A Molecule's Journey

Built to Serve: Break Down Roadblocks to Commercial Manufacturing Success

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Built to Serve: Break Down Roadblocks to Commercial Manufacturing Success

A guidebook for today's biopharma executives outlining key considerations to help ensure commercial manufacturing success

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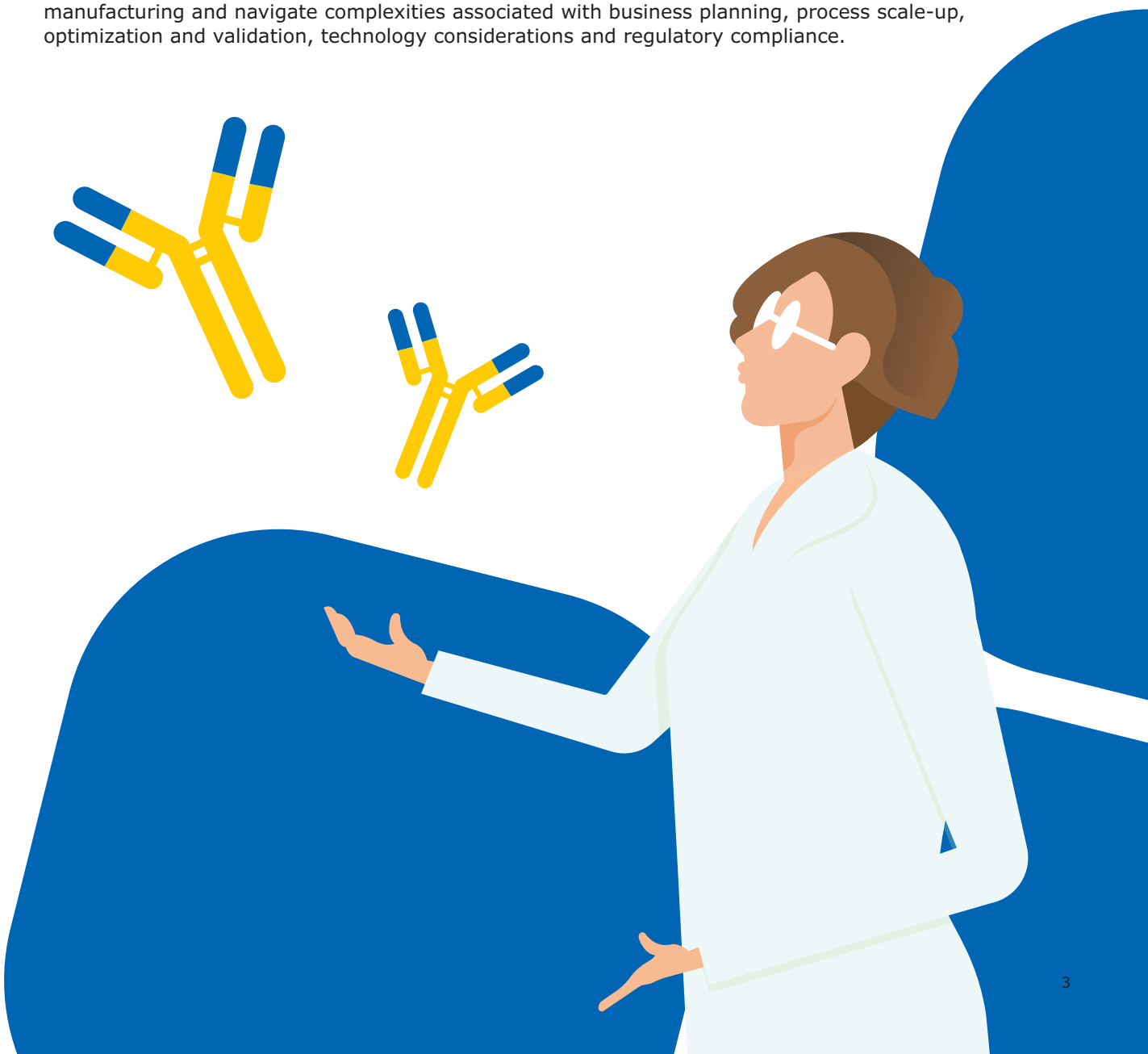
Selection and implementation of a commercial manufacturing strategy that will ensure long term success is among the most critical decisions a biopharmaceutical company will make.

