected contractor once the process is complete. Make it clear that although all information shared will be treated confidentially, none of that can be considered to be intellectual property. In other words, if the CMO has an idea it will let you use only if you choose that company, then its team should keep that to themselves. Some sponsor organizations exclusively enter into one-way confidentiality agreements for just this reason. Others specify that only the proposer's pricing information will be protected. Accommodating such considerations may add time to the RFP process, but they are prudent. Waiving them requires full knowledge of the potential consequences.

Each contractor offers something different. The goal of an RFP process is to zero in on your top few CMOs' capabilities, capacities, and competences. Creating a straightforward and precise proposal provides consistency across vendor responses and presents the easiest route for objective comparison. A starting point would include key components listed in the "Request for Proposal" box.

Send your RFP to the top CMOs on your list at the same time, all with the same deadline. In some cases, a contractor's inability to meet a reasonable timeline that others can meet presents a "red flag." Table 1 shows that one vendor was late in processing its confidentiality

agreement (commonly referred to as a "CDA") and therefore got the proposal late, so it submitted a proposal later than its competitors did. For that, the company earned a "?" for commitment to timelines.

Quite often, a clinical plan begins, "Manufacture clinical trial material" with a start date of the previous day! It's important to understand the time required to identify CMOs, screen them, send an RFP, receive responses, evaluate and visit, make a selection, and negotiate a contract. Often the associated timeline is squeezed right from the outset. For all but the simplest CMO selections, this process will probably take a minimum of three months, of which the response time for an RFP is rarely less than two weeks.

Invariably, contractors that receive RFPs will contact you and want to arrange a conference call to ask questions and get clarifications. These conference calls can be quite useful, and they serve the (intentional) purpose of allowing you to interview some high-level technical staff who would have oversight responsibilities for your project. Use these meetings well, but also keep track of all additional information that you disclose. At the end of these interviews, you should send a summary clarification to all proposers, giving each one the additional detail that others have received individually. If you don't do so, the proposals are likely to diverge, and a fair comparison will be more difficult.

STEP SIX: SCORING

Score your proposals. When you receive the proposals, read them thoroughly. Make sure that they include all the information you requested and that they've conformed to your working assumptions. Identify areas where the proposals differ from each other, and consider how you will accommodate those differences in your evaluation. When you've found a basis to make apples-to-apples comparisons, you'll need a method

for quantifying the results.

One useful method is a weighted attributes analysis. This technique is a semiquantitative approach to aid in decision making when many factors influence an evaluation process. Each attribute is weighted based on its importance to the success of a project, and vendors are rated on their quality relative to each one. The ratings are multiplied by the weighting factors, and a summary score is calculated for each grouping of attributes, then for each CMO overall. A weighted attributes analysis is just one of many forms of analysis that can work. Table 2 provides an example.

Determine how to assess and weight qualitative data before you receive any proposals. Your analysis will be fair and blinded if you decide on your attributes and weightings before assigning scores. When building an analysis tool, do not underestimate intangible factors such as the ability to communicate, time-zone differences, and good references.

At this stage, you should be ranking and scoring on "nice-to-have" criteria as well as comparing cost, timeline, capabilities, capacity, and viability of each business. You might form your opinion of the viability of a business by reading annual reports and press releases and by assessing how busy the company's manufacturing area and support laboratories look during your visit. In a layered selection process, new teams are brought in for evaluation, and different evaluation criteria are applied as the process progresses (1). Developing scoring criteria that address from the start every stakeholder's responsibilities for project success can help prevent such situations. We've seen manufacturing partnerships ruined by poor scoring or weighting — or by shifting project responsibilities among parties that didn't share a common priority for project execution (7).

You may unearth new show stoppers in your RFP and analysis exercise. When a show stopper

Table 2: Example weighted attribute analysis for evaluating proposals: CMO #2 has the best weighted average.

