PHARMACEUTICAL ONLINE

BEST PRACTICES WORKING WITH CDMOs

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In pharmaceuticals, working effectively with contract development and manufacturing organizations (CDMOs) is an art as well as a science. This e-book begins by giving advice to emerging pharma companies on how selecting a CDMO is similar to “betting the house” in a card game. The next article shares how a CDMO addresses two critical areas — CMC support and quality assurance — can often dictate how effective a CDMO can be in supporting and accelerating the timeline for the drug sponsor’s drug development program through commercial manufacturing. The third article shares recommendations on how to find common ground with your CDMO when assessing risks, and it also provides tips to facilitate trust.

Once you’ve selected your CDMO and begun working with them, you can transform your relationship into one that sets all your manufacturing “red lights” to “green lights” for pipeline acceleration and speeder time to market. Shared qualification audits add to the win-win relationship. Another article shares a better path for CDMO relationships as the pandemic continues. The last article in the e-book highlights post-COVID supply chain opportunities and strategies for both pharmas and CDMOs.

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BETTING THE HOUSE: CDMO SELECTION FOR EMERGING PHARMA

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Successfully completing an NDA and securing approval for a drug is a significant accomplishment for an emerging company and a major milestone in its young life. All the emotion from long days, FDA reviews, tight deadlines, clinical studies, and numerous patient and investor meetings is finally realized when the company can sell its new drug and improve lives.

An essential step in a company's evolution is the selection of a contract development manufacturing organization (CDMO) to develop and manufacture its drug. How an emerging company selects a CDMO to produce materials for clinical trials and commercial production is like the high stakes of "***betting the house***" at a pivotal point in a card game. A good gambler knows how to assess the risks and odds to know when it is best to "bet the house." In a similar manner, selecting the right CDMO can lead to successful clinical trials and rapid commercial growth, while making the wrong selection can seriously impact the future of a company. Given that "luck" is often defined as the intersection of preparation and opportunity, proper preparation is essential to this process.

Improving the odds of selecting the right CDMO for your organization requires an evaluation of market analysis, manufacturing and quality assessment, financial discussion, and several other key factors. Teams of people, both present and future, will be brought together to meet stringent regulations and address several drug manufacturing and compliance issues in a collaborative environment. Both the sponsor and the CDMO need to know they can build strong relationships between the people in the two organizations to address complex issues while meeting tight deadlines.

For this critical decision, emerging companies may be limited in the necessary business, technical, and negotiation skills and/or time needed to assess options. Often, as an emerging company enters this phase, several important questions arise, such as:

- What gaps are in our drug development technology process? Where can we use a partner to help us successfully manufacture our drug?

- Does the CDMO have the capacity and technology to meet our drug manufacturing requirements?
- What is the CDMO's track record with the FDA and other regulatory authorities?
- What criteria should we use to evaluate CDMOs?
- How are successful partnerships structured from a legal, financial, and regulatory perspective?
- What risks should we consider as we evaluate CDMO options?
- How do we structure sourcing and quality agreements to ensure source of supply and regulatory compliance?
- How do I get the best price from a CDMO to manufacture our product?

Fortunately, these questions and others can be addressed through a well-managed sourcing process that minimizes risk and improves the odds of a successful partnership. While it may appear to be a time-consuming process, a well-organized sourcing process builds trust between the sponsor and the CDMO, thereby minimizing the risk of failure. Each step provides the sponsor team with a better understanding of a CDMO's technical, quality, financial, and management capabilities to meet their goals.

A strategic CDMO sourcing framework starts with a long-term perspective between the sponsor and CDMO and can be structured in four steps:

1. Timeline definition from drug development through commercialization phases
2. Alignment on CDMO relationship framework
3. Development of a request for proposal (RFP)
4. Execution of supply and quality agreements

Managing this four-step process can be conducted in a few months or several months based on resources (internal and external) as well as market conditions.

To understand how this process relates to your specific company needs, each step is outlined in this article.

TIMELINE DEFINITION

An emerging company's success is defined by how they manage their development timeline and complete critical milestones. Several timeline management factors include:

- The stage of drug development: early-stage or late-stage clinical trials
- Planned submission period for FDA/governing authorities for study review and approval
- Expected commercial launch timing

During this step, a sponsor will be able to refine their approval time window, technology development needs, and potential sales volume. All these factors are important when identifying CDMOs and making initial assessments. For example, some CDMOs may have the cell and gene therapy technology knowledge that is critical to producing a drug while others may have capacity to grow or have capacity limits to producing certain drugs. Therefore, based on the sponsor's drug technology platform and the CDMO's capabilities, it will be important to clarify the overall timeline and milestones to align expectations and build a strong relationship.

ALIGNMENT ON CDMO RELATIONSHIP FRAMEWORK

From a long-term perspective, it is important to develop a complementary approach to skills, capabilities, and cultures between the sponsor and CDMO. Over the duration of a multiyear agreement, both parties will experience tight timelines and complicated issues requiring a strong working relationship. Some aspects to consider include:

- Depth of staff technical capabilities
- Maturity of process development
- FDA compliance and quality experience
- Relevant therapeutic experience and knowledge
- Responsiveness, problem solving capabilities, and general interest in the product

From these aspects, it is possible to define detailed technical and business requirements needed for an RFP.

- Drug profile
- Drug substance manufacturing
- Volume
- Packaging requirements
- Data sharing and/or IT system interface requirements
- Capacity requirements
- Inspection audit history (FDA/EMEA and other regulatory agencies)

Documenting these details will provide the sponsor with information to start evaluating the CDMO marketplace and identifying a short list of target CDMOs. At this point, a sponsor can start contacting CDMOs to understand their interest in working with them. While not yet the formal RFP phase, this process can help a sponsor take a prospective number of suppliers from a dozen down to three to five that are very interested and meet most of the essential criteria.

REQUEST FOR PROPOSAL

The development of a comprehensive RFP includes input from multiple functions and requires diligence to ensure accuracy across important criteria such as: production requirements/specifications, regulatory requirements, and evaluation criteria. While there may be a temptation to cut corners and expedite this process, it is very important to take time and collect all the relevant information and develop a comprehensive RFP process. A poorly designed RFP creates a disincentive for suppliers to participate in the RFP process and further creates confusion when proposals are submitted.

