Best Practices for CDMO Evaluation, Selection, and Management

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Your company's product development, scale up, and manufacturing strategy continuously evolves throughout the product development lifecycle. Being an agile organization with multiple process development and manufacturing avenues is key.

When executed properly, outsourcing manufacturing scaleup to a CDMO can be an expeditious way to further mobilize the science and drug products. With careful planning and strategic upfront investments, you can avoid common pitfalls and successfully integrate a CDMO into your organization.

When your product is ready for scale up the first instinct may be to immediately begin searching for a CDMO to start manufacturing product. To provide a smooth transition from the lab to CDMO, there are important factors you must first understand and steps to take prior to searching for and engaging with an external partner. If this process is not executed properly, there is a risk of wasting valuable time, resources, and the potential to not have the requirements for success.

CDMO Scope, Evaluation & Selection

Defining the scope

Before reaching out to any external partners, first define the scope of the process internally and determine exactly what you will be looking for in the marketplace. It is important to understand what processes are being done in-house and what is required from the external partner.

A CDMO could be used to either lead and/or supplement in the following areas:

- Early Drug Development
- Process Characterization
- Tech Transfer
- Toxicology Lots
- Pre-clinical/Clinical/Commercial Manufacturing
- Stability Studies
- Analytical Method Development

It is crucial to allow for enough time during the CDMO vendor evaluation and selection process, in order to conduct a comprehensive and exhaustive search. Planning well in

advance and establishing a realistic timeline will save you from settling on a vendor that might not be the right fit. In some cases, the selection and evaluation process can take up to six months. Align on the scope of what your organization requires from a technical standpoint and start the interactions early, well ahead of when you require material to be produced regardless of phase.

Assessing an External Partner

Once scope and internal expectations are aligned, it is now time to move on to assessing specific CDMOs. It is important to create and perform a competitive bidding process to carefully analyze your options. Providing a bid tab structure can be helpful during the evaluation process, so all potential companies categorize and define their proposals in a consistent format. First, develop a scope of work, send out a questionnaire to several organizations, review their responses with a small internal team, then conduct onsite interviews with senior staff members focused on how they plan to tackle the project. Following these steps should lead you to selecting the right contract and development manufacturing partner for the job.

Some key areas to focus on during the evaluation process:

- Senior leadership
- Internal expertise
- Project management
- Quality Assurance, Quality Management Systems and Quality Programs
- GMP Policies and Procedures
- Regulatory
- Reliability
- Equipment readiness
- Facility capacity
- Company culture, mission, and values
- Current applicable clientele

Alignment on these factors across the organization is critical. Make sure you speak to several different levels of the CDMO staff this will verify the message is consistent throughout the organization.

Much of the effort will be up front during the evaluation, selection, and onboarding processes. At this point, teams are to work together, level set, and establish expectations for a successful partnership. Negotiating contracts in a collaborative fashion can be very effective and demonstrate a teamwork driven approach

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while being fair to both parties. Spending the time to establish clear expectations of the teams is valuable and provides a healthy baseline for both parties to work from. Areas of focus on are scope definition, macro execution plan, ownership of key areas, level 1 schedule, and budget. Changes will happen, having the foresight to agree on a change management process, communication plan, review and approval flow is encouraged.

CDMO Onboarding

To commence a successful partnership with the CDMO, one needs to get buy in from their team and senior leadership and begin to foster a patient-focused culture built on collaboration, quality, and safety. Reinforce early and often to your CDMO that this is a valued partnership. Transparent and timely communication is a must. Educate your partner on the importance of what you are setting out to accomplish together and how important their role is in your company's overall mission.

Key items to be aware of:

- Provide as much background about the product as you can
  - This will help the CDMO partner identify at a personal level with your product and patients versus just being another client
- Keep your mission and its outcomes relatable
- Be patient focused to reinforce a sense of purpose behind the process
- Build team unity and trust by creating an open culture
- Lead on-going teambuilding exercises and postmortem reviews
  - Do not only perform these at the end
- Ongoing education and training
- Ensure there is a continuous feedback loop and lessons learned in real time

Hosting workshops and continuous education is a valuable way to engage with the entire team. These provide an opportunity to check in and communicate lessons learned in a collaborative manner. Group trainings also help establish team dynamics and show how each member can contribute; keeping them engaged and solution driven.

Some examples of valuable trainings and workshops are:

- Tech Transfer
- Facility Operations Preparation
- Start Up
- Batch Review and Release
- Overall Lessons Learned

Partnership Best Practices

Bringing together two organizations effectively can be tricky and takes time. To do this effectively, allocate experienced talent and clarify roles and responsibilities early. Establish organizational charts, use team to team mapping, plus identify a single point of accountability for the different workstreams. Ensure your teams are working together effectively by checking in periodically and continuously drive execution. Do not be afraid to push accountability and decision making down into the organization, as all decisions do

not have to come from the top. Be proactive in making team changes to either side when necessary, match skill sets to strengths. Communication across the projects, teams, and organizations is critical.

Creating a Communication Plan

Start by creating a structure for governance, communication flow, and an escalation pathway.

