Effective Quality CDMO Contracting

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For many pharma professionals, using contractors has been an established requirement throughout their careers, but for others, the idea of contracting to a third party is an anathema.

The exponential growth in the costs incurred by the pharmaceutical industry, the rise in virtual biotech companies, the increasing complexities and costs of maintaining facilities, and the intent of many pharmaceutical companies to de-risk internal facility development and outsource where possible have led to a surge in demand for CDMOs by small and large companies alike. This demand is not likely to diminish in the foreseeable future, which leads to the question of how to identify and select a quality CDMO.

The CDMO market is large and growing; data from 2019 before the pandemic began showed the market in Europe alone was worth $37.17 billion[1] and at that time was estimated to increase by nearly 7% annually over the 2020–2030 decade. Biotech companies accounted for 18% of drug products in development phases in 2019, while Big Pharma only accounted for 6%, nearly half of the Big Pharma pipeline that was in development only eight years previously,[4] supporting the premise that emerging and virtual biotech companies are developing their own assets via outsourcing rather than incurring in-house R&D expenditures and overheads for a variable load drug product pipeline.

Choosing the right CDMO is a complex and difficult task and, given the regulatory framework within which the industry operates, it is essential that companies seeking a CDMO get the right partner for the operations to be sourced. This brief article will discuss the approach to finding and managing the optimal CDMO and highlight some common pitfalls.

Contracting of development and GMP operations is not new and has been discussed by many authors; however, in summary it is useful to review the extract from the FDA's guide for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements 2016* below.[3]

> *"However, agreements between owners and contract facilities sometimes do not clearly define the CGMP-related roles and manufacturing operations and activities of each of the parties. When all parties clearly understand their CGMP-related roles and manufacturing responsibilities, the owners who use contract facilities, contract facilities that provide services to owners, and, ultimately, patients who take the drugs manufactured under these arrangements may benefit in many ways. Contracting can enhance speed and efficiency, provide technological expertise, and expand capacity."*

The crux of this is that the onus is on those seeking contractors to clearly define and control their drug products, ultimately for patient safety.

Request For Proposals

Many companies have existing processes for vendor selection, and many include the requirement to issue a request for proposal (RFP)[2]; however, a great deal of thought and planning must be undertaken prior to seeking engagement through an RFP at this early stage of CDMO identification. The contracting company needs to consider key aspects of the project work to be outsourced and how that will be managed and resourced internally.

The RFP is a key step in identifying a good CDMO. Achieving a meaningful RFP requires a frank sharing of targets for the desired drug product and therefore should only be done under a robust nondisclosure agreement. The golden rules are to define, specify, and identify; a vague RFP leads to confusion and ultimately an imprecise client proposal. Best practices are:

- Specify the active drug substance and key or desired excipients (if known).
- Include a process flow.
- Identify any known key processing parameters.
- Define the output drug product (dose, volume, etc.).
- Define the target patient population, e.g., adults, pediatric, or neonatal.
- Identify the markets in which the products will ultimately be used.

The following aspects of the RFP, while not exhaustive, are key to enabling a satisfactory vendor selection process.

Target Product Profile

This is a good starting point for any contractor searches and discussions. Consider the market in which you operate and the market in which you wish to operate, such as clinical trial site locations and first file location (e.g., Europe, Japan, or North America). All will have bearings on the location of the CDMO selected and, more specifically, whether the CDMO has expertise in developing or manufacturing drug products for those markets. What is the drug product classification: is it a beta-lactam, a large molecule, or a sensitizer? Is it a parenteral, solid oral, or topical or even a combination of dosage forms? These are all key aspects that will impact vendor selection. While these questions may seem rudimentary, it is surprising how often a contracting client will reply “we are not sure” or “still to be determined”.

Technical Detail

Feedback from vendors all too often states that a lack of clarity or technical detail makes it difficult to produce a robust proposal for a client. Even with a fully detailed description, the client’s needs can sometimes be difficult to discern. At a minimum, the technical aspects should include:

- position statement information: what is required, i.e., dosage form, market specifications
- specific deliverables, development manufacture stability clinical trial supplies, etc.
- project scope
- timeline for deliverables or final product, any milestones or proof-of-concept work?
- minimum requirements, for example, concentration or the ability to manufacture on specific equipment
- submission requirements, including specific markets or regulatory filings needed, such as IMPD or IND or supporting a MAA or NDA

On a more basic level, the client should clearly detail whether this is a project for development, scale-up, or scale-down or for manufacturing and monitoring.