While emerging companies vary in staff size and capability, it is important to get input for the RFP from different functions, such as clinical operations, quality, technical operations, finance, and marketing. Colleagues from these functions will provide important evaluation criteria for two important sections of an RFP: technical/service and financial. Within each of these sections, a company will need to define which criteria are essential and can be defined in a "yes/no" or "go/no-go" framework.

For example, criteria for technical/service can include:

- Quality system
- Production capacity
- Regulatory track record
- Warehouse and storage capability
- Analytical processes and release testing
- Technical product support

To develop and assess these criteria, an emerging company may need outside support given their resource constraints. For example, you may determine that the first three items are critical criteria where you need support and know that your internal team can manage the remaining items.

Once the RFP criteria are defined, the composition of the actual RFP becomes more of an administrative process requiring diligence from the team to ensure proper documentation and clarity in the proposal request. With an RFP and a targeted group of CDMOs, a sponsor can issue the RFP, solicit proposals, and evaluate options.

This process allows time to review written responses and conduct supplier oral presentations to identify several aspects needed for a collaborative relationship. Sponsor teams often find this approach provides an easier way to negotiate by taking the time to evaluate offers and ask questions to ensure a good fit and strong partnership.

EXECUTE SUPPLY AND QUALITY AGREEMENTS

Once a final CDMO is selected, the analysis and proposal should be shared with the executive team and/or the board depending on the governance structure given the significant financial and risk impact on your company.

After internal review and agreement, there are a few critical follow-up steps that need to take place. These include quality audit, sourcing and quality agreement development, equipment order, and engineering studies and validation batch production.

While each of these four steps needs to be developed for a specific sponsor's situation, the overall focus for any CDMO selection should follow a spirit of long-term relationship development. This mindset will allow the sponsor the opportunity to grow their partnership with a CDMO not only with one product but also future products.

IMPROVING THE ODDS FOR SUCCESSFUL DRUG DEVELOPMENT

In a competitive and regulatory intensive market, companies cannot afford poorly performing relationships with their CDMOs. Just as a skilled card player knows how to improve their odds and manage through several challenges, emerging pharma companies can greatly improve their ability to successfully complete clinical trials and launch new drugs by using a simple but effective sourcing process and building strong long-term supplier relationships.

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CMC AND QUALITY CONSIDERATIONS WHEN ENGAGING YOUR CDMO

Bikash Chatterjee
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Deciding to use a CDMO to support your drug development program adds complexity and risk if the right partner is not identified and engaged. Before pursuing an outsourcing strategy, it is essential to define what processes will be kept in-house and where your CDMO partner will take the lead. This partner can be used to either spearhead or support several areas in the drug development road map, from the earliest stages in drug development through process characterization, tech transfer, and analytical method development to post-approval clinical commitments.

The evaluation criteria should encompass the CDMO's management team and senior leadership, under several important aspects: internal CMC (chemistry, manufacturing, and controls) support capability and expertise, project management capabilities, quality assurance, quality management systems (QMS) and supportive programs, regulatory affairs support capabilities, equipment qualification and process validation expertise, technology and manufacturing capability and capacities, and company culture, mission, and values.

CMC AND QUALITY ASSURANCE FRAMEWORK

Understanding that a drug sponsor's requirements for a CDMO partner will change as a product moves through its clinical program toward commercial manufacturing is fundamental when evaluating a CDMO's ability to support your program. Consider that this is a long-term relationship proposition that could easily span 10 years or more. How a CDMO addresses two critical areas — CMC support and quality assurance — can often dictate how effective a CDMO can be in supporting and accelerating the timeline for the drug sponsor's drug development program through commercial manufacturing.

Evaluating a CDMO's quality and operations systems and personnel in isolation will not provide a complete picture of the metrics for a successful relationship. The reality is that the drug sponsor's infrastructure and systems must interact with the CDMO's systems to effectively leverage their expertise and capabilities. Including this aspect as part of the assessment exercise will help prevent any issues going forward.

CMC CONSIDERATIONS

Specific considerations as they relate to a drug sponsor's ability to effectively utilize a CDMO for drug development are as follows:

Drug Modality Experience

The CDMO's ability to understand the critical operations related to the functionality of a drug's modality can impact the level of oversight and participation required by the drug sponsor. This element alone can foretell potential challenges as the program moves to commercial manufacturing. For example, basic knowledge of a unit operation's impact on process reproducibility is a good indicator of how an organization can integrate process experience that is not routine. If an operator can clearly convey that they understand what is critical when disassembling, cleaning, and reassembling spray guns and tips for a simple oral solid dose (OSD) drug development process, or a more sophisticated spray drying or Würster process, that is a good indication that a CDMO has learned from past mistakes and has taken proactive measures to prevent any future problems.

Process Characterization Expertise

The level of understanding that the technical staff commands regarding identification of critical process parameters, raw material characterization design of experiments (DOEs), and statistical analysis will provide insight into the CDMO's ability to support and provide the data required to support an NDA or biologics license application (BLA) filing. You should understand their approach to protocol development, how they handle sampling plan justification, and drug sponsor justified characterization requirements, such as demonstrating content uniformity. A CDMO with a working knowledge of process characterization will be more vigilant as you move to managing routine commercial variability challenges.

Method Development Expertise

How a CDMO approaches method development or method transfer provides insight into their understanding of the sources of variability that can be an issue with late-stage clinical supply and commercial manufacturing. The rigor and specificity of the method development and transfer process is a good indicator of the kinds of issues the CDMO has anticipated and integrated into its routine operations. For example, confirming that method development is not performed on QC equipment — a simple evaluation criterion — is a small but important indicator of future potential laboratory issues.

Data Management

The flexibility that a CDMO employs when in the development phases vs. commercial operations will indicate whether a drug sponsor can realize some timeline acceleration from early access to data during process development and gives you an indication of their commitment to data integrity. The maturity of the systems and processes a CDMO employs is a good sign that they understand the potential issues that could be encountered in the later stages of development and that could impact your filing and commercial manufacturing.

