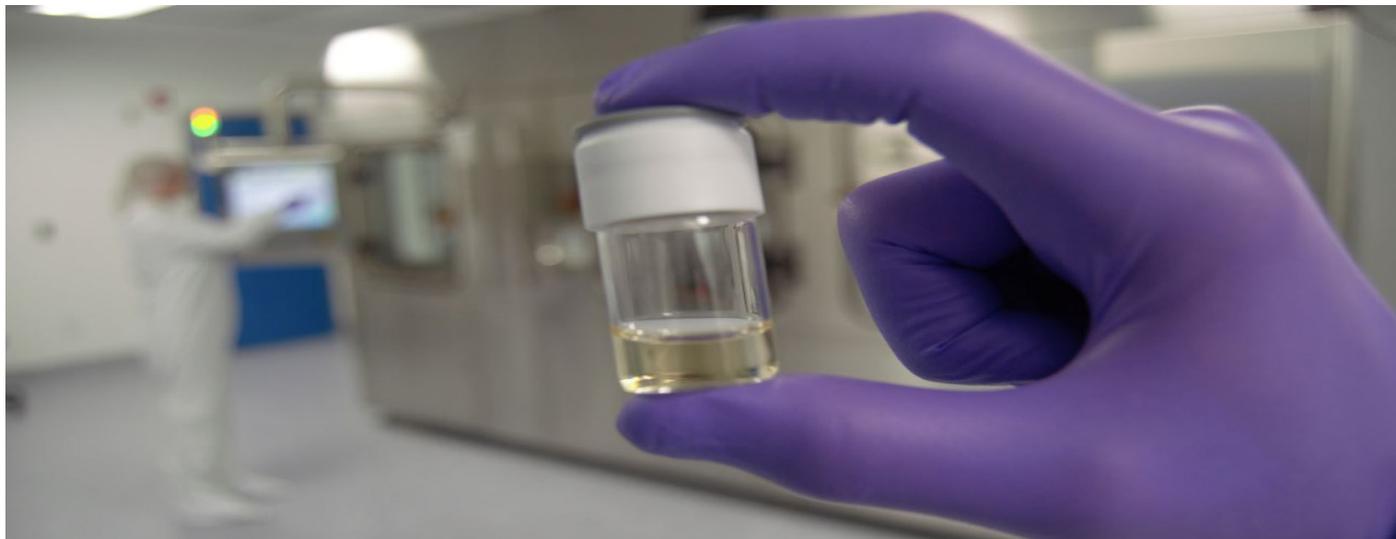


Understand Your Process: A Key to CMO Risk Mitigation



Introduction



The global pharmaceutical industry outsourced an estimated \$65 billion in drug manufacturing volume to contract manufacturing organizations (CMOs) in 2016, according to the research firm Mordor Intelligence. Pharmaceutical companies contract out to CMOs to reduce capital expenditures and the costs of manufacturing, to gain access to specialized manufacturing methods, and to gain redundant capacity to mitigate the risk of supply interruptions or unanticipated spikes in demand.

The advantages of contract manufacturing come with certain practical risks. Many of those risks

are associated with inadequate communication and knowledge transfer between the drug's originator and the CMO. Most can be minimized.

Throughout this paper on CMO risk mitigation, we will approach the subject from the perspective of a sterile drug product CMO. The principles are equally applicable to other dosage forms, as well as in API manufacturing. Our focus will be to establish methods to reduce project risks when moving from the laboratory to a GMP manufacturing setting.

The objective of this paper is to help managers who evaluate contract manufacturing:

- Determine how to work with the CMO to determine critical process parameters;
- Explore strategies to control or eliminate process variables; and
- Learn how to bridge the gap from lab scale to manufacturing scale.

Successful Collaboration with Your CMO

No matter how careful and comprehensive your supplier selection process is, it can give you only a high-level understanding of a supplier's capabilities and culture. Inevitably, unknowns will remain after you've selected your CMO. These unknowns represent project risks.

How do you identify and mitigate these risks before you select your CMO?

Start with due diligence in the supplier selection process. The process must involve someone from your organization (or a consultant) with the knowledge to assess whether the supplier has the requisite skills, experience, and infrastructure to carry out your project. Infrastructure is tangible; it should be the easiest of these criteria to evaluate. A site visit is critical, not only to see the facilities but to meet key personnel. Be sure to ask for references from clients with similar projects.