Every drug is unique and there are many options and factors to consider when it comes to identifying the best approach to commercial GMP manufacturing. The right strategy must align with your organizational objectives and be cost-effective, deliver the necessary quantity of drug substance, reduce risk and meet regulatory expectations. In this guidebook, our experts share key considerations for biopharmaceutical companies as they advance to commercial manufacturing and navigate complexities associated with business planning, process scale-up, optimization and validation, technology considerations and regulatory compliance.



Business considerations

Outsource for Speed and Efficiency

Select the Best Partner

Evaluate Regulatory Expertise

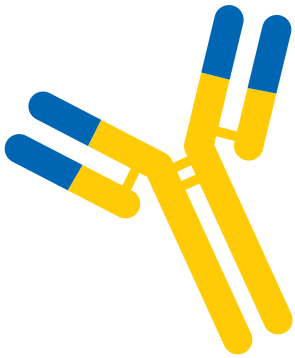
Outsource for Speed and Efficiency

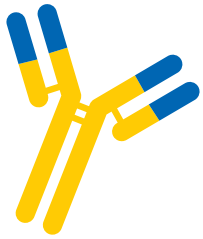
Several factors should be considered when determining whether to outsource commercial production of drugs and include the size of the molecule pipeline, filing strategies, the therapeutic indication of drugs and expected production capacity needs, visibility regarding production forecast and peak demands and the willingness of a company to take risks.

Outsourcing to an experienced contract testing development and manufacturing organization (CTDMO) can deliver significant advantages in terms of speed, flexibility and risk reduction. In cases where there will be limited market demand, such as that for an orphan drug, investment in a manufacturing facility may not be warranted. Similarly, outsourcing may be the best option when there is a need to move quickly upon receipt of a breakthrough designation or fast-track approval; a CTDMO partner can initiate large-scale production much more rapidly as compared to building or converting an existing facility. Outsourcing is also an effective strategy to reduce risk and maintain flexibility when the timing to get regulatory approval across multiple geographies is uncertain or is delayed.

Select the Best Partner

Once the decision to outsource commercial production is made, it is essential to select the right partner. This is a difficult and complex process and one that is vital to the long-term success of your commercial manufacturing. There are many CDMOs, but not all are equally suited to deliver against business and manufacturing objectives and timelines; such as the evaluation process which should start early and be rigorous. The first choice must be the right choice, as a mistake may become a risk for the viability of the entire company, not just for the therapeutic program itself.





Evaluation of CTDMOs should include assessment of many factors including, but not limited to, experience with molecules similar to that which will be outsourced, analytical capabilities, quality systems and availability of proven process templates. Another important consideration is to confirm that the CTDMO has the necessary capacity and flexibility in terms of availability of production slots. In addition to a broad range of expertise and experience, a strong working relationship with the CTDMO is a cornerstone of success and must be built on trust, transparency and a shared spirit of collaboration.

Evaluate Regulatory Expertise

The drug filing strategy is critical for commercial success and will dictate how your process should be developed and validated, which regulatory authorities will be reviewing the filing and who will be inspecting the facility where commercial production will take place. Given the complexity of the regulatory landscape, your outsourcing partner should also be evaluated in terms of their familiarity and experience with regulatory authorities and the number of filings they have overseen. To mitigate risk in this area, the CTDMO should have extensive experience with agencies around the world and the capability to support all aspects of compliance from drafting IND/IMPD/BLA/MAA submissions to post-approval. Importantly, your CTDMO should have a clear understanding of regulatory expectations, and according to the needs of your specific project, translate these expectations into proven risk assessment and risk mitigation methodologies.