3 Stages Of Process Validation Framework

One of the challenges CDMOs face is their ability to support both development and legacy commercial products. Try to understand how organizations implement the FDA's 2011 process validation requirements, how they accommodate legacy commercial products approved prior to 2011, and how they deploy their Stage 3 CPV (continued process verification) program. This will indicate how prepared they are to conduct the studies that are necessary to support all three stages of process validation. This is an area where the drug sponsor may have to take on additional responsibility. The CDMO should have a defined framework or process for accommodating constantly evolving expectations from regulatory bodies without impugning their existing commercial programs.

PHASE-APPROPRIATE QMS

A phase-appropriate QMS speaks to the fact that the level of quality oversight and involvement evolves as a drug moves through the development process. While a complete GMP assessment should be performed as part of any CDMO evaluation, there are several areas that give indications that a CDMO could become a successful commercial partner.

Training And Competency Assessment

Training is one of the core pillars of a robust GMP framework and is one of the primary contributors to developing a quality culture. CDMOs are constantly confronted with new processes and programs as they expand their customer

base. Effective training programs translate to lower systemic excursions and that equates to a lower cost of poor quality (COPQ). CDMOs should be able to articulate how they utilize their training programs to accommodate new processes, novel technologies, and drug modalities on the floor. In addition, a clearly defined job skill matrix for every position in the organization should be in place. A review of the training records should reveal that all training is combined with some level of competency assessment. Most importantly, there should be a clearly structured on the job training (OJT) framework. An effective OJT program ensures employees can translate the intent of each GMP document into practice and understand how they relate and support each other. Capturing the learnings as the program moves along the drug development process will pay dividends as the program expands to commercial manufacturing.

Deviation System

The deviation system captures excursions and non-conformances across the drug development life cycle. How a drug sponsor's quality organization will participate and interact with the CDMO's QMS is an important facet to define at each stage of the product's development but is especially true for the deviation system. The rigor of all root cause investigations, the investigators' training and preparation, and the processes used are important components to assess. The specifics of the interaction may be captured in the quality agreement or may be partially captured in the QMS. In reviewing and approving all deviations, expect the drug sponsor's role to escalate as the product moves to commercial manufacturing, which could impact the program in terms of time and cost.

Data Integrity

Ensuring the integrity of the data generated by a CDMO is paramount to a smooth drug development partnership. A CDMO should have a mature data integrity program in place, especially in the laboratory. The staff should be able to define these processes, why they are required, and how they fit together. The quality group should have a framework for routine data integrity audits, not only in the lab but also on the shop floor. Even during early development, there should be a process defined for capturing GMP data as part of their GxP IT management system.

Quality Culture

Characterizing an organization's culture is not always simple. A culture of quality means the organization does the right thing even when no one is watching. A drug sponsor is placing responsibility in the CDMO's infrastructure and systems but also trusts that the organization will do the right thing, even when they are not present on-site. Several aspects influence a culture of quality, such as leadership's commitment to quality, empowerment of employees to address quality issues, the technical staff's awareness of factors that affect product quality, and structured programs to celebrate quality achievements. Interviewing staff and gauging their level of engagement and their leadership's engagement are good ways to determine how commercial issues will be handled and if the CDMO will be suitably prepared for pre-approval inspection (PAI) and commercial manufacturing.

Change Management

Ensuring that a clearly articulated change management framework is defined and in place as a drug sponsor's program moves through the development life cycle is critical. A common definition of minor, major, and critical changes, and the level of interaction and approval needed at each level, will go far in ensuring there are no unpleasant surprises downstream. A CDMO must juggle multiple programs and should be able to plainly articulate how it manages multiple program changes on process and test equipment and on operational and quality systems. It is important to recognize that any deficiency in a different drug development program can derail your program if it results in enforcement by a regulatory agency.

AVOID MISTAKES AND LOST TIME

Identifying the right CDMO partner can be a complex undertaking, but lack of structure can lead to mistakes and lost development time. Recognizing that the CMC and quality expectations will change as your program moves toward commercial manufacturing is key to your assessment. It's important that both drug sponsor and CDMO work together efficiently to lower the overall risk for both parties and ensure that the foundation for key systems and processes is plainly defined.

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PLOT A SUCCESSFUL COURSE: CRITICAL RISK ASSESSMENTS WITH CDMOS

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As a consultant, I am routinely engaged by clients to facilitate complex microbial and viral risk assessments. By nature, these are critical risk assessments that have direct implications for patient safety and product quality. When these risk assessments are performed by a biopharma company, and it has *direct* oversight of the manufacturing operations and facility, the risk management process proceeds as expected. Risks are identified, root causes of pain points are discussed, and risk control measures are brainstormed and implemented. In these cases, the organization comes together to explore and solve problems. I have often noticed that during initial sessions, sharing of information is tentative and measured but, over time, the risk team develops a rapport that is unified by a shared culture, patient safety, and product quality.

What happens when a biopharma company entrusts another group of individuals to manufacture its product? Is the only common ground that which is founded by audits, deviations, and quality agreements?

In the instances where I have been engaged with biopharma companies and their CDMOs, the landscape of risk management looks nothing like those where direct oversight is the operating paradigm.

FIND COMMON GROUND WHEN ASSESSING RISKS

When a biopharma company and its CDMO come to the table for a risk assessment, there are a set of challenges related to differing cultures and risk perceptions, but the goal of the assessment is the same – to evaluate the risk using the risk management process. Typically, these risk assessments include nearly two times the recommended number of subject matter experts (SMEs) due to participation of duplicate personnel from each organization (two people from quality, two from manufacturing, two from microbiology, etc.).

During risk initiation, the teams explain the manufacturing process and detail the facility design and management structure. While the scope of the risk assessment is

established and the risk question is drafted, the team works well together, is engaged, and they actively listen to one another. A hurdle that commonly presents itself during initial conversations is related to agreement on risk ranking criteria. When using likelihood and severity, the likelihood ranking criteria are generally straightforward and are based on number of failures/ deviation rates or a set of measurable elements. The challenge can be determining the severity criteria, which highlights the differences in risk perception from each organization. Considering that the relationship between the biopharma company and its CDMO is founded in a business transaction, failures are often viewed as business or financial impacts. While this is a critical element to consider, the intent of a quality risk management processes is to evaluate risks from a patient perspective. Establishing the impact of failures from a patient perspective with both parties will ensure there is a common goal relating back to the safety, integrity, purity, and quality of the product. Building the risk assessment with this as a joint mission will enable the teams to view risks from the same perspective.