Quality & Technical Agreement (QTA)

This defining document is critical to how the relationship between the client and vendor is structured. It is easy to fall into the trap of assumptions or camaraderie, especially if the vendor is already known to the client from previous activities. Refer to guidance from your local regulatory agency, for example, the FDA’s guidance that I noted earlier in this article.

Practicalities

Boots on the Ground

Before seeking the services of a CDMO you need to decide how you will manage the work; this is primarily accomplished by having an experienced individual or a team on the ground embedded within the CDMO for the duration. This allows for ease of communication and reduces the risk of delays due to misunderstandings; however, it requires a greater resource commitment. The alternative is a CDMO at arm's length primarily functioning autonomously with scheduled updates to the client. There is no right or wrong way to do this, but it is worth deciding the intended route before engagement as this will dictate how the proposals are reviewed.

Evaluating Vendor Experience

What essential experience does the vendor need to fully meet the client's expectations? This is an important aspect as it underpins the vendor's ability to complete the work successfully. What has their past performance been like? Have you experience with them from other projects? These are key questions to ask, along with any provided references or recommendations. What is their relationship with regulatory agencies like (if applicable)?

Many of the above criteria can be grouped into one overarching category: communication. Poor communication on the part of either the contractor or vendor is one of the biggest reasons for unforeseen delays, project mistakes, or even total failure. It is important to define roles and responsibilities very early in a contract discussion and to develop and nurture an open dialogue between parties. Often, parties have single-point communication contacts; in such cases it is essential that these contacts have the experience and intercompany links to facilitate this. It is also imperative that they have a detailed, pragmatic, working knowledge of the drug development and manufacturing process, and, if relevant, commercialization. Cross-company team meetings, steering teams, and virtual meetings all have a role to play depending upon the contact sought, location, and time frame of the project. Good communication always leads to a successful project.

Evaluating RFP Vendor Responses

Evaluation of the vendor responses is the final key stage in the decision-making process and there are several areas to concentrate on during evaluation:

1. Does the CDMO management team have sufficient experience to manage the project or, more correctly, do they have the appropriate experience, such as, for example, experience with parenterals or inhaled delivery systems?
2. Does the vendor have robust quality assurance and a suitable quality management system? Has this been verified?
3. What project management does the vendor provide?
4. Do they have sufficient internal expertise in the techniques or drug delivery systems being developed, and are there any specific requirements?

Identifying and managing the correct CDMO or contract partner for your projects is not an impossible task; it is, however, fraught with pitfalls and sometimes difficult conversations. Identifying the right company, in the right location, with the right experience and facility is essential. Those seeking CDMOs should not be swayed by a business development department promising aggressive or impossible timing that does not pass a sanity check. All vendors should be examined by someone with experience who can assess not only their capability but also their expertise and any additional rationales the vendors bring to the discussions.

Contracting of development and GMP operations ultimately must yield a quality data set and/or quality product, as companies are paying for a quality process. Ultimately, obtaining the quality drug product that patients demand starts with engaging the correct contractor.

Risks

There is always a risk associated with contracting work. You need a CDMO that you can trust, with a good track record, well-trained personnel, and that is sufficiently resourced. It is no good selecting a CDMO to ease your own resource constraints if you end up fighting for resources within the CDMO. Nothing is risk-free; understanding and mitigating the risks are key and having a good CDMO you can engage with is a key starting point to that relationship and risk mitigation.

Caveat Emptor (Or What Happens When It Goes Wrong)

There are no guarantees with a vendor selection process; things go wrong even with the best planning. This applies to all vendor selections – the company you select may suddenly downsize or be purchased by a competitor. In those situations, all you can do is be as flexible as you can and, with a clear goal in sight, continually communicate that to the vendor management team. Aside from these strategic issues, other situations may occur, such as material changes to the input API or excipients, process changes driven by manufacturing experience that could not be foreseen, or analytical method errors or failures that require method redevelopment and/or validation. Again, you must remain clear in your goals and maintain open communication with the CDMO. The aim is for the CDMO to deliver your project and for you, as the client, to achieve your goals.

Selecting the right CDMO for your work is not easy and should never be assumed as such; however, the CDMO network is full of skilled and experienced pharmaceutical experts, and the key is locating the perfect one for your work. Contracting work to vendors is not going to disappear; it's a growing trend and CDMOs are a key part of the pharmaceutical industry.

References

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