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# Best Practices for Designing and Building a Pharmaceutical Manufacturing Facility

February 1, 2021 <u>Allison Cacciatore</u> Page Number: s19-s21



For drug sponsors that are considering building their own manufacturing facilities, an expert project team is crucial.



To achieve delivery of a facility that operates at design capacity upon handover, there is a dual-pronged approach to consider: the facility and the product. Drug sponsors want to bring new products to market as quickly as possible to reach patients and positively impact lives. The current speed of new product drug discovery by many companies simultaneously creates a pace of market competition that does not allow for

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delays. Historically, contract development and manufacturing organizations (CDMO) have been a good option for bringing products online quickly, but new product demand is outpacing even this capacity, leading drug sponsors to choose building their own factories as a faster avenue to the marketplace. When relying on CDMOs, drug sponsors can focus on the drug product and drug substance; however, when choosing to build their own facilities, the process characteristics and facility design are both critical and must be tied together to achieve success.

## In-house or contract manufacturing

When deciding between using a CDMO or one's own facility, several considerations exist that take into account time and available resources. It is best to have vertical integration when a new product has the potential to become profitable and successful over a short time interval. Other considerations are when time to market is of the essence, coupled with limited CDMO availability and the possibility of capital investment. The advantages for owning one's own factory include drug sponsors having control over business priorities from project execution through manufacturing and maintaining ownership of product and process aspects as a core competency. It also provides self-reliance for all aspects of delivering product to market; the drug sponsor chooses the priorities of the teams that are making and releasing product. The drug sponsor does not need to have concern about another customer of the CDMO taking priority over their product or having to navigate the CDMO with their own person-in-plant acting as an advocate. Building one's own factory puts the control over business priorities from project execution through manufacturing directly into the drug sponsor's hands. This control can be vital to the successful launch of the new venture; however, with a capital investment, focus must shift from simply producing goods to the design and oversight of a best-inclass facility.

#### Regulatory Action

#### Supply Chain

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A product in early phase needs to evolve to be usable for commercial manufacturing. What is done in lab scale for early-phase trials is not scalable without significant impact to the operation or to the manufacturing environment. Hand manipulations on a tabletop in a good laboratory practice environment must mature to a fully characterized process that will likely be automated by Phase III to commercial launch and full-scale production. The requirements for lab facilities, including environmental monitoring and frequency, are substantially less stringent than full-scale good manufacturing practice (GMP) manufacturing. GMP facilities require, for example, cleanable surfaces throughout the facility; walls or floors with coved bases; step down between room classifications; segregation between personnel and material entry and exit; or dedicated heating, ventilation, and air conditioning systems dependent upon biological classification.

Synchronizing process development with facility capability will result in a facility that can more readily realize design capacity upon startup. Appropriate project scope definition and priority setting can facilitate project execution and successful delivery. Current practices employed by drug sponsors have shortcomings that can be minimized with the proper effort and planning. For example, understanding the true performance criteria for the facility by using sufficient process data related to critical quality attributes of the product during design leads to improved decision-making and mitigates schedule delays. Examples of critical quality attributes range from hydrophobic or hydrophilic products requiring humidity control capability, or equipment performance characteristics such as what process gases are required and ensuring that those gases are available in the production suites.

## Creating a team

Although no amount of planning can fundamentally eliminate all risks, evaluating the needs of the project team, including both team size definition and composition, early in the process can prepare a project for its best trajectory for success. A project team will include a project manager and team members needed for executing design, construction, fit out, and testing to start up the facility. Problems that arise can be remedied early by providing adequate resourcing to accomplish timely decision-making when chance events occur. In addition to having an experienced project leader who is skilled at consensus building and conflict resolution, a key concept for success is to have the same project team members throughout the project lifecycle to provide continuity. When project team members understand the nuances of the drug substance and drug product as well as the requirements for facilities, they will keep the project moving ahead in a linear direction and not fall victim to rework.

Additionally, oversight by drug sponsor leaders who possess the appropriate expertise and dedicated bandwidth to focus on the project is extraordinarily valuable. By using the leadership's expertise to establish key project success metrics associated with decision making throughout the project, and early definition of key considerations such as factory flexibility and time to market, project goals and team members will be aligned, and project trajectory will be linear. For example, using tools such as decision trees and a methodical approach will align to structured decision making which, in turn, will drive results. Project oversight by leadership will keep things moving in the right direction, as long as that leadership is committed to the success of the project and has backed the decision-making process where the new facility was chosen in lieu of using a CDMO.