FACILITATE TRUST

With risk ranking criteria defined and agreed upon, the risk management process progresses to "hazard identification," the portion of the risk assessment where the team's job is to brainstorm sources of harm. For microbial and viral assessments, sources of harm often include failures related to personnel, equipment, raw materials, process, facility, and utilities. Preventing the failures from occurring links back to the prevention and detection controls in place.

For microbial and viral risk assessments, this list of controls is lengthy. To document the current practices, the facilitator is commonly reliant upon the SMEs to provide detailed descriptions of how gowning occurs, the aseptic technique training, equipment cleaning, etc. The most effective means of sharing this information would be for the CDMO to share the governing standard operating procedures (SOPs) with the risk team. When SOPs are not shared, the risk assessment process is delayed while discussions about "current controls" and "anticipated future state" are merged and indistinguishable. Determining the "truth of record" becomes an art form. The facilitator must find ways of asking questions that are open ended enough to allow for dialogue and questions that are "closed" enough without being accusatory.

The risk assessment cadence is often driven by the level of trust between the biopharma company and the CDMO during the risk assessment. For example, when there is a low level of trust, the assessments can progress very slowly and data is not shared readily. When the teams have a mature level of trust, the assessments are smoother and there is less "back and forth" in understanding the current operating structure. Despite the speed of the risk assessment, through the process the two parties learn more about the critical portions of the process and understand one another's perspective more clearly. The detriment is often to the reputation of the quality risk management (QRM) process — teams can walk away from the assessment with a negative opinion of the risk management process and associate it with disagreement, confusion, and repetition. However, the QRM process is what assists us in a structured way to dissect a difference of opinion and to examine complex processes from a common foundation. By implementing some of the tips listed below, you can preserve your business relationships with your CDMOs, as well as your perspective on effective quality risk management processes.

1. Establish up front (and remind each other often) that the ultimate goal of the partnership is for the betterment of the patients. Keep this reminder visible and at the foundation of the relationship.

2. Acknowledge that both parties have different risk thresholds. Find the intersection between the two perspectives and use that as your guide in decision-making.

3. During quality agreement negotiations, develop a list of risk assessments in which both parties will participate. Define risk communication mechanisms in the quality agreement.

4. Have a candid discussion about how documents will be shared and the level of transparency expected by both parties.

5. Ensure that leaders from both parties are aware of joint risk assessments. Invite them to the kickoff session to participate in foundational conversations about the risk assessment objective.

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BOOSTING PIPELINE ACCELERATION WITH A STRATEGIC PHARMA/CDMO RELATIONSHIP

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Anyone who has driven down a mid-city avenue while running late for an important meeting knows the rush of relief that's felt when all the traffic signals ahead are synchronized to green. It's the same sensation a portfolio manager (PM) gets when all the bars in a Gantt chart fall into place to create an accelerated project timeline.[1] Achieving synchronicity in early development requires a high level of agility and coordination across multiple technical functions. Many cities strive to achieve this smooth continuous flow to their traffic patterns. *"Traffic Signal Synchronization is a traffic engineering technique of matching the green light times for a series of intersections to enable the maximum number of vehicles to pass through, thereby reducing stops and delays experienced by motorists. Synchronizing traffic signals ensures a better flow of traffic and minimizes gas consumption and pollutant emissions."*[2] PMs strive for the same level of coherence, coordination, and efficiency in driving the maximum number of programs toward the clinic in the shortest amount of time possible.

Availability of clinical manufacturing capacity can be a rate-limiting factor for early pipeline programs. Without diligent capacity utilization forecasting, scenario planning, and adherence to platform processes, pipelines can quickly become derailed by the often-turbulent dynamics of early development. Furthermore, to hedge against these dynamics, PMs will often stack pipelines with more and more candidates. While these factors present a challenge to internal resource and capacity management, they create an opportunity for PMs and CDMOs to seek more strategic modes of working together.

A recent Outsourced Pharma editorial by Louis Garguilo, *"Big CDMOs Back on Emerging Biopharma Radar,"* provided insight into how Deborah Choquette and Joanne Beck of Boston Pharmaceuticals made their selection of a strategic CDMO partner. Among the criteria mentioned in the article were the CDMO's desire "*to work with us in a real partnership scenario*," as well as having the needed capacity, resources, and project

management capabilities. An earlier article, *"Inflation Bites Biopharma in the Outsourcing Budget,"* hit on another critical need for both small and large pharma alike – flexibility. Beck emphasized, "'*Penciling us in' with a letter of intent versus a down payment is so incredibly helpful. I don't want to miss this point*." Flexibility is a critical differentiator in the topsy-turvy world of early phase portfolio management.

Whether centralized technical functions in a matrixed clinical development organization for big pharma or decentralized functions spanning a virtual development network of service providers for an emerging startup, each functional node is akin to a traffic signal along the development road. The PM's aim is to keep all nodes engaged in the highest value activities in such an orchestrated way that no efforts are wasted, and all resources are aligned to the priorities of pipeline acceleration and, more importantly, *pipeline advancement*.

Each functional node along the clinical development continuum has its own rules that dictate its capacity to perform work. These nodes include cell line development, cell culture process development, purification process development, analytical methods development, formulation development, scale-up, tech transfer, GLP tox supply, GMP manufacturing, and clinical supply management. The rules include cycle time, number of concurrent projects that can be accommodated, and other node-specific constraints that limit throughput. In an ideal situation, all capacities would be matched and cycle times synchronized to enable a continuous flow of candidates through the development pipeline. In practice, this is rarely the case, and the workflow is subject to operating in *fits-and-starts* as portfolio dynamics take their toll and cause priorities to shift and work plans to change.

