Monoclonal Antibody Manufacturing Strategies for the 21st Century

Abstract
One of the greatest challenges facing biopharmaceutical companies is ensuring adequate manufacturing capacity for products that are under development and potentially years away from commercialization. Companies without existing manufacturing capacity must decide among several alternatives, including building internal manufacturing capability, acquiring existing manufacturing facilities, outsourcing production to a contract manufacturing organization (CMO), or combinations of these. We present the strategic and tactical implications of various “make versus buy” strategies and discuss such critical aspects of developing appropriate manufacturing strategies for biopharmaceutical products as capital investment and risk, CMO selection, and the timing and cost of building manufacturing capacity.

Introduction
With monoclonal antibody products now the dominant component of the biopharmaceutical market and continued interest in this exciting class of products driving overall sales of biopharmaceutical products in the future [1,2], BioProcess Technology Consultants recently published The Development of Therapeutic Monoclonal Antibody Products, a comprehensive report outlining the complex technical, regulatory, and strategic Chemistry, Manufacturing, and Control (CMC) activities necessary to successfully advance new monoclonal antibody products from discovery to first-in-human clinical trials and the market as quickly and economically as possible[3]. As discussed in the report, one of the greatest challenges facing companies developing monoclonal antibodies and other biopharmaceutical products is securing adequate manufacturing capacity for products under development and years away from commercial launch. Companies face a choice among several alternatives for securing both clinical and commercial manufacturing capacity, including building or expanding internal capabilities, outsourcing to a contract manufacturing organization (CMO), partnering with or licensing to companies with suitable manufacturing capacity, or strategies that combine aspects of some or all of these approaches. While long-term strategic planning for the manufacture of biopharmaceutical products entails a large amount of uncertainty and risk, it is an exercise no organization can ignore as its success will depend, in part, on developing a manufacturing strategy that is aligned with the company’s overall business objectives and fulfills the needs of the company’s product pipeline.

Key Issues in Developing Manufacturing Strategies
With the time for construction and start-up of a conventional manufacturing facility being three to five years or more at costs in excess of $250 million [4] and availability of external capacity uncertain, the development and implementation of a suitable manufacturing strategy may require the expenditure of a significant amount of money and result in large opportunity costs due to the potential allocation of limited funds away from other important corporate initiatives. These economic decisions are confounded by the fact that investment decisions must be made fairly early in product development when there are still significant technical, clinical, and regulatory risks associated with drug development, and the probability of the product successfully reaching the market is still low[3,5].

As a result, estimating long-term manufacturing capacity requirements is inherently difficult. If too much in-house capacity is built, the company will be left with an underutilized asset and suffer the consequences of the high opportunity costs of resources that could have been better utilized elsewhere. On the other hand, if insufficient capacity is available when needed, the company may experience delays in advancing a product candidate through clinic trials or lose substantial revenue due to the inability to meet market demand. Choosing the right manufacturing strategy that sufficiently mitigates risks and maximizes financial returns while maintaining flexibility to take advantage of alternate opportunities can be difficult. The manufacturing strategy should be based on both objective and subjective factors and should account for the various probabilities of uncertainty in such areas as the need for future operational
flexibility, return on investment (ROI), and the timing of major product development milestones. When evaluating whether to build or acquire internal capabilities (“make”) or to outsource (“buy”), the focus should be on optimizing internal company opportunities given that there is generally limited capital available for competing initiatives, such as manufacturing capacity versus R&D capacity for pipeline development.

The multiple considerations important for developing a comprehensive manufacturing strategy along with the various sources of uncertainty that must be addressed by the strategy are summarized in Figure 1. While a manufacturing strategy relying entirely on either in-house manufacturing or outsourcing may be feasible and practical for some organizations, in many situations the best overall strategy may be a hybrid approach that encompasses elements of both make and buy approaches. Also, it is important to continually review and update a manufacturing strategy as a company’s emphasis on either make or buy strategies may change as the development of its products proceeds.

For early product development, an in-house manufacturing strategy increases control and reduces the risk that unavailable clinical manufacturing capacity will cause a delay in the manufacture of clinical trial material and the initiation of first-in-human clinical studies. Under this strategy, a company will manufacture clinical trial materials internally for use in early stage development, clinical trials, and initial product launch. The control afforded by in-house manufacturing can also be important if the manufacturing process is particularly complex or proprietary and represents a potential competitive advantage for the company. The company may then choose to continue in-house production of the product to supply Phase 3 clinical trials or commercial product following successful product approval and launch or the manufacturing strategy may shift to a buy strategy. This shift from a make to buy strategy may be appropriate later in the product life cycle, particularly if the existing in-house manufacturing capabilities are insufficient to meet market demand or if internal resources are required to support newer programs. Likewise, as the product matures, the company’s manufacturing technology may no longer be proprietary or a source of competitive advantage, thus making outsourcing a more logical choice at this stage.

As an alternative, a buy strategy may be adopted early in the product life cycle when risk and uncertainty are greatest and conserving an organization’s limited capital resources are of primary importance. This situation is especially true for relatively small or young organizations whose limited capital resources are of primary importance. This situation is especially true for relatively small or young organizations where the company’s emphasis on either make or buy strategies may change as the development of its products proceeds.

