

BIOPHARMACEUTICALS

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# Outsourcing clinical phase biologics development

Preparing for successful sponsor-CMO teamwork



**T**he long-term nature of outsourcing biologics process development and GMP manufacturing over the course of clinical trial development can involve unforeseeable events that could be a source of conflict between the sponsor and the CMO. In this article, we present the CMO's perspective on various potential sources of sponsor-CMO conflicts, preventive actions to circumvent conflicts before they occur, and strategies for resolving conflicts as related to process transfer, development, and GMP manufacturing of biologics.

A successfully outsourced GMP manufacturing program is built upon a common goal and the management of numerous factors in the complex collaboration between the sponsor and contract manufacturing organization (CMO). The successful collaboration involves a synergistic exchange of each party's knowledge and experience, combining detailed understanding of the product's intrinsic properties, experience in process development and manufacturing, and GMP regulatory requirements for manufacturing, toxicology, and clinical trials. In this article, the authors will present potential sources of sponsor-CMO conflicts, preventive actions to circumvent conflicts before they occur, and strategies for resolving conflicts as related to process transfer and development, and GMP manufacturing of bulk biologics.

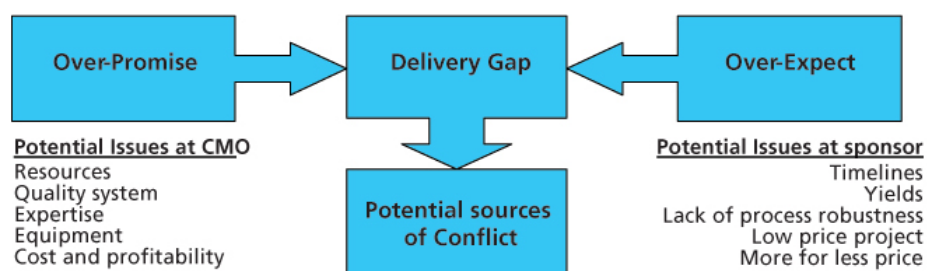


Figure 1.

Figure 1. Sponsor-CMO conflict management for clinical phase biologics

### Conflict prevention in CMO selection

Numerous articles have already been published reviewing best practices in CMO selection (1–3). It is clear that the selection of a suitable CMO is the first step in the prevention of conflicts. Mid-project changes in the service provider will only incur losses of time and money. As a rule, sponsor–CMO conflicts arise when a delivery gap is created in terms of product quality, quantity, cost, and timelines (see Figure 1). When the sponsor and the CMO first meet to discuss the potential partnership, it is important that the CMO not overpromise and that the sponsor not overexpect; aligning expectations is the first step toward minimizing a delivery gap. The interaction must be open, must highlight technical difficulties and pain points of the project, resource bottlenecks, and specify gaps in expertise of each party. A clear articulation of the project's scope, deliverables, and timelines should lead to the mutual acknowledgment of constraints related to the project. It should also bring about a mutual understanding of what the resources required to complete the project are.

At this stage, the CMO is responsible for accurately identifying the process steps that are incompatible with its existing facility or incompatible with the level of expertise required for the project. Doing so will ensure that the CMO avoids underperforming. For its part, the sponsor should have a total awareness of what is and is not known about the product to be developed and should be transparent about the state of development of the process, analytics, scales of previous runs, yields for each step, purpose of each process step, which process steps are problematic, and the behavior of the molecule during the process and under storage conditions. The desired quantities of material should be based on requirements for preclinical, clinical, future market needs, technical considerations, such as scale and process performance, characterization, and stability studies; the evaluation of these will require the intervention of both parties. Should incompatibilities exist, the two parties should brainstorm alternative approaches to meet the sponsor's expectations. This often has the added benefit of building trust between the two parties.