The crux of such a resource planning challenge might be an overabundance of seemingly good ideas to test in the clinic that outstrips the available capacity to accommodate such a workload. One obvious solution to this dilemma is ruthless prioritization to winnow the number of candidates down to what can best be accommodated by the available capacity. The dilemma persists when even the remaining highest priority programs simply outstrip capacity.

BALANCING OPERATIONAL EFFICIENCY & FLEXIBILITY WITH YOUR CDMO

There is an inverse relationship between capacity utilization and flexibility. The more tightly scheduled a manufacturing line is, the less opportunity there is for shifting its schedule to accommodate an early phase asset. While operational efficiency dictates that capacity be fully utilized, the needs of clinical development are best served by the agility that comes with excess available capacity. Herein lies the opportunity for pharma/biotech PMs and CDMOs to work together more strategically and flexibly.

Pharma/CDMO relationships can range from the transactional-based contractual agreement for a single candidate to a strategic service level agreement that allows for greater levels of flexibility. Just as there is a need for internal client capacity management to leverage the benefits of platform processes, it is critical that a strategic CDMO position itself to become a like-for-like interchangeable option for its client partner. The major commercial CDMOs have become successful largely through *operational excellence* and *efficiencies of scale*. As mentioned in the articles cited above, some major CDMOs are adopting more flexible models to accommodate early pipelines. Smaller clinical phase CDMOs are also well positioned to achieve success through offering low-cost readily accessible capacity to augment a client's internal process development and manufacturing capacity.

The benefits of a strategic pharma/CDMO relationship are numerous. The most critical factor of any such relationship is literally that – *relationship*. By leveraging a single partnership to meet the needs of early phase clinical development, the two partners can build trust and confidence in each other's abilities to deliver on their promises. In making a shared commitment to each other's clinical demand and manufacturing capacity, the joint team can open themselves up to dynamic forecasting and scenario planning to best anticipate sudden changes in clinical demand.

Cost management is always a key consideration. Here again, CDMOs have an opportunity to provide a cost competitive option in the *make-versus-buy* equation for their customers. Labor and capital are significant cost drivers. While large pharma is constrained by internal labor equity and facilities built to premium construction specifications, a CDMO can leverage *phase appropriate* investment in capital and serve as a training ground for early

career talent. However, neither of these cost savings strategies can be allowed to compromise product quality or operational excellence. Indeed, when effectively managed, they can become enablers of both.

Establishing a truly strategic partnership requires that the pharma/biotech and CDMO work together to position the relationship to offer a strategic advantage to *both* parties. By augmenting a pharma's internal clinical development capacity, a CDMO can greatly enable early phase pipeline acceleration. By being open and collaborative with a CDMO, PMs can secure a greater number of options in their quest toward synchronizing all the development stoplights to green.

By externalizing a portion of process development and manufacturing capacity management, the incremental cost of development for pharma shifts from a fixed cost with fixed capacity to a variable expense with scalable capacity. This type of hybrid internal/external capacity arrangement can enable PMs to absorb transient surges in clinical demand or achieve a greater balance of internal workload for resources that might be delivering beyond their designed capacity.

There are two dimensions to the traffic signal synchronization conundrum:

1. the volume of traffic, and
2. the management of the signals.

Extending the analogy further, the aim of the pharma/biotech PM is to put high-performance vehicles on the road, i.e., candidates in the pipeline that can effectively accelerate through the signals and make it to their pivotal trial destination. By working together in strategic partnership, PMs and CDMOs can better manage the flow of pipeline traffic, allowing a biopharma to flex its capacity needs with greater agility and get more candidates to their intended destinations in less time.

REFERENCES/NOTES

1. "Portfolio manager" here refers to the aggregate of therapeutic area and functional leaders responsible for managing a company's pipeline of emerging clinical candidates.
2. https://www.cityofirvine.org/signal-operations-maintenance/traffic-signal-synchronization

ABOUT THE AUTHOR

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SHARED QUALIFICATION AUDITS: A WIN-WIN-WIN APPROACH

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In November 2021, the FDA published an update to the Resiliency Roadmap for FDA Inspectional Oversight, sharing the agency's success in grappling with the impact of COVID-19 on domestic and foreign inspections and its effective use of remote interactive evaluations to support surveillance activities.

Throughout the pandemic, the agency has demonstrated more than ever the value of using a risk-based approach to inspectional activities, which must be embraced and mirrored in industry when it comes to supplier and vendor audits, especially by early-stage pharmaceutical companies.

ARE QUALIFICATION AUDITS REQUIRED FOR PHASE 1?

Qualification audits are not explicitly required as per the FDA's cGMP guidance for Phase 1 investigational drugs but are generally considered a best practice in the industry. For early-stage pharmaceutical companies, qualification audits are the outset of GxP activities and are carried out prior to the start of Phase 1 clinical studies. Generally, sponsors will perform qualification audits of the CDMOs and CROs they intend to work with. However, unlike Big Pharma, where qualification audits are used as part of the vetting and selection process, qualification audits for early-stage companies are conducted post selection and contract negotiation and are used to validate the selection made and evaluate the compliance of the vendor's quality system against regulatory requirements and industry standards. These audits are also used to establish rapport with the vendor and discuss project-specific requirements and how these are to be executed as per the vendor's systems, processes, and controls.

It is common, and value-added, for these audits to be performed by sponsors' quality assurance consultants, who are also involved in the day-to-day quality and compliance oversight of the vendor. When the auditor is familiar not only with the vendor's facility but with its staff and procedures, the business relationship is furthered and efficiencies are gained.