process scale-up considerations

Ensure Continuous Supply

Accelerate Timelines

Define the Raw Materials Supply Chain

Ensure Continuous Supply

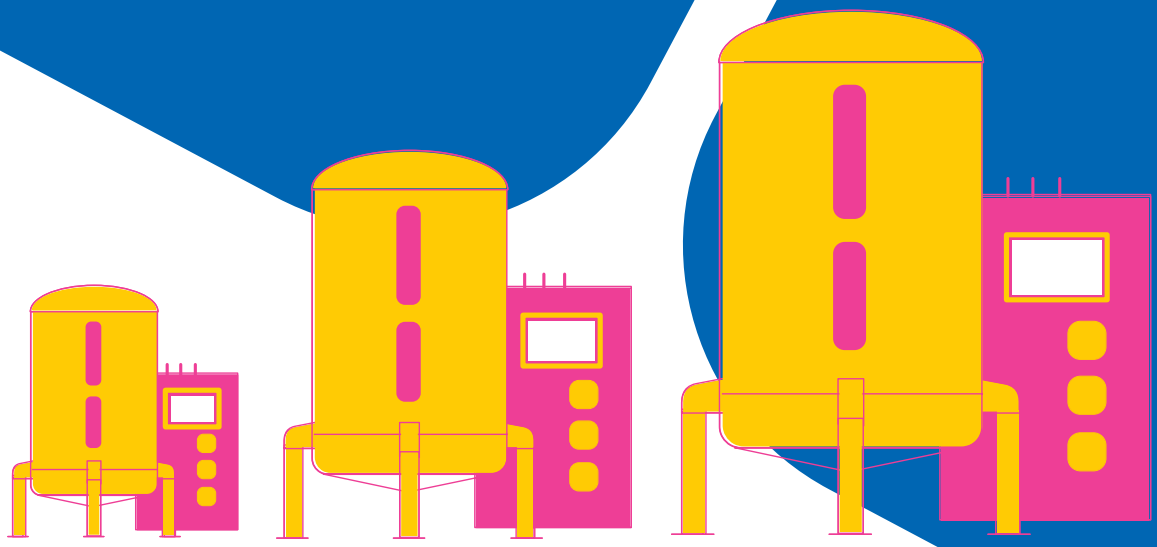
The goal of process scale-up is to quickly increase the quantity of drug produced per batch while maintaining the same product quality and minimizing risk. Scaling a process to commercial levels requires an understanding of the expected market demand for the drug and the necessary frequency of batch manufacturing to ensure continuous supply. Knowing the expected market demand facilitates identification of the batch size that will be used in production; scale-up runs can then be executed at that size, ensuring that all batches and data generated will be at full scale.

It is also important to ensure that the commercial process effectively maintains the critical process parameters and that the cost per gram of the drug will be reasonable for the targeted patient population. The ability to maximize the cost-effectiveness of a process relates back to leveraging a CTDMO with experience not only with similar molecular types but also the breadth of technologies that can be used to optimize process economics.

Accelerate Timelines

A typical scaling initiative takes a 3L process and increases it to 2000L with intermediate volumes and pilot runs. This stepwise approach can require up to three months, slowing progress towards important commercial milestones. Characterization and use of the same brand of bioreactors at different scales can accelerate this process while maintaining the same critical process parameters and ensuring safety, process efficiency and robustness. This approach provides a clear advantage in terms of time and cost and can be offered by a CTDMO with a portfolio of bioreactors ranging from bench to commercial scale.

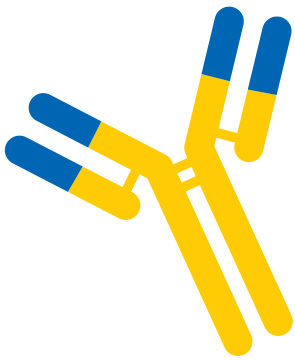
By leveraging a deep understanding of process dynamics and increasingly sophisticated technologies, process scale-up from bench scale bioreactors to commercial scale becomes more predictable, faster and consistent. Direct scale-up from bench to 2000L is enabled and can be performed within the timeframe needed for a fast track application or to supply clinical material quickly, such as that needed to address disease outbreaks. Elimination of these intermediate steps can significantly reduce scale-up timelines and save upwards of $1 million per molecule – accelerating the time to market and delivering a competitive advantage.



Define the Raw Materials Supply Chain

As a process scales to production levels, it is essential to ensure a robust supply chain is in place and all suppliers are qualified. A focused and strategic approach to supply chain management can help avoid possible drug shortages and mitigate the risk of man-made and natural disasters.