Keep costs in perspective. Guard against letting the price tag of a proposal play a disproportionate role in supplier selection. The cost of a failed batch or major quality issue invariably outweighs any savings you might get from taking the lowest bid. Consider using a scorecard approach to narrow down a final selection in which cost is only one of several critical factors.

Once selected, your CMO should expect to be subjected to a **Quality Audit** (a step that is completed sometimes during due diligence) and must be willing to sign onto a **Quality Agreement** that includes performance metrics. Provisions should also be put in place to allow feedback during and after each project.

Risk Reduction

After Project Initiation

Effective preparation can prevent surprises and generate confidence in the success of the collaboration. But how can you mitigate risks once a project is underway?



Set performance expectations early

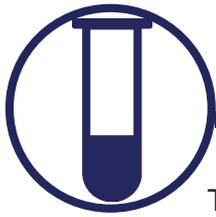
Establish a set of project milestones before a project is initiated and ask for regular progress reports. These should include:

- Target dates for key milestones (e.g., completion of technology transfer, manufacturing readiness, batch manufacture, and release dates); and
- Specific, ideally quantifiable targets for critical quality attributes.



Get to know the supplier

Partake in a kickoff meeting and frequent, regular mid-project progress meetings/calls. Establish clear lines of communication. There should be a primary point of contact for the CMO – typically a project manager. Ensure you have access to other key team members and management (when necessary). Make sure that the supplier knows that communicating bad news is just as important (if not more so) as communicating good news. Strive for continuity of the team from start to finish – sometimes a change of personnel is necessary, but frequent changes increase risk (e.g., in the loss of institutional knowledge).



Transfer as much of your knowledge about a process as possible – as early possible

The CMO will need access to development reports, your experience from previous manufacturing (if any), and any safety information you can impart. If possible, be onsite during lab-scale runs, but in any event, ensure laboratory process chemists/formulators are scheduled to either participate or advise during the production of the first plant-scale batch. There are professional standards for this kind of knowledge transfer. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed a widely accepted model, called ICH Q10. This pharmaceutical quality system can be implemented throughout the stages of a product lifecycle. Consider adopting this model.



Avoid letting a relationship become adversarial

Point out where things are not going the way you want. Accept responsibility for problems when they are not of the CMO's making.



Take it in stages

Consider a stage-gate process to assess readiness to move on to each successive step in setting up production.

Your goal before moving to production scale should be to identify
Critical Process Parameters (CPPs).

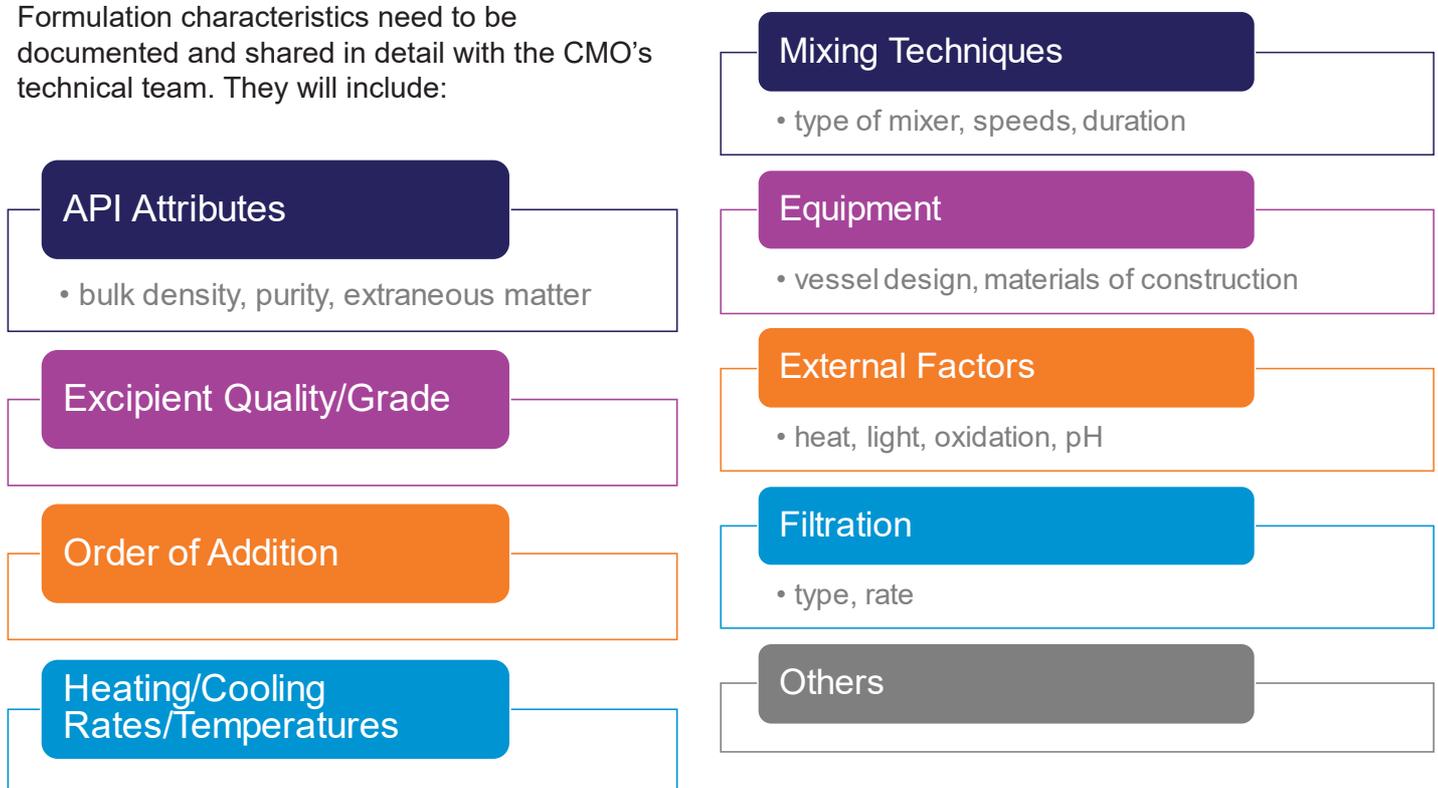
Identifying Critical Process Parameters (CPPs)