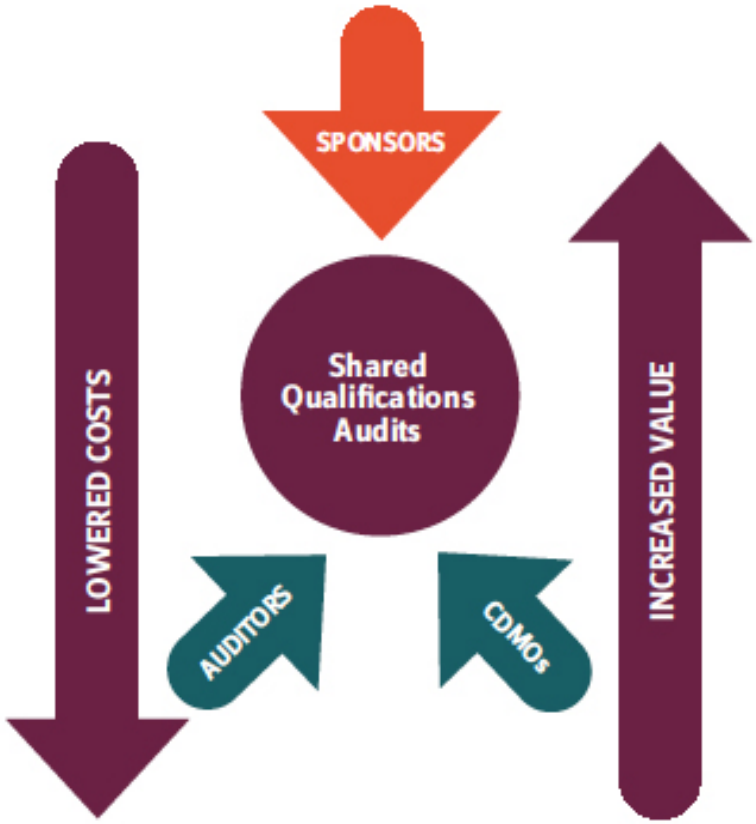

Figure 1: *Shared responsibility for increased adoption of shared qualification audits*

WHY AUDIT?

Sponsors strive to work with CDMOs that specialize in early-stage development and manufacture for delivery of cGMP drug substance, intermediates, and drug products in record time. These CDMOs offer the technical know-how, flexibility, and speed needed for the early stage paired with a phase-appropriate quality management system that can support the changes, deviations, and optimization expected when non-validated processes are scaled up from the lab to the plant.

It is noteworthy to mention that CDMOs that specialize in early stage and do not manufacture commercial products are exempt from registering with the FDA as per 21 CFR 207.13(e) and are therefore not subject to regulatory inspections on a regular basis.

Without regulatory oversight, risk emerges, making it imperative for the sponsor to evaluate the CDMO's compliance and ensure adequate systems and procedures are in place for the performance of the contracted services. Thus, qualification audits become an integral part of the sponsor's vendor oversight and the CDMO's continuous improvement programs.

SHARED QUALIFICATION AUDITS ARE A WIN FOR ALL PARTIES

Auditors may at times be asked by more than one sponsor to perform qualification audits of the same CDMO. Unlike requalification audits, where the focus is to verify product-specific requirements are being met and performance of contracted services is in line with the quality agreement and statement of work, qualification audits are generic and lend themselves to being "shared" by sponsors.

Shared qualification audits provide a cost-saving alternative for sponsors by opening the possibility of the splitting of expenses associated with the audit, and for CDMOs by reducing the resource-intensive cost of hosting multiple audits. Depending on the size of the CDMO, resources used to host and manage sponsor audits may not be dedicated, which can take a toll on the availability of quality assurance staff and other functional heads to focus on operational needs and priorities. By establishing best practices for the sharing of audits, the sponsors, the CDMOs, and the auditors can position themselves for successful and more rapid adoption of this value-added trend.

SHARED AUDITS ARE CURRENTLY AUDITOR-DRIVEN

Once the need for a qualification audit is identified, the auditor can generally determine if the opportunity exists for the audit to be shared among sponsors. Key factors to be considered are the scope of services to be covered by the audit, the standards being audited against, and when the audit needs to be performed.

If all factors support the opportunity for sharing the qualification audit, the next step is for the auditor to confidentially approach the parties involved and inquire if there is interest in pursuing this alternative. It is recommended they approach sponsors first, separately, and explain how shared audits work and the benefits they provide. Once sponsors are comfortable and in agreement with pursuing a shared audit, the next step is to contact the audit host and discuss the logistics. It is important to ensure the audit host is amenable to accommodating a shared audit and agrees on specifics related to issuance of each sponsor's audit report, findings, and requests for sponsor-specific responses, to maintain confidentiality throughout. In my years of experience as an auditor, CDMO audit hosts are generally familiar with and welcoming of shared audits and are agreeable to host these across two or more sponsors, where appropriate.

REMOVING BARRIERS TO INCREASED ADOPTION

Over a decade ago, a somewhat similar approach was explored for excipient manufacturers' audits, given their extensive use across the industry. Sizable efforts were made to establish and harmonize excipients' GMPs and make a case for "purchasable" audit reports of excipient manufacturers. However, this did not catch on in the industry as expected.

Although shared audits are becoming more prevalent since the onset of the COVID-19 pandemic (given the added flexibility that virtual and hybrid audits bring to the audit table), the adoption of this trend in the pharmaceutical industry has been slow and is far from where it could be. For CDMOs that host anywhere from 50 to 100+ audits per year, a handful of shared audits does not drastically impact the extensive resources required to manage multiple audits on a weekly basis. The increase in adoption of shared audits is a shared responsibility that reduces auditing costs and increases value.

For starters, CDMOs must take a more active role in championing the feasibility and benefits of shared audits, endorsing and proposing these where appropriate, while exploring suitable avenues for the sharing of audit information. Their amenability to open their doors to auditors representing multiple sponsors must be recognized, as well as their interest in pursuing creative arrangements with independent auditors for generic qualification audits.

In addition, sponsors can support the adoption of shared qualification audits by educating themselves on what these are and being open to the benefits they provide, while being reassured that confidentiality is at the forefront of every auditor's professional ethic.

Lastly, auditors must continue to spearhead the adoption of shared qualification audits where possible. By liaising between CDMOs and sponsors, auditors are in the privileged position to continue to develop best practices and increase the visibility of these audits and the value-add they provide to early- stage pharmas and the industry at large.