### Sources of conflicts following CMO selection

Assuming the appropriate CMO was selected on the basis of manufacturing capacity, process development, and GMP experience, and was followed by a compliance audit, the potential sources of conflict can be associated with the four broad steps in an outsourced project: business terms, technology transfer and development, project management, and compliance. An efficient contractual strategy can

preemptively manage conflicts before they arise and can ensure that expectations, resources, and deliverables are understood mutually and can be allocated as required during project development (4–5). The specific needs of the project are often not definable before the project is initiated, so a contractual strategy that is both flexible and binding offers advantages over contractual approaches that attempt to cover the entire scope of the project, from development to GMP production, under a single technical agreement contract. Because the technical agreement cannot take into account all the eventualities of the project, it is inherently less flexible for the evolution of the project, and hence more likely to give rise to conflicts. A more flexible approach is to divide the contract into three distinct portions: the master service agreement (MSA), the project agreement (PA), and the quality agreement (QA). These agreements will reflect details outlined in the initial project quotation.

### Business-term tools Quotation

The quotation should not only serve as a starting point for the selection of an appropriate CMO, but should also be used subsequently as a reference map throughout the lifetime of an outsourced project. It should contain detailed information with respect to price, duration, start dates, development strategies, and deliverables based on the available information provided to the CMO. In the early phases of biologics process development and manufacturing projects, it is typical to define only the delivery date and estimated target amounts of GMP material. The sponsor then expects the CMO to offer a development strategy that meets the sponsor's deliverable requirements. As the development portion is variable from product to product, the quotation should be detailed enough for the sponsor to evaluate the CMO's proposal, and yet be flexible enough to provide pricing and timing outlines that vary with the project's complexity. Quotations that offer this degree of transparency will help educate first-time, early-phase biopharmaceutical developers in terms of the time dependencies of various development steps. A Gantt chart can further highlight which steps are of variable duration (e.g., fermentation development), which are fixed in duration (e.g., GMP batch release), and what the time and cost requirements for each step to budget and plan. As a conflict-resolution tool, the quotation should provide sufficient information to allow a mutual understanding of pricing policy for additional work. For example, the quotation should include the cost and timelines associated with the transfer of a well-defined process as well as a per month, full-time-employee, or batch price for additional, optional optimization work, or other alternatives discussed at the point the CMO is chosen.

## MASTER SERVICE AGREEMENT

Discussions on the MSA should be initiated in parallel to the quotation. The purpose of an MSA is to lay out the legal contractual framework between the two parties, thereby allowing each party to protect their respective interests. The agreement should cover aspects that are not related to the technical deliverables of the project, including the legal responsibilities of each party with respect to the performance of service, data, reporting, material, intellectual property, licenses, third-party intellectual property, payment terms, warranties, duration, termination, confidentiality, insurance, indemnities, limitation of liabilities, and governing law. It should not include project details and quality matters, which will be respectively addressed in the PA and the QA. Separating contractual terms into these instruments allows the parties to put in place the terms in a stepwise fashion, designating the appropriate persons for each negotiation. The legal experts from both parties should agree on the legal clauses stated in the MSA, while the project managers independently move forward on the technical aspects of the project based on development results in a scientifically sound manner. This contract, once signed, initiates the start of the project as specified in the project agreements.

## PROJECT AGREEMENTS

The PAs are annexes to the previously signed MSA and are an important conflict-management tool. The PA should describe the first project-specific tasks outsourced to the CMO by the sponsor. They are part of the legally binding contract. A project can have multiple PAs at the same time. For example, PA-1 can detail the transfer of a fermentation process, and PA-2 can detail GMP cell banking. Each PA should identify in detail the scope of the work to be done, which can be as comprehensive as required, including allocation of human resources, facility resources, deliverables, delivery date, and price. Each PA acts as a yes-no decision point with respect to the general strategy agreed upon in the quotation. The outcome of one phase of the project will determine the scope of subsequent PAs. The content of the PA is often drafted by the various team members: the project manager, the scientists, and project leader, and the appropriate persons directly involved in development and GMP manufacturing. As a legal document, the PA is signed and approved by both the sponsor and CMO before work is begun. The significant advantage of a PA is to be able to define the phases of the project in a scientifically sound manner.