CPPs are key variables affecting a production process and when monitored, can detect changes in critical quality attributes. Even in a never-before-manufactured product, identify CPPs before attempting to manufacture. In sterile product manufacture, CPPs fall into two main categories:

- **Formulation Parameters** – Typically reliant on the sponsoring company's expertise; and
- **Fill/Finish Parameters** – Elements of the CMO's experience and expertise.

Formulation Parameters

Formulation characteristics need to be documented and shared in detail with the CMO's technical team. They will include:



There is a good deal of complexity here, and it is frequently not realistic to conduct an exhaustive CPP study particularly for an early phase clinical project. Work closely with your CMO to identify a manageable number of critical parameters that merit exploration and focus on those. There is no point in becoming preoccupied with factors that cannot be changed (e.g., API impurity profile) or are unlikely to impact the process. Remember: **The FDA does not expect you to explore every possible variable – only those likely to impact product quality.**

The goal is to identify and demonstrate a process capable of repeatedly and robustly delivering bulk drug product of the required quality and quantity. You'll need to develop a set of in-process control specifications to track and verify product quality throughout the process. You'll need to document process limits (i.e., how long can the process run before quality begins to suffer?).

Fill/Finish Parameters

From a fill/finish perspective, there are a separate set of issues to manage. These include:

Materials Compatibility with the Formulation

- tubing, fill needles, containers, connectors, etc.

Sensitivity to Manufacturing Environment

- (clean room or isolator) temperature, light, oxygen levels, residual sterilant levels

Closure System

- vial/syringe, stopper, seal

Filling

- speed, duration of fill, fill tolerance, headspace content

Your CMO knows its facility better than you do. They can help you take advantage of their expertise which will allow them to follow their standard process.



Standardized Process

The simpler the process, the fewer things can go wrong. Pharmaceutical manufacturing is inherently complex. It is, of course, highly regulated. Process changes and deviations are likely to carry significant consequences. You'll want to work closely with your CMO to identify CPPs and, ultimately, to reduce and eliminate process variables.

Whenever possible, utilize formulation procedures that are familiar to your CMO – try not to insist on procedures that are markedly different than what they are familiar with unless it is absolutely necessary. Don't require them to reinvent the wheel just for you.

Use **standardized batch records and operating procedures** whenever possible. The best reason to stick with these standards is that the people doing the work are already familiar with them. People who are operating a familiar process are less prone to error. If you must employ unique and different methods, make sure they are well-understood and **flagged as non-standard** to all concerned.

Use of **validated procedures** ensures the highest degree of regulatory compliance (e.g., use of pre-sterilized manufacturing supplies from qualified, validated processes). Any significant deviation from the validated process may require a time-consuming and expensive re-validation.