# Facility design decisions and risk

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As the design of a new best-in-class facility unfolds, drug sponsors find themselves facing many decisions that are similar to the criteria that would be used to choose an appropriate CDMO, but they also face additional decisions that include a clear understanding and early definition of business performance drivers, such as supplychain considerations and amount of risk tolerance. It is important to consider ----

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Rather than relying on others to perform manufacturing processes, the drug sponsor must now monitor the course of the project and make decisions along the way to stay on track to guide the project to on-time completion.

# Single purpose or polyvalence

The initial project definition must include performance characterization and operating assumptions such as whether the facility will be product-specific or a flexible model for multiproduct use. With a traditional singular design, the path is more straightforward. Process definitions will need to be clear, including accurately defined and appropriate critical quality attributes and critical process parameters to provide the quickest path to project completion. Conversely, if the process is ill-defined at project inception and the trajectory for final product in unknown or still not well defined, a flexible facility could be the best choice. The agile nature of a flexible facility lends itself to easier changes in use as the product and process definition matures.

Whether the choice is for a nimble, flexible facility or a quick, traditional facility, keeping in mind operational readiness activities from early-project phases onward over time will be advantageous at project completion. Activities including items such as defining the quality management system, writing standard operating procedures, and preparing facilities maintenance inventory will minimize impact and prevent delays during start up by integrating these and similar activities into the overall project schedule.

Value engineering is an organized and systematic approach to examining required functions in a project and their associated cost. The key to successful value engineering is to reduce cost without sacrificing quality. Another advantage throughout the project design phases is executing value engineering as a trade-off exercise during the programming phase, which proves more valuable than as a point-in-time exercise during the project detail design phase. Lifecycle implementation of value engineering then can be viewed more positively by the project team and not seen as simply a cost-cutting measure by ensuring that selected low cost options still provide high value.

# Collaboration and leadership

Throughout the life of the new building project, the team itself becomes crucial to project delivery. From effective leadership to accurate communication, project success is a collective effort between the project team and drug sponsor whose goal is getting product to market. The project plan and schedule must contain accurate requirements for regulatory approval based on the defined differences between clinical manufacturing and commercial manufacturing of the product. This will require that the team understand and remain focused on those changes so that they are effectively incorporated into the new facility design and implementation. This will lead to the volume of supply being at design capacity at startup and not requiring rework when the project is handed over to manufacturing operations.

Success hinges upon considering performance definitions and operating assumptions throughout the project lifecycle that in turn will lead to seamless

project execution. When facilities meet design criteria at handover, their products save money and reach patients faster. Keeping focused on the synchrony between process and facility throughout the project can lead to optimal project execution and may prove one's own factory is the best choice.

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# Reshoring Pharmaceutical Manufacturing to the US: Can We Do It?

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Advanced manufacturing technologies are available, but challenges need to be addressed.



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The application of innovation strategies often achieves a business' competitive advantage. One definition of innovation is either doing different things or doing things differently (1). In the past few decades, creating new ways of doing business has encouraged global corporations to look at competitive scenarios that provide lower-cost advantages. The innovation strategies designed to achieve cost improvements

included business orchestrations or alliances, outsourcing, supplier leverage, and the offshoring of companies' manufacturing activities to either lower tax or lower labor cost jurisdictions (2,3).

As demonstrated by recent experience during the COVID-19 pandemic, despite the expectation of providing a company with competitive advantages, the risks of extensive offshoring likely surpass its benefits (4–6). The pandemic showed that the potential impact of commerce disruptions on the worldwide supply chain of goods sold is a significant risk element of offshoring strategies. Moreover, other supply chain disruption events such as geopolitical situations, as well as other business risks such as competencies and knowledge loss, brand damage, or deficient intellectual property protection policies of manufacturing recipient countries are significant sources of risk to weight against offshoring benefits (2,5,7). Specifically, regarding pharmaceutical products, the risks of disrupting the supply chain are much deeper than simply financial; literally, tens of millions of patients in the United States and abroad depend critically on reliable access to medicines to maintain quality of life, and in many cases, life itself.

Refocusing the innovation lenses, from offshoring to reshoring

In the light of the significant threat that a future geopolitical or pandemic event poses to the pharmaceutics supply chain, reshoring manufacturing activities is the right business decision both for business continuity and for national security reasons. The translation of both needs to a coherent and viable business model for pharmaceutical manufacturing depends upon our ability to establish a strong foundation of technology innovations. It is important to identify innovations that would support making a reshoring strategy successful, not only in the short term when supporting government policies are in place, but in the long term, when sustainability depends on profitability. Taking generic-drug pharmaceutical manufacturing as an example, the authors seek to propose a viable pharmaceutical