Simple structure (example provided):

1. Core Team: Responsible for all day-to-day tasks and are accountable for all the operational details.
2. Leadership Team: Responsible for a mixture of details, strategy, and should work to address any issues escalated up by the core teams. This can be on an ad hoc or by exception only basis, or a routine meeting.
3. Senior Level Steering Committee: Responsible for meeting quarterly to discuss strategy, contracts, future business, team personnel and assess high-level updates on how the entire program is progressing.

It is critical to create a communication and escalation plan for how deviations on the production floor will be handled. Having a plan in place allows the team to react quickly when deviations arise. It is important to communicate outwards and upwards when something previously unforeseen occurs. Production should not continue until the issue has been evaluated and ultimately resolved. Real time communication and notification to the client is required, especially regarding deviations or a nonconformance. Proceeding without performing some type of triage and identifying a root cause could lead to an entire batch being compromised.

Deviations and Nonconformances

In your communication plan, develop a set of procedures which evaluate deviations and nonconformances to determine criticality rating and ultimately identify the root cause. Each issue on the floor should fall into one of three categories: critical, major, or minor.

Provide a contact list to the CDMO with 24/7 emergency numbers and a clear outline or call tree so they know who to contact based on technical expertise when something goes wrong. Post this list where it can be easily accessed by all production floor staff. The production floor will be instructed to talk through the issue on the phone with the appropriate subject matter experts (SME) outlined in the plan. The immediate steps should be to define the problem, review options, determine time sensitivity and escalation path, identify the audience and the criticality rating (critical, major, minor).

Assessment of the nonconformance usually involves some type of triage directly related to the impacted process steps. A critical and major deviation will be more time consuming and cause more impact than a minor, with the potential to delay production. In the event of a critical and/or major deviation, production could be paused, while the appropriate SMEs are notified to assist in conducting a formalized criticality rating. A root cause analysis should be performed, eventually leading to a corresponding Corrective Action.

A minor deviation should not be as time consuming, however still requires a notification to the appropriate SMEs. Minor deviations can usually be corrected on the manufacturing floor quickly with a short-term fix thereby allowing production and processing to continue.

Your organization will ultimately be responsible for ensuring compliance with quality and the commercial agreements, so awareness of any issues that occur on the production floor is expected. Additionally, there should be supervision over the execution of the lot, batch review, and specification setting. It is your teams' job to facilitate communication and coordinate error resolution between the Quality department and CDMO project team.

Creating and Implementing a Project Plan

Creating and implementing a detailed project plan, strategy and schedule will allow production activities to move forward smoothly. When building a schedule, think of key dates, highlight milestones, and create a "go or no-go" milestone at each major phase. This will allow potential issues to be identified and resolved before proceeding as it brings all workstream leads to the table for a final assessment before starting a key task or process step. Detailed project schedules should be kept at the core team level while linking them at the major milestone level as part of the overall project schedule. The two need to be linked, but not duplicated.

Example of a Typical Approach:

- Technical Transfer
- Facility and Suite Start Up
- SOPs for Operations and Maintenance
- Operation Readiness for Manufacturing
- Batch Records
- Engineering Runs:
- GMP Clinical Manufacturing
    - Process Characterization
    - Analytical Development
    - Stability Studies
    - Process Performance Qualification Runs
    - GMP Commercial Batch

Part of the overarching project plan should be dedicated to operational readiness. Creating an operational readiness plan is critical to catching problems before they arise. Engineering, Clinical, PPQ, and Commercial phases will all have different requirements. These should be established and reviewed before starting each phase of manufacturing. Create tasks, establish resources, and drive alignment across all teams.

Each major milestone within your process should have some type of “go or no-go” checkpoints. Ensure these are sized appropriately for their criticality. Some phases will require an extensive checklist, while others might only be a few items.

Types of checks are:

- Facility and Suitability Assessments
- Batch Record Readiness
- SOPs
- Batch Record Review
- Non-Conformance & CAPA’s Investigation Support
- Change Management
- Product Related Deviations
- System Reliability
- Manufacturing Training Verification
- System Troubleshooting

Conclusion

For optimum outcome, both parties must understand this is a partnership, and not a delivery service. Your organization will be required to provide continuous ongoing support throughout the entire process – plan for it. A team member should be making weekly or monthly visits to their site to ensure adherence to programs, policies, and procedures and to actively monitor scope, schedule, and budget. The recommendation would be to have owner presence for all key manufacturing steps.

Be as willing to receive criticism and feedback as much as giving it. Always create feedback loops as part of the process to drive continuous improvement. Push accountability and decision making as far down into the organization as you feel comfortable doing so. Not every decision should get escalated or must come from the top. Get the heavy lifting done up front as it will pay off down the road. Plan the work, work the plan!

Placing your process and the fate of your product in the hands of another organization can appear daunting. Implementing these strategies and processes can save your organization valuable time and resources. The key to a successful partnership is careful upfront planning, research, and well-planned execution. Utilizing a CDMO can be an effective and streamlined option to bring your innovations to the patients who need them most.