Attributes	Rating (1 = worst; 5 = best)				Weighted Scores			
	CMO #1	CMO #2	CMO #3	Weighting (0 = low; 4 = high)	CMO #1	CMO #2	CMO #3	Total Available
Process transfer cost	1	3	4	4	4	12	16	20
Timeline	3	2	1	2	6	4	2	10
Accuracy of proposal	5	3	2	3	15	9	6	15
Purification process	2	4	1	4	8	16	4	20
Location	4	3	5	1	4	3	5	5
Average =	3	3	2.6		Weighted Average =	7.4	8.8	6.6
					Total =	37	44	33
								70

arises, you have to confront and confirm it — and if it is real, then end negotiations with a vendor that can't meet the criterion.

STEP SEVEN: PERSONAL VISITS

Visit the top two or three contractors in person. CMOs may not allow a formal quality audit before a contract is signed, but be sure to bring your quality representatives for an informal “technical visit” at least. If your project is large, you may consider a company’s resistance to a preuse quality audit as a red flag. Again, spend as much time as possible listening rather than talking. Arrange a tour and get copies of all presentations made. Ensure that decision makers from both sides meet and that discussions are aligned for key technical and quality personnel. If disputes arise or further work must be done, your decision makers must have a good working relationship.

Your visit is also your best opportunity to move past the business development group and take a true measure of the business. Chat with people in the laboratory or production area if you can. Look over the state of their equipment, the cleanliness of the facility, and stock in the warehouse. Determine the company’s level of flexibility: What can they make happen for you, and what will need to involve someone in another building or city? Ultimately, you should think about hiring a contract manufacturer similarly to hiring an employee, by looking for both expertise and fit with your team.

STEP EIGHT: NEGOTIATING CONTRACTS

Consider entering contract negotiations with at least two vendors. Things can go wrong in these negotiations, and your position is stronger if you’re legitimately able to walk away. In the absence of show stoppers, don’t let any of your final three candidates get away until the ink is dry on a final contract. If your budget can justify it, having a second contractor performing development work and verifying the primary contractor’s results is ideal, especially if you don’t have internal laboratories or expertise. Doing so can spread your supply chain risk and give you leverage in negotiating commercial supply agreements later.

STEP NINE: REANALYSIS

Revisit your analysis tool. You may learn new facts in contract negotiations that cause you to adjust your

earlier evaluations. Don’t be afraid to be frank if it seems that terms have been changed since your selection was made. This is another good reason to keep a back-up contractor. You may also revisit your analysis tool with internal stakeholders as your project progresses. If uncooperative parties are endangering its success, then remind them of their role in the selection and obtain renewed commitment to the project. This may seem like a dirty trick the first time you do it, but you’ll find much more attention is paid to the selection process the second time around!

STEP TEN: PROJECT MANAGEMENT BEGINS

Manage your project according to the criteria by which you selected the contractor. Hold your supplier and you yourself accountable to those criteria. For example, after selecting a vendor because it can meet a very aggressive timeline, do not put the project at risk by failing to order back-up critical path supplies — just in case the primary order doesn’t arrive, or it fails to meet specifications when it does. In managing a CMO, use clear and consistent communication with multiple points of contact for a successful technical transfer. Even with advanced technical know-how, a contractor still needs input and guidance at each step of the process. No assumptions should be made concerning the quality of your final product.

Detailed management of CMOs is beyond our scope here. In transition from a selection team to a management team, the details of the selection (and commitments made in the process) should be communicated and documented. The tone set in the selection process should carry over into management and execution.

Choosing the right manufacturing partner is critical for your success as a drug developer. Spend the time required to make a good decision: glean as much tangible and nontangible information on all your options as possible and then objectively comparing them. You should have an idea about how to evaluate and weight nontangible factors into your decision. And once you have made your choice, manage the partnership according to those criteria. Although everyone has preferred methods for vendor selection, our suggestions have worked well for us and our clients. Next time

you're faced with the daunting task of selecting a CMO, consider streamlining the process with these 10 steps to alleviate some of the associated stress.

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