Baxter

BioPharma Solutions

Bringing your Sterile Injectable Product to Market: Considerations for Collaborating with a Fill/Finish CMO

WHITE PAPER EDITION

Bringing your Sterile Injectable Product to Market: Considerations for Collaborating with a Fill/Finish CMO - CMO Selection, Request for Proposal (RFP) Delivery, Proposal Review, and Project Award.

When should a CMO be solicited?

As your company determines that outsourcing of the fill/finish of your product will be required, it is important to send out your RFP at the appropriate time. Should you send the RFP before you have identified much of the scope of the project, you may receive a proposal from a CMO that feels incomplete. On the contrary, if the RFP is sent out too late, or too close to your planned GMP batch date you may find that the timeline can be difficult to achieve. Table 1 outlines the pitfalls of sending out an RFP too soon or too late. As shown in the table below, the ideal time to begin looking for a CMO is between 12 and 18 months from your planned GMP production batch.

Table 1

RFP Timing

[*The Right Time*]

Too Early — Too Late

Jan → Feb → Mar → Apr → May → Jun → Jul → Aug → Sept → Oct → Nov → Dec

Consequences: Information and/or scope of project is not fully known	12-18 Months from GMP	Consequences: Timing requested does not account for lead times of critical components of the project
• CMO will not issue a proposal • CMO delivers proposal, but it is incomplete • All pricing is not covered • Pricing will be dated once project starts	• Information should be known (components, DS availability, etc.) • Allows CMO time to kickoff project and place orders for equipment, components, etc. • Drug Substance (DS) readiness	• Supply chain issues with placing orders and receiving according to the timeline / Lead times are too long to meet planned GMP batch date • Rushing technical transfer can cause issues to arise, thus causing more delays

Request for Proposal (RFP)

The Request for Proposal or RFP is the likely first document your CMO will see that provides information about the product, process, and scope of what is needed to be performed at the CMO. The RFP will be provided after the Confidential Disclosure Agreement (CDA) is completed. RFPs should be clear, detailed, and robust. As your potential CMO is reviewing the RFP they are considering this product in their production, QC, packaging, and warehouse areas.

Further, the details provided will have a direct correlation to the information you receive in the proposal. Table 2 outlines items to consideration when drafting the RFP prior to sending to CMOs.

Table 2

Area of Focus	Details & Rationale
Container Closure	• Drawings or part numbers • Lyo Cycle details/duration
Drug Substance	• MSDS • Container for DS and Storage conditions
Excipients	• CAS number • Testing requirements (US/EP/JP)
Process Flow Diagram	• Allows the CMO to visualize your product flow as you have designed it. • Allows the CMO to consider how to approach the tech transfer internally as it pertains to equipment, in-process testing etc. of the process.
Allowable Time out of Refrigeration (TOR)	• Allows CMO to begin to design the process knowing how much TOR is available
Batch Size/Units per batch	• Allows CMO to evaluate capacity on proposed line
Product sensitivities	• Light, Oxygen, etc.
Packaging	• Bulk or full packaging • Inspection (manual or automated) • Whether serialization is required
Analytical	• Incoming DS ID test • Inprocess and finished product testing • Testing type for each (Elisa, HPLC, etc.)
Capacity Requirement	• Annual forecast - Planned commercial batches in the coming years. (high/low)
Timing	• CMO Award date/ Planned date for first GMP batch

Proposal

Once the RFP has been provided to potential CMOs, a proposal should be issued between 2 and 4 weeks depending on the CMO's internal process. The proposal should be clear, robust, and cross functional - multifunctional in a sense that the proposal will cover technical transfer costs, equipment cost, assumptions of the project as well as price for not only the technical pieces but also the unit/batch price itself.

A robust proposal will have the product assumptions from the RFP but should also address any request that the CMO cannot support. For example, the CMO may not have the capabilities to aid in extractable and Leachable (E&L) testing or filter validation. The CMO should be clear so that these longer lead time items are discussed up front.