Use **standardized equipment** whenever possible – the machines, instruments, and consumables originally used in the process you had validated, and to the extent possible, disposables with a history of adoption in the pharmaceutical industry. The disposables used in your process should:

- Be pre-sterilized using a validated process;
- Require minimal assembly; and
- Have established and documented performance characteristics (e.g., mixing rates).

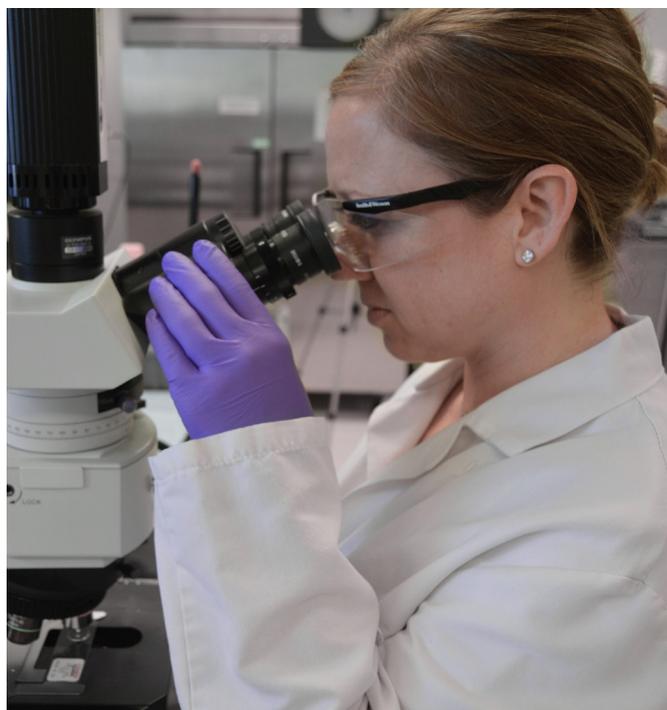
Take advantage of automation whenever possible. The single most prevalent source of deviations in drug product manufacturing is human error. A good example of effective automation in drug manufacturing is **automated/robotic filling**, which eliminates most human interaction with critical components. Once you have a lab-scale process you can rely on; the final challenge is to bridge the gap from lab scale to manufacturing scale.

Moving from the Laboratory to the Manufacturing Floor

Manufacturing-scale production is qualitatively different from lab-scale production. There will be new risks. So, when scaling up a new process for GMP manufacture, be sure to learn as much as possible about that process before it goes to the plant – experimenting at plant scale is risky and expensive.

Preparing for GMP

Start by ensuring that the CMO familiarizes you with its standard procedures for critical GMP-scale processes (e.g., compounding, filtration, filling, etc.). Seek to verify that CMO laboratory development personnel understand their manufacturing facilities (surprisingly, this is not always the case). As we noted in our earlier discussion of critical process parameters (CPPs), it is impractical to cover every conceivable risk factor. Focus on determining what parameters are most likely to impact the quality of your finished product. If you don't know, then allow time in the lab to explore.



Consider a design of experiments (DOE) approach to scale-up, documenting:

- ANTICIPATED VARIABLES;
- WHICH COMBINATIONS CAN BE MODELED; AND
- THE OUTER BOUNDARIES – WHAT HAPPENS IN CASE OF UNEXPECTED EVENTS
(E.G., IF THE API TAKES LONGER TO DISSOLVE THAN EXPECTED, WHAT WILL BE THE IMPACT?)

Establish a written protocol and gather data that methodically documents what happens to each process variable when you scale it up. Once a process has been established, run one or more lab batches at the largest scale possible before transferring production to the plant. In these test runs, model as closely as possible the conditions on the manufacturing floor, using equipment that mimics plant-scale equipment. In planning for these lab batch runs, consider:

- Are any CPPs candidates for in process control (IPC) methods?
- Should you involve Operations/Production personnel during lab batch execution?

Document each lab batch according to a **developmental batch** record to set the stage for GMP batch record preparation. Be sure to note any unexpected results and brief Operations to avoid surprises. As the project sponsor, you should consider having your people onsite during this critical step to observe and advise. Capture lessons learned and overall experience in a written report and disseminate it to all parties who need this information especially Operations Department personnel.



Sharing Expertise

Remember: You chose your CMO for its expertise. The CMO may have experience with similar molecules – learn from that experience. However, if the molecule is truly unique, the onus will be on you to help the CMO understand what is critical.