Key considerations include identifying the lead time for raw materials and equipment, use of multiple or dual-sourced suppliers to mitigate supply interruption and the need for access to detailed information when and where it is needed.



process optimization considerations

Identify Process Improvement Goals

Balance Target and Timelines

Understand the Impact on Validation

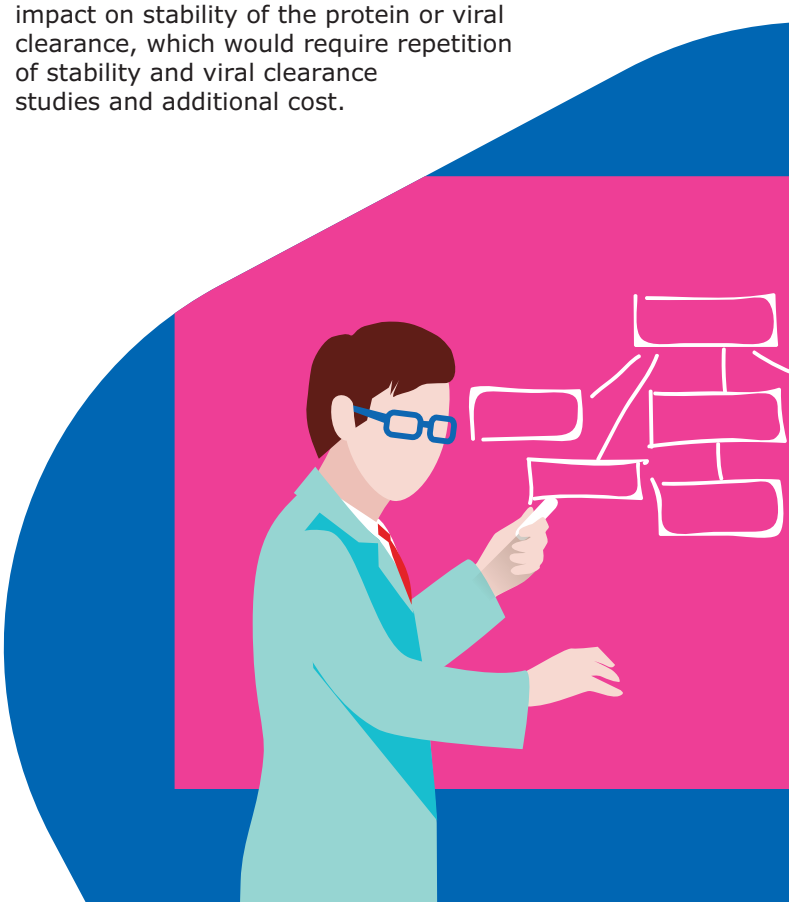
Identify Process Improvement Goals

The essential first step of process optimization is to determine the appropriate target based on a range of factors including anticipated market size, capacity needs, peak demand, clinical development and the drug filing strategy. Once the target is set, a gap analysis should be used to highlight the differences between the existing process and the process capable of delivering against that target and the route for improvements. The path forward can then be defined with recommendations for the optimal scale, scale-up strategy, timing and process performance requirements. Process improvements may focus on upstream activities, with a goal of increasing titer from the bioreactor or replacing a raw material of animal origin, for example. Or the focus might be downstream with a goal of fine-tuning process parameters such as columns changed to increase global yield or improve final purity of the product.

Undoubtedly, challenges arise during optimization. A CTDMO that has experience with a breadth of molecule types and processes will be able to offer valuable insights and apply problem solving acumen to deliver the necessary performance goals.

Balance Target and Timelines

During process optimization, an important consideration is how to strike an effective balance between the time and money to be invested in the existing clinical process versus the expected benefit. To achieve a particular target, a set of activities must be undertaken which will impact timelines and cost. In addition, optimization of one parameter may impact other parts of the process. For example, if a raw material is removed from the process, it may have an impact on stability of the protein or viral clearance, which would require repetition of stability and viral clearance studies and additional cost.



Ultimately, optimization should be guided by an understanding of which changes will deliver the highest value without causing a cascade of other necessary changes as a result. It is important to remember that the right level of optimization is not necessarily equivalent to highest or lowest extremes possible for the target.

Understand the Impact on Validation

In addition to the time and cost associated with optimizing parameters to reach a process-related target, removing or changing a step can impact process validation. These changes may render as obsolete some of the historical data collected at the clinical scale for process development and production. This impact on validation should remain top-of-mind when delivering against critical project timelines.