Once the proposal is issued, a follow up call between the companies should be arranged. This call allows your team to ask questions and allows the CMOs to explain their technical transfer process and why some line items are required and why some may be "To Be Determined". Items that are to be determined can stem from information not provided, or simply needing to be clarified as whether they are in scope. This requires a conversation between to the two teams to determine what should be considered in or out of scope.

Figure 1. Outlines the key elements in a proposal.

Figure 1

Items to consider prior to awarding the business

After the proposals have been reviewed, a visit to the various CMOs should be considered. Visiting a site and meeting key stakeholders face to face can help the companies determine if the pending relationship is a cultural fit. The CMO should have cross functional support, including but not limited to, Manufacturing, R&D, Quality, Regulatory, Supply Chain, Tech Services, etc. available to have specific discussions that do not typically occur on the proposal review call. In addition, the facility should be toured in order for the CMO to describe specific items such as material/product flow, site metrics, LEAN initiatives, and regulatory history, to name a few. A detailed agenda with the items that the client would like to see should be provided to the CMO to allow for a productive meeting.

Another consideration is an audit of the facility. The CMO should be prepared to host a potential client in an audit to answer any quality questions. The CMO should also provide their regulatory and various agencies inspection history. If your company would like to schedule an audit, this should be requested as soon as possible after the proposal has been provided. Auditing schedules fill up quickly as they are managing client audits and internal audits as well as planned and unplanned agency audits.

Awarding the business

Once the business has been awarded, the next step would be to schedule a face-to-face kickoff meeting at the CMO. This meeting allows for the joint team members to meet each other and discuss the project at a deeper level. The kickoff meeting is 100% about the scope of the project. The scope must first be defined before moving forward. When the kickoff meeting has concluded, each team member and functional area should have a clear understanding of what the scope of the entire project is as well as what each functional area is responsible for. The CMO meeting facilitator should invite team members from each area as it is broken down (see bullets below). The client should have as many functional areas represented whether it is an onsite meeting or a virtual meeting.

The following are examples of functional areas, and how scope is discussed and ultimately determined.

- Drug Substance: how many containers per batch. How many bottles are allocated to 1 batch? How many bottles can the CMO store at one time?
- Excipients: what excipients will the CMO procure? Will the client provide specific excipients? What testing is required? (USP/EP/JP)

- Analytical: what is the method for incoming ID? Will this test be a method transfer, verification, or method development? How does the client's approach to testing validation match up with the CMO?

- Technical transfer: CMO Technical Services should provide a process flow map and identify items that can be durable and/or disposable. Items discussed should be filter type, open or closed system for formulation, product sensitives, etc. This is not a process set in stone at the kickoff, however after the meeting has concluded, the transfer team should know the process flow and how it fits at the CMO.

- Engineering: The engineering team at the CMO will work with Technical Transfer to order equipment (product contact and/or non-product contact) that fits decisions made.

- Supply Chain: discuss lead times of components, excipients, equipment etc. Will the client be providing any materials for process validation for example?

- Process Validation: what is the client's approach to process validation vs. the CMO? How many product configurations are planned for the product? Will a bracketing approach be utilized?

- Regulatory: What is the regulatory approach and filing strategy? What help can the CMO provide for the filing?

- Tour the facility: Allow the CMO to show the building(s) where your product will be formulated, filled, inspected, and packaged. Also consider touring the QC area and allow time for CMO to answer any questions.