## QUALITY AGREEMENT

The QA is a PA that covers GMP manufacturing of the product and is also annexed to the MSA. It should describe the respective roles and responsibilities related to quality and GMP regulations, and it should be outlined in a clear, straightforward manner. The sponsor's quality-assurance department or its representatives should ensure that quality aspects are properly managed in GMP drug manufacturing following a site audit of the CMO.

The QA should define the legal responsibilities of each party with respect to quality matters, such as manufacturing authorizations, audits, and inspections, facilities, staff and training, suppliers, third-party approval, raw materials, records and retention, product manufacture, storage, packaging and shipping, quality controls and out-of-specification management, change control and deviation management, complaints, and product recalls.

## Project go-live

## PROCESS TRANSFER & DEVELOPMENT

Once the MSA and PAs are completed, the sponsor and the CMO should agree on preventive actions before development and GMP manufacturing operations are begun. To avoid conflict during process development at an early stage of the project, the CMO should be impeccable on the competency and expertise of its personnel, the equipment suitability, the quality of the reporting, and communication. Those in charge of development and GMP manufacturing should be aware of the PAs signed by both parties and should be of adequate expertise to lead process development and transfer to the GMP manufacturing facility. Second, the equipment in process development should be of the highest quality and should be comparable to GMP production equipment to ensure that transfer to the GMP production team is smooth and efficient. As a rule of thumb, the equipment should not represent a constraint that forces the CMO to come back to the sponsor with bad news.

Finally, during process development, the sponsor should be kept informed through frequent informal communication and documented reporting. The frequency of teleconferences should be low enough to enable the CMO to ensure data reliability, yet high enough to ensure that the sponsor is sufficiently informed of ongoing progress: weekly communication is generally sufficient. Development reports should keep the sponsor apprised of key outcomes of the development stage and should reflect the scope of the different PAs. Finally, the CMO should share the sponsor's priorities; its development experience should benefit the sponsor.

In spite of clear and careful agreements between the parties, the development stage can nevertheless be frustrating for both parties. Relevant expertise and technical mastery notwithstanding, there is no guarantee the CMO can provide deliverables and meet the sponsor's expectations. It is likely that the parties will lose faith in the partnership. Conflicts that arise at this point are often related to people, time, financial resources, and the CMO's scientific expertise. If a particular PA step does not satisfy the sponsor's target expectations, the development plan should be adapted with respect to the results of the initial PA in a scientifically sound manner. Because the plan entails process development, this adaptation may involve extra work and extra cost. In such situations, the following points are crucial:

- There are no questions with regard to the equipment, personnel expertise, and data generated
- Scientifically sound alternatives and their time and cost consequences are presented to the sponsor
- Authorization of a new PA is given by the sponsor before the CMO embarks on alternative development avenues
- The CMO acts with humility and acknowledges its limitations
- The sponsor acts in good faith and acknowledges the work is performed by the CMO, all the more when the product is difficult to handle or timelines are very aggressive.

When advancing in a science-based manner, transparency in communication and detailed reports allow an accurate assessment of the work performed, even when development meets dead-ends.

## GMP MANUFACTURING OF CLINICAL BATCHES

Risk assessments should be performed before initiating GMP manufacturing to ensure that product quality will be met. The CMO is responsible if it chooses to go ahead with GMP production when the risk of batch failure is high. Reasons for anticipated failure can include a lack of process robustness, insufficient process knowledge, and analytics' undemonstrated fitness for purpose. At this point, additional development activities must be discussed to avoid over-promising. Finally, both parties should agree on the product specifications in accordance with regulatory requirements as well as the procedures and the method of production before starting GMP manufacturing. Target production yields and the customer's needs to supply the clinic should be in good agreement with development data or process history upon normal operating conditions.

Following the risk assessment, the process is transferred to the GMP manufacturing facility. The technical transfer should never be jeopardized. The CMO is responsible for allocating all resources necessary so that the technology transfer is successfully achieved. The technology transfer should be documented, and the sponsor should be informed of the transfer's completion and any issues encountered. Likewise, the quality system in place must ensure the following points during the production of the GMP batches:

- The GMP personnel are adequately trained
- Equipment is qualified
- Operations are traced, recorded, and checked
- No cross-contamination occurs in a multiproduct facility.