An advantage can be gained through use of outsourcing where a partner organization has oversight of a process from the earliest stages of development for clinical scale manufacturing – all the way through scale-up, optimization and validation for commercial scale. Hands-on experience with the initial stages of process development can help inform and accelerate efforts to optimize for GMP production.

process validation considerations

Consider the Product Life Cycle

Determine the Right Time

Apply a Risk-Based Approach

Consider the Product Life Cycle

Process validation is a critical step towards successful registration and commercial manufacturing. The main objective is to demonstrate that the manufacturing process is capable of consistently producing acceptable quality products within the commercial manufacturing conditions. A key consideration to keep in mind is that process validation involves a series of activities taking place over the lifecycle of the product and process. It should not be viewed as a one-time event or an activity performed just prior to commercial launch. This life cycle approach also helps ensure that regulatory authorities are confident that a process is consistently under control and can remain in control.

Determine the Right Time

A stepwise approach to process validation was published by the US FDA in 2011. This systematic approach provides a framework for ensuring that sources of variation are identified, understood and effectively controlled. Three stages are:

- Process Design: The commercial process is defined based on knowledge gained through development, scale-up activities and GMP clinical runs.
- Process Qualification: The process design is confirmed as being capable of reproducible commercial manufacturing. This step includes qualification of equipment, facilities and utilities as well as performance process qualification (PPQ) runs at commercial scale.
- Continued Process Verification: Ongoing assurance is gained during commercial routine production that the process remains in a state of control

A robust validation strategy includes these stages and also takes into account the expected time to market and any regulatory designation such as a breakthrough therapy or fast track approval. This collective set of information helps guide the appropriate effort of validation at the right stage of the life cycle. For example, the desire for a high level of process knowledge during the design stage requires a level of resources and time and might not be compatible with fast track development during some clinical phases.

Apply a Risk-Based Approach

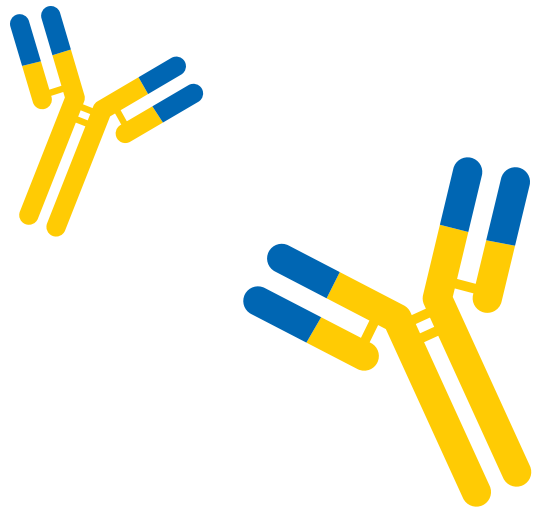
Application of a risk-based approach guides determination of when and how to conduct the required process validation studies. The risk assessment helps to identify, mitigate and control potential risks across all three stages of process validation in terms of the impact on product quality, identity, purity, potency and safety. A critical enabler of a risk-based approach is robust coordination and management of a significant amount of data throughout the product life cycle. The data enable informed decisions and provide the rationale for directing validation activities. Importantly, the data can then be used in documentation shared with regulatory authorities.

single-use technology considerations

Leverage Single-Use Expertise

Remain Flexible and Adaptable

De-risk Technology Transfers



Leverage Single-Use Expertise

Single-use technologies offer well-recognized benefits for biopharmaceutical manufacturing. But what is the best way to take full advantage of this approach? A CTDMO with proven expertise and broad experience with these technologies and implementing them across clinical and commercial manufacturing is best suited to derive the greatest value from single-use for your particular drug. An experienced partner will be able to customize an effective balance of speed and risk depending on the specific needs of the manufacturer. They will also be best suited to navigate complexities and offer strategic counsel informed by decades of experience manufacturing hundreds of biologics with single-use technologies.

Remain Flexible and Adaptable

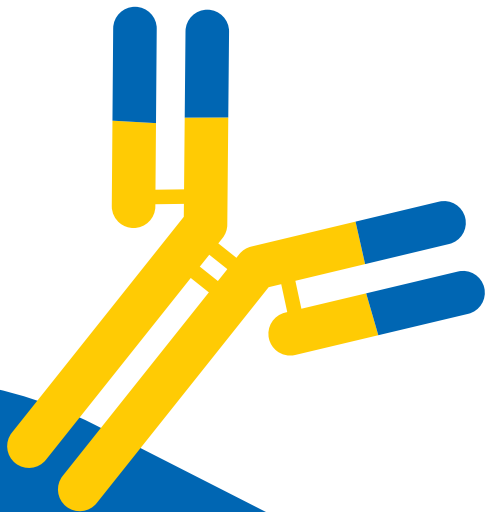
Time is money and market demand changes over time. Single-use technology allows a CTDMO to be fast, flexible and responsive to change, important considerations for commercial manufacturing over the long term. Single-use systems offer a more simplified approach and are relatively standardized as compared to stainless steel systems and operations which are highly customized and complex. This simplification and standardization translates to faster, easier and de-risked process validation, increases productivity and enables rapid addition of capacity in response to changing market demand.

De-risk Technology Transfers

At some point during the life cycle of a drug, a technology transfer is likely to take place and awareness of this is a key consideration when choosing the approach to commercial manufacturing.

The transfer might be from the CTDMO back to the innovator company's own manufacturing network or the drug might be out-licensed or acquired by another company. Regardless of the scenario, the transfer must be seamless and efficient and run the manufacturing process at the receiving site with no or minimal changes from the original process developed at the originator site. Inefficiencies in the transfer will results in production delays and increased costs.

A technology transfer will be faster, easier and less risky if the manufacturing process is based on single-use technology, due to its standardization of equipment and less complex operation. New manufacturing locations can quickly come up to speed with rapid installation and start-up relative to older legacy systems.



Regulatory Compliance Considerations

Anticipate the Global Demand

Use Processes Adaptable to Scaling

Open the Lines of Communication

Anticipate the Global Demand

Given that a commercial process should be fixed and strictly controlled to avoid variation that could impact quality and patient safety, the need to make changes at this stage should be avoided. The need for changes can be minimized, in part, by understanding the expected global demand and aligning this with the planned scale of commercial manufacturing. Produce too much product and money is wasted. Produce too little and the process will need to scale further, which will necessitate going back through process validation and possibly require submission to regulatory authorities. This can happen when a company receives approval in one country and wants to pursue approval in other geographies but must first upgrade manufacturing processes to meet the new demand.

When additional scale-up is needed, it is imperative to demonstrate that the process remains within the expected boundaries and variation is not introduced into the product. It is important to keep in mind that some changes only require internal documentation while others require regulatory approval.

Use Processes Adaptable to Scaling

As much as possible, processes should be designed so they are adaptable and reliable when scaling. This approach will provide an advantage should the commercial manufacturing process need to be scaled due to unexpected demand, such as the scenario described above.

Chromatography is an example of a process step that is typically very easy to scale. In contrast, precipitation is much more difficult to scale and validate as it depends on the volume being processed and determination of the best conditions can be challenging. As such, it may be advisable to develop the process in a manner such that a precipitation step is not needed. Another consideration is the cell line. If the same cell line is used throughout clinical and commercial manufacturing, it must support the necessary production capability and be amenable to scaling.

Open the Lines of Communication

Frequent communication with regulatory authorities is important when a commercial submission is planned. A CTDMO partner with extensive experience working with global regulatory agencies can facilitate and ensure proper preparation for these interactions. Companies should be mindful that while the core validation work is the same, different agencies and inspectors may focus on different aspects of the process in their reviews of submissions and inspections. With extensive knowledge of the process, the partner will be able to effectively tailor the communications to address specific needs of different regulatory authorities while overseeing success of the validation and reliability of the commercial process.

Conclusion

Advancing a drug into commercial manufacturing is a major milestone for a biopharmaceutical company and reflects years of intense focus and dedication to addressing patient needs. While the goal line is approaching, risk remains. There are many options and considerations related to the commercial manufacturing strategy that must be explored and addressed to best position the organization and the program for success. Decisions should be guided by the need to optimize the balance of speed, risk and flexibility that will ensure the highest levels of quality and safety.

Companies that are moving into to commercial manufacturing for the first time, as well as those that have navigated this route before, will benefit from the knowledge and counsel of a CTDMO with a proven track record. Each program and drug candidate is unique and the depth of expertise and broad experience of a CTDMO can help companies be more agile, navigate complexities and mitigate risk. From process scale-up, to optimization and validation, the right partner can help your organization get to the finish line.

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