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A BETTER PATH FOR CMO RELATIONSHIPS AS THE PANDEMIC CONTINUES

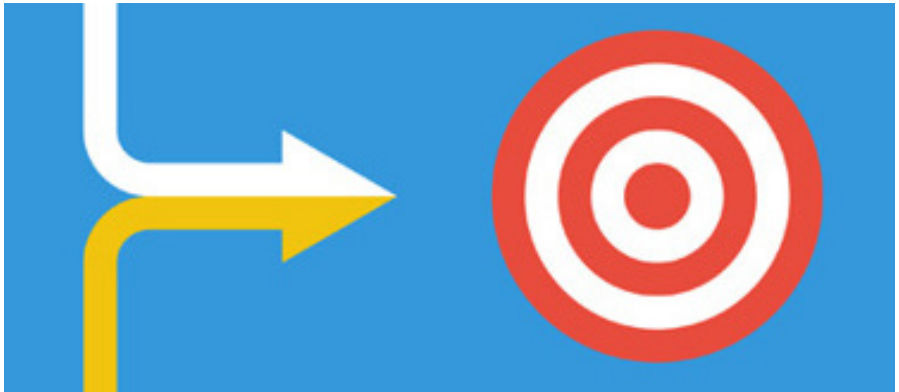
Ajay Pazhayattil
VP, Regulatory Affairs & Compliance, Capcium Inc.

The successful vaccination drives in the U.S. and other countries were backed by the incredible efficiency in COVID-19 vaccine production. It is time to recognize the diligent efforts of the individuals employed at material suppliers and CMOs who worked through the peak pandemic months just like frontline healthcare professionals.

The immediate future now presents opportunities with the launch of new streams of biopharmaceutical product pipelines. CMOs are creating manufacturing capacities based on newly emerging treatment pathways and practices of medicine. While it is an exciting time of expansion, commissioning projects during a restrictive atmosphere presents challenges. Here, we discuss how drug sponsors and service providers can work together to continue down the path of outsourcing success.

CMO SUCCESS FORMULA

The 2020 McKinsey survey, "COVID-19 And Cell And Gene Therapy: How to Keep Innovation On Track," identified attributes such as regulatory compliance, awareness of customer requirements, segment experience, industry reputation, cost, and assurance of safeguarding IP as the top factors for choosing your CMO. Post engagement, attributes such as transparency, responsiveness, and meeting delivery commitments become important as well. Informed CMOs put in immense efforts to go above and beyond client expectations on the listed attributes. To meet these client desirables, CMOs are developing capabilities that provide high flexibility with a higher degree of automation. Employing customer transparency technologies and maintaining high customer satisfaction are priorities. Processes are available for CMOs to ensure integrity of data, proprietary data privacy, and security. Maintaining a steadfast CMO industry reputation is achieved through attributes such as quality of



work, reliability, etc., and it also depends on the organization's success in being relevant by continually innovating and showcasing those manufacturing innovations at major industry virtual events and webinars and in publications. Competitive costing of CMO services is becoming commonplace, requiring agile costing models and options. Differentiating themselves and offering value-added services, developing payment models, and providing dedicated client support are other activities CMOs are focusing on.

The FDA has published recommended quality metrics for drug manufacturing, such as LAR (lot acceptance rate), PQCR (product quality complaint rate), and IOOSR (invalidated out-of-specification rate). Whether or not the FDA intends to make reporting mandatory and publish them, such metrics can now be mandated by clients. CMOs, in order to successfully meet such metrics, are automatically obligated to maintain quality cultures, high compliance, and integrity. Checks and balances to minimize compliance risks and maintain operational excellence and strategies to maintain high service levels are built-in traits of CMOs targeting high facility EBITDA.

BEING A TRUE PARTNER

A CMO provides its manufacturing services amid varying levels of customer expectations. Clients can range from clinical to commercial organizations. To be effective, client points of contact must be aware of the CMO's multiclient, multiproduct operational circumstances. Constantly being cognizant about the boundaries goes a long way in solidifying the client- CMO relationship. CMO departments are normally mandated to allocate project hours to a specific project activity. Hence, preplanning sessions for smart use of your CMO's interaction time and tracking of those interaction sessions can be effective in improving efficiency of knowledge transfer activities, when required. Agreements need to establish the number of on-site visits/audits. However, added layers of compliance monitoring can disrupt operational efficiency as CMOs do receive a large number of pre-engagement and routine client audits in addition to the mandated regulatory audits. Rather, clients may consider a full-time person-in-plant working side-by-side with CMO employees for specific phases of a project. Client organizations increasingly use consultants for CMO management, which can cause an added layer of complexity. In cases where more parties are involved, the delivery timeline metric should be carefully monitored so those delay factors are captured.

The CMO's activities involving a range of diverse projects provide an excellent opportunity for CMO employees to gain valuable experience. The fast-paced nature of the CMO's work develops SMEs, but they get very little opportunity to reflect on how their contributions help in bringing critical medicines to the market. Presentation sessions providing product insights and direct-to-employee gratitude events at your CMO's site will be highly appreciated by the employees. It is important to establish an incentive plan as soon as you engage with a CMO. For example, organizations that perform consistently on product quality, delivery, responsiveness, etc. need to be significantly rewarded with more autonomy, such that it results in further excellence benefiting the product. Your CMO and its internal resources are your manufacturing quality and operational excellence SMEs that you need to rely on.

A lot of planning goes into making a single batch of product. For instance, a fill/finish operation includes timely sourcing of raw materials and components, line scheduling, storage, change parts, cleaning, testing, documentation, training, resource planning, assuring utility availability, calibration, qualification, gowning, maintaining room grade, dispensing, formulation, sterilization, filtration, transfers, environmental sampling, testing and monitoring, filling, primary packaging, controlled chamber storage, secondary packaging, inspection, decontamination, waste management, and cold-chain shipping activities. Since aligning the activities and executing the manufacturing steps involves meticulous coordination, swift batch injections and last-minute change orders from clients can affect the operational performance level of the entire facility, thus impacting other client products. CMOs develop SOPs that are fit for the facility's activities. They may not always align with client procedures. The procedures are, however, designed to meet regulatory and general client expectations. Client-specific procedures for general activities may be developed if necessary; however, that comes with the risk of failure to execute, especially if the execution is nonroutine. Critical failure investigations are handled and justified per CMO procedures. When additional testing or more time for investigations is needed, providing the CMO with a batch order for a nonimpacted process/product line will be desirable. When needed, a client's technical team's hands-on involvement during brainstorming and root cause analysis is certainly an advantage. While the CMO leads the investigation, any support, such as statistical data analysis

and external testing, may be provided to accelerate investigation completion and establish the findings.