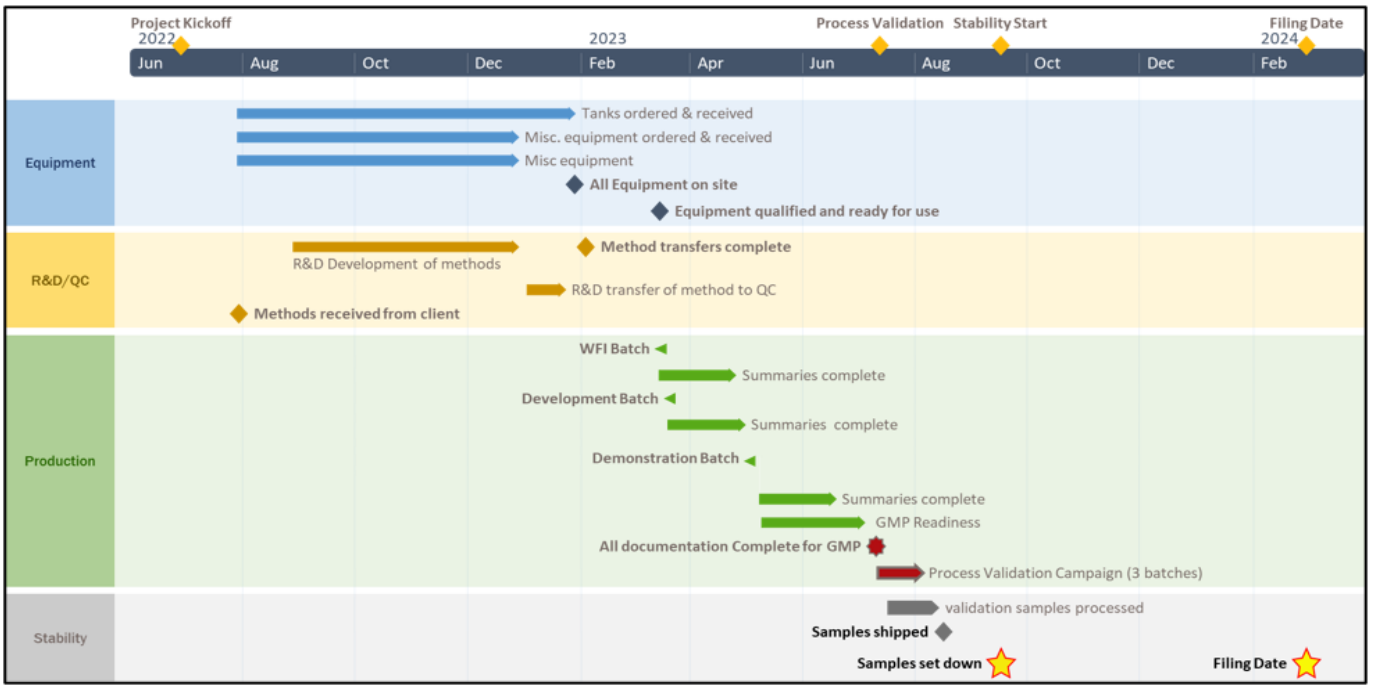
- Project Management: Discuss the high-level timeline of the project. Potentially, the timing has changed between the proposal and the kickoff meeting. Project norms should be discussed in terms of project management tools that are to be used, frequency of joint team meetings, establishment of a steering committee and contractual agreements are all examples.

Project Timeline

Timelines are a great way to monitor the progression of a project while understanding critical path activities. Examples of a potential timeline that can be discussed at the kickoff is provided in Figure 2 and Figure 3. It is difficult to place the project into a detailed Gantt chart prior to the kickoff meeting, however, a Gantt should be established after the kickoff meeting when scope has fully been defined. Timelines should represent the client's regulatory strategy as well.

Figure 2

Figure 3



In Conclusion

With increased market expectations and new, more stringent regulatory hurdles, for many, establishing a partnership with the right CMO is more cost effective than investing internally in their own infrastructure. Selecting the "right" outsourcing partner is a strategic priority for pharmaceutical and biotech companies seeking to get their product to market as quickly as possible.

It is important to take the time to carefully vet each CMO under consideration for your project, as described above, in order to find the CMO partner with the right scientific expertise and industry experience to keep your project on track and ensure timely market entry.

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920980-00 2022