One feature of your CMO's approach that is worth exploring in detail is its commitment to automation, at each stage of the process. Automation is not a frill and is not principally a labor-saving expedient. Humans are the number one source of errors in manufacturing—increasing automation greatly reduces opportunities for mistakes. Ensure that you and your CMO are on the same page about this. Give yourself the time you need to succeed. Manufacturing is hard enough without the added pressure of tight timelines. Yes, this is easier said than done. But, deliberately build in a time buffer to account for the unforeseen. Build in ample time for technology transfer to ensure it is completed well in advance of manufacture, to allow for preparation and review of the high-quality batch record, and training for key personnel.

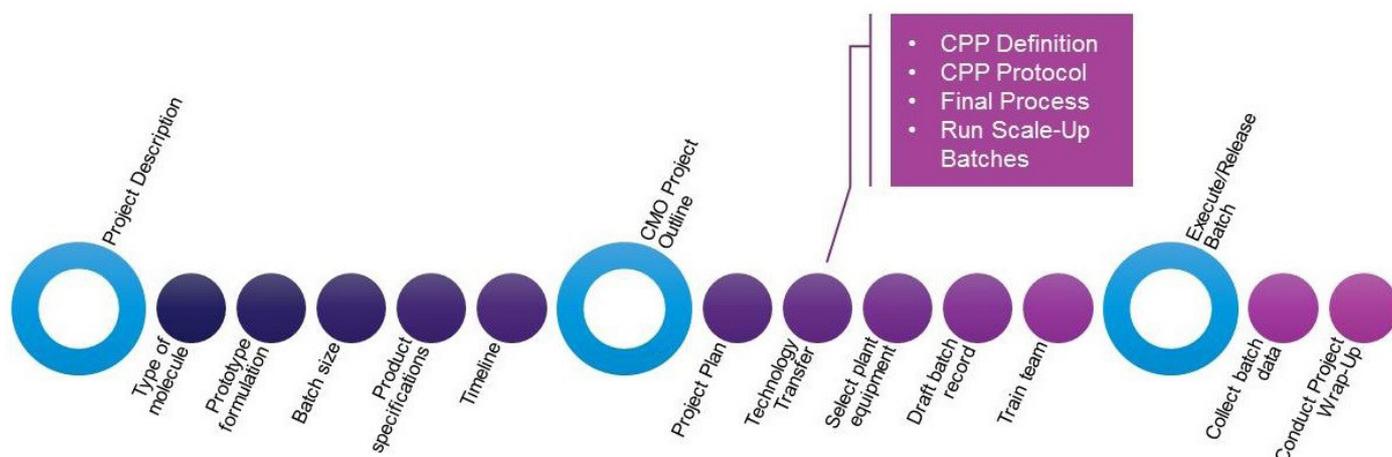
If you are contracting out manufacturing of a drug for which you already have a well-established process in-house, your focus should be on figuring out what is different in your new CMO's facility compared to where the process was previously run. Some of the differences will be obvious:

- **Scale** (not just vessel size, but other factors like process duration);
- **Equipment type** (e.g., type of filter/dryer, dispensing pumps); and
- **Raw material sources and grades.**

More subtle differences may include:

- **Isolators vs. clean room; and**
- **Means of sanitization (e.g., vaporized hydrogen peroxide vs. other sterilants).**

There are many variables to be considered in detail, but the following graphic depicts a summary of the CMO based manufacturing process and where this paper's risk mitigation points fit:



Prepare for the Next Campaign

Almost invariably, you and your CMO will learn something when manufacturing your first GMP batch. Using the performance metrics established during tech transfer activities, evaluate whether further exploration of CPPs may be necessary. For example:

- Process – Did impurities match expectations? Were yield losses as expected?
- If further scale-up is necessary – Do you anticipate that time to produce a larger batch will pose issues?
- Will other process variables impact product quality, such as:
 - Mixing;
 - Reaction rates;
 - Heating/cooling;
 - Filtration;
 - Dispensing rates; and
 - Other process-specific factors for more complex formulations (e.g., suspensions or emulsions).

Don't think of your first manufacturing campaign as an experiment. Treat it as a dress rehearsal for your next campaign – don't repeat past mistakes!

You and your CMO are partners. Give each other honest feedback as to what worked well and what could be improved, in the process, facility/equipment or personnel. By adopting a collaborative approach and taking advantage of each organization's strengths and knowledge, you can help minimize risks to your strategically critical drug manufacturing project.



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