Impact of Technology Improvements on Manufacturing Strategies

Increasing Volumetric Productivity for Mammalian Cell Culture Processes

Over the past two decades, the biopharmaceutical industry has seen a dramatic increase in the volumetric productivity of mammalian cell culture, particularly in the production of monoclonal antibody products. In the late 1990s, expression levels of 1 g/L for monoclonal antibodies were considered stellar and most products were produced at expression levels well below this. By the mid-2000s, the state of the art for production of these products had improved to 1-2 g/L with some companies reporting levels as high as 5 or 6 g/L. Recently, several groups have even reported monoclonal antibody titers of 10 g/L or more[6,7]. While these higher product titers are not yet routine, it is reasonable to assume that high expression levels coupled with downstream process yields of 70% or better will result in overall process yields of 4-5 g/L or better for many monoclonal antibody products currently in development[8].

Figure 1: Manufacturing Strategy Considerations

Sources of Uncertainty:
- Number of products in pipeline
- Timing of development stages
- Clinical plans
- In-house manufacturing capacity and scale
- Outourced capacity availability and quality
- Build capacity timing and scope
- In-licensing / partnering

Key Considerations:
- Pipeline demand
- Capacity requirements
- Supply
- Make / Build
- Hybrid
- Buy / Outsource

The diagram illustrates the key considerations in developing a comprehensive manufacturing strategy, including the impact of technology improvements on manufacturing strategies.
In parallel with the improvements seen in the productivity of manufacturing processes, there is also an ongoing shift in biopharmaceutical product development away from large “blockbuster” products serving broad markets towards more personalized medicines aimed at smaller market niches. As a result of these two trends, the quantities of product required for each particular indication will decrease (on average) and the future volumetric requirements for biomanufacturing facilities will be smaller, potentially making it easier for companies to build in-house manufacturing capacity due to the reduced capital requirements for these facilities[9].

Growing Acceptance of Single Use or Disposable Technologies

Single-use or disposable technologies have gained widespread acceptance throughout the biopharmaceutical industry as a means of increasing operational flexibility, reducing the capital investment required for manufacturing facilities, and decreasing ongoing operating costs for these facilities. Single-use and disposable technologies are currently used in almost all aspects of biomanufacturing, including cell bank storage, seed inoculum preparation, harvest and clarification, cell concentration, process monitoring, aseptic processing, and, to a limited extent, downstream processing. To date, single-use bioreactors (SUs) have been used primarily for mammalian cell culture but applications for microbial systems are increasing. The one area where single-use or disposable technologies have not yet made significant in-roads into manufacturing processes is the area of product purification, especially chromatography. However, even this is changing, and many systems are now in development for this critical unit operation as well [9,10].

The advantages of single-use or disposable technologies in biomanufacturing have been confirmed in several recent studies which have shown that the use of disposables in biomanufacturing can reduce the capital investment by 20% or more [11,12] and reduce the construction time by up to one year for such a facility compared to a conventional (“all stainless steel”) facility[13]. Nevertheless, single-use and disposable technologies are not appropriate for all situations, especially for certain unit operations at commercial scales so that a thorough analysis of the financial and operational impacts of their use should be evaluated before implementing them in a new facility. Strategic considerations, such as technological maturity and supply chain reliability for each disposable component should be assessed before committing to their use in a commercial facility.

A facility incorporating the maximum use of disposable technology may also have greater operating flexibility compared to conventional facilities since much of the equipment will be portable rather than hard piped, allowing for improved process portability and better ability to manage and implement process changes. Also, the reduced time required for equipment cleaning means that change-over times between production technologies to be used and the ability to deliver quickly and manage and implement process changes. Also, the reduced time required for equipment cleaning means that change-over times between manufacturing campaigns for different products will be less. This, coupled with the elimination or reduction of cleaning and validation costs for multi-product operations, will also decrease the operational costs of a facility and improve its overall efficiency[9,14]. The reduced capital outlay and the shorter construction time means that a company can delay a decision in the construction of a manufacturing facility until later in product development allowing the go/no go decision on facility construction to be based on greater data, thereby reducing the risk of construction, an important strategic and financial advantage.

Make vs. Buy Manufacturing Strategies

Outsourcing

If internal development and manufacturing of a company’s product portfolio is difficult to manage due to a lack of resources or commitment within the organization, or if reducing internal operating costs and reducing capital outlays is a strategic priority, outsourcing manufacturing to one of the many contract manufacturing organizations (CMOs) that provide manufacturing services to the biopharmaceutical industry may be the best option to meet product supply demands. There are many CMOs who specialize in either the production of early stage clinical trial material or material for commercial supply who can provide the necessary services to companies seeking to outsource manufacturing[1]. This is especially true today as capacity utilization at many CMOs is relatively low, thus allowing companies greater choices in choosing a contract manufacturer and more flexibility in negotiating pricing and scheduling[9].