Just like monitoring a CMO's performance, it is also important for the client to gauge the performance of its own internal point of contacts. The source data for such assessments should be routinely (anonymously) sourced from your CMO partner. Special attention may be given to aspects such as the expertise level on the activities performed, responsiveness, input and collaboration, cycle time, and engagement etiquette. Such data can help in developing and maintaining an effective external manufacturing operations team.

ACKNOWLEDGE YOUR CMO'S CAPABILITIES

The CMO's documentation and data are your evidence of successful batch execution, which is available for regulators' verification during submission or on-site inspection. Developing a cordial give-and-take relationship with your CMO is critical. Supporting the CMO's teams in the ways mentioned in this article yields positive results. Continually communicating the importance and value of the product manufactured at the CMO and building employee ownership of the product and process have been seen to be effective. The goal should be to focus on patient safety and efficacy, followed by compliance, since CMOs must assure regulatory compliance for their own continued existence. Acknowledgement of your CMO's management of diverse lifesaving products and clientele will lead to developing approaches that support their operating model. Rather than taking non-issue CMOs for granted, developing incentives for such performers can only create a special affinity and encourage them to maintain their service levels.

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POST-COVID SUPPLY CHAIN OPPORTUNITIES AND STRATEGIES FOR BIOPHARMAS AND CDMOS

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The COVID-19 pandemic exposed the dependence on global supply chains, as well as the limited domestic manufacturing capacity in the U.S. for critical medicines and medical devices. Recurring drug and medical device shortages and quality issues related to offshoring also have encouraged U.S. commercial customers to purchase from domestic manufacturers. The government policy response has been an intense focus on building up domestic manufacturing capabilities.

Recent executive orders from the Biden administration, as well as proposed or pending legislation, have focused on boosting supply chain resilience to address national security, public health, and safety concerns, both now and for the future.

For biopharma execs engaging with CDMOs, rethinking domestic manufacturing goes beyond supply chain evaluation. Leaders should address three main areas to holistically assess their global operating model.

HOLISTICALLY ASSESS STRATEGY AND PORTFOLIOS

Biopharmas and their CDMOs should take a holistic view of the potential redirection of drug purchasing by government and commercial customers to domestic manufacturers, to understand how it impacts their revenue and margin. Biopharma executives should consider asking: What product-level revenue and margin are “at risk” to competitors with domestic manufacturing capabilities? What new sets of risks and opportunities are created with the prospect of domestic manufacturing capabilities? How will a reshoring or nearshoring effort affect our current investment road map and capital allocation strategy? And how does the company prioritize investments in new assets, capabilities, processes, and technologies to achieve its operating model strategy (build vs. buy vs. partner)?

Numerous factors should be considered, including strategies around the industry's shift toward large molecules, biologics, sterile injectable, and potential opportunities to accelerate and include domestic manufacturing as an enabler. Other considerations include changes in federal and state government purchasing requirements, competitive domestic manufacturing capabilities, and market share growth opportunities by product.

Executives should also examine existing product-level manufacturing and supply chain cost trade-offs, product portfolio strategy, launch plans and financial forecasts, and manufacturing capacity and partnerships with CDMOs, as well as alignment to growth strategy, capability road map, and M&A opportunities.

ANALYZING SUPPLY CHAIN AND MANUFACTURING OPERATIONS

Trying to reshape a supply chain that took decades to build will be a complicated and expensive process. The economic costs of reshoring active pharmaceutical ingredients and finished product manufacturing are likely to be significant; reshaping the strategic architecture of the global supply chain also can create increased operating expenses in the future. When trying to redesign the global supply chain and examining CDMOs, biopharma executives should consider asking: How can we minimize the cost impact from exiting current supply sources and potential disruptions? What other risks do we need to consider and mitigate? And how can we transform at speed and still build value-led sustainability?

Biopharmas should analyze supply chain operations and costs and be prepared for structural shifts. Leaders should have a clear understanding of the complexity of the global value chain, the impact to current trade flows and fulfillment capabilities, and what new technologies and processes may be required to facilitate domestic manufacturing. Additionally, executives should map out necessary capital investments and the timeline to upgrade or build new facilities, plan exit strategies from existing supply sources and potential disruptions, and explore incentives from federal or state governments and price/volume support to achieve scale economies.

TAX, TRADE, AND POLICY CONSIDERATIONS

Many biopharmas have leveraged their internal manufacturing capabilities and CDMOs to develop complex tax-efficient supply chains that encompass a global operating footprint. While it is not yet clear what will become law, proposed international tax law changes should be evaluated against the impact on a company's existing and future operating model. Tax executives in biopharma companies should ask: Is the current legal entity structure and intellectual property (IP) ownership impacted by potential legislative changes? How would a change in manufacturing location and/or manufacturing outsourcing alter the company's tax position or tax controversy risk? Are there any potential tax costs associated with exiting current manufacturing locations? Are there any incentive programs that should be evaluated?

Areas of consideration include U.S. tax deferral position if using CDMOs, transfer pricing model sustainability, and impact to value drivers; impact to existing incentive regimes and potential clawbacks; location- and activity-based federal programs; and competitive state and local discretionary funding.

Current geopolitical and economic trends may favor a move to domestic manufacturing, but these considerations must be weighed against any financial costs, transition risks, and effect on future manufacturing flexibility. Biopharma executives should use this opportunity to holistically examine their global operating model, including their CDMOs, beyond supply chain considerations. Consider the following preparatory measures to respond better to further government policy development and the potential redirection of drug purchasing to domestic manufacturers:

- Assess feasibility across your portfolio and the opportunity for enhancing domestic manufacturing.
- Evaluate the complexities and capabilities required to support domestic manufacturing imperatives.
- Understand the value of "revenue at risk" and margin impacts.
- Benchmark anticipated incentive offers.
- Create optionality based on possible scenarios.
- Identify potential tax implications and exit costs.

By broadening the focus and examining relationships with CDMOs, biopharma companies can work to achieve competitive positioning and protect revenue at risk.

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