## CONFLICT RESOLUTION IN GMP MANUFACTURING OF CLINICAL PHASE BIOLOGICS

Outsourcing biologics manufacturing is costly, and dealing with conflicts that involve financial arbitration is always challenging. This statement is particularly true when GMP batch quality specifications are not met or production yields are not achieved (see Figure 2). Identifying financial responsibilities in these situations is often stressful and contentious. Senior management and appropriate decision-makers for both parties should immediately be informed of the issues and should take time reaching their conclusions following a thorough investigation. The investigation should be structured and systematically documented and should address the following technical and quality questions:

- Are the people trained in all affected operations?
- Is the equipment qualified?
- Are there any major or critical deviations in the method of production?
- Is the process robust or validated?
- Are critical steps identified or operating ranges well defined?
- Is the issue related to cleaning or cleaning validation?
- Are release specifications accurate with respect to product knowledge?
- Was an out-of-specification investigation opened by the quality-control laboratory?
- Is the out-of-specification root- cause assignable to a laboratory error?
- Are in-process controls as expected with respect to historical data?

This investigation should allow the development of a rationale for discussing the financial responsibility of both parties. In every case, successful conflict resolution depends on the quality of the investigation at the CMO and the sponsor's understanding of the issue and root cause. Videoconference or face-to-face meetings are helpful in clarifying perceptions and promoting dialogue between the sponsor and the CMO. Generally, good conflict resolution, supported by facts and documented evidence, should benefit both parties and strengthen the partnership. ■

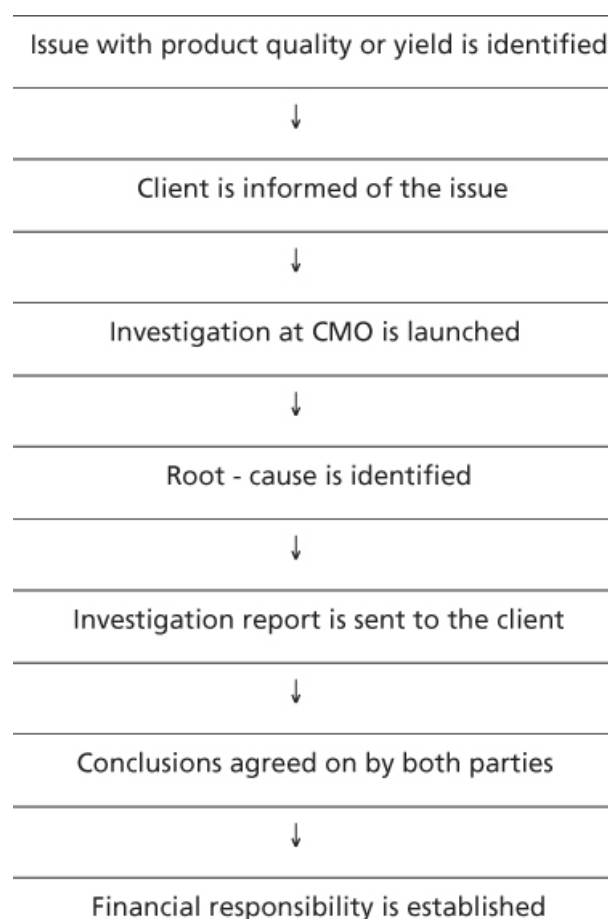


Figure 2. Conflict resolution protocol

## CONCLUSION

Jointly building and documenting various tools before initiating a project will ensure that both parties are on the same page with respect to project goals. The use of a structured contractual framework based on a MSA, PAs, and QA provides the necessary flexibility to move process development and GMP manufacturing forward in a scientifically sound manner and under clear contractual terms in ways that a single technical agreement cannot. The reduced flexibility of a technical agreement can be a source of conflict. Although the MSA, PA, and QA are important conflict-resolution tools, successful projects benefit from collaboration, transparency with regard to capabilities and expectations, expertise, project status, and identification of specific subsequent milestones.

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