If a company’s product pipeline is particularly large, it may be wise to work with more than one CMO in order to spread the risk of manufacturing across multiple entities; however, this should be balanced with the need to provide each CMO with sufficient business to gain a high level of attention within a particular CMO and the additional management burden of overseeing more than one CMO. While some cost and time savings can be achieved by placing all of the outsourced products with a single CMO, doing so carries a downside. The switching costs can be quite high from a current CMO to a completely new CMO. If a natural disaster or other force majeure event, regulatory compliance problem, or a change in ownership occurs at the CMO necessitating a switch to a different CMO, development and commercial programs can be put at risk if all production needs are placed at a single CMO.

Nevertheless, there are downsides to pursuing an outsourcing strategy. Outsourcing can delay development of internal manufacturing competencies if these are needed in the future. Additionally, sufficient capacity at a CMO may not be available or it may not be accessible at the time when it is needed, thus causing delays in the availability of material for clinical trials or market supply. Relying on a CMO for product supply may also increase the regulatory risks. For example, a product company is ultimately responsible for product quality and cGMP compliance regardless of whether the product is manufactured in-house or at a CMO. Working with a CMO does not absolve the company of this responsibility even though they may lose some control. For example, serious compliance issues at the CMO, regardless of whether they are directly related to the sponsor’s product or not, could endanger supply of the product or cause unnecessary regulatory delays.

Furthermore, if a company relies on a CMO’s proprietary manufacturing technology or experiences business, technology, quality, or regulatory delays as a result of the CMO, it may be difficult to transfer manufacturing processes to other CMOs or internally to a company’s in-house facility, which may cause further delays or problems with product supply. As a result, companies pursuing an outsourcing strategy must carefully consider all options and choose a CMO only after thorough investigation and evaluation of all options.

Organizations with strong quality systems and excellent inspection histories are key requirements when outsourcing for commercial production. For clinical manufacturing needs, prior experience with the production technologies to be used and the ability to deliver quickly and meet aggressive timelines are often top considerations. For both commercial and clinical manufacturing, cost and geography, while important, are only part of the consideration for CMO selection. In addition, the sponsor company should budget adequately for the internal time and resources required to successfully manage an outsourced product.

To ensure selection of the most appropriate CMO for a particular product and project, a consistent, step-wise procedure should be used[15]. This process should begin with the definition of key requirements and selection criteria, prioritized and weighted as to their relative importance and the matching of these selection criteria to the long list of potentially available CMOs. The most efficient means of identifying and selecting the best CMO for a particular manufacturing project is through the use of a detailed request for proposal (RFP) process which allows CMO proposals to be compared, analyzed and ranked based on technical, quality, regulatory and business fit with the project needs[15,16].

Aside from the technical and regulatory requirements of a particular manufacturing project, CMO selection criteria should also incorporate
the company's manufacturing strategy and consider the input of various functional groups such as supply chain, process development, quality control, quality assurance, and manufacturing. During the CMO selection process, it is important to remember that not all CMOs may be capable of meeting the timing requirements of a particular project or be able to meet the project-specific technical requirements. When developing and implementing an outsourcing strategy for manufacture of either drug substance or drug product, or both, it is important to remember that the typical CMO selection process takes an average of six to nine months to complete for products in early stage development and may take up to twelve months or longer for selection of a CMO for the manufacture of product for Phase 3 clinical trials and commercial distribution.

In-house Manufacturing

Building a facility along with a development and manufacturing organization to support a pipeline provides increased control and flexibility for a company advancing its product pipeline through the development stages. This increased control and flexibility, however, must be balanced by the increased capital requirements associated with this strategy as well as the risk associated with the inherent difficulties in accurately predicting capacity requirements for products in development and on the market. This inherent uncertainty is due to the fact that a new manufacturing facility is often built based on pipeline projections five or more years into the future. When considering a make strategy involving the construction of a new manufacturing facility, it is important to keep in mind the improvements in manufacturing processes and use of disposables described above. In general, manufacturing facilities of the future will be more flexible, easier to operate, more readily replicated or expanded to increase capacity through modular design, increased use of single-use technology, and increased use of “grey space.” These facilities will most likely be smaller and will be built with lower capital investments than current facilities. The layout and design of these facilities will simplify material and personnel flows and the use of disposable technology will reduce the number of equipment pieces and overall utility requirements. As a result, these facilities will have significantly reduced or even completely eliminated steam-in-place (SIP) and clean-in-place (CIP) requirements[17]. Despite this, they will produce higher quantities of product as a result of manufacturing technology improvements.

Facility Construction

Monoclonal antibody pilot plant construction costs typically range from $20 million to $60 million (or more), depending upon capacity, use of single-use technologies, and the level of automation incorporated into the facility. The timeline for construction of a monoclonal antibody pilot facility from the beginning of the conceptual design to initiation of manufacturing ranges from about two to three years for conventional facilities to one to two years for facilities incorporating a high degree of disposable technology[18]. A number of factors can impact the overall construction timeline and costs for a new manufacturing facility, including the use of engineering and construction “best practices” (e.g., modular construction, the use of single-use or disposable technologies, etc.).[19].

Acquisition of Existing Facilities

Acquiring an existing facility rather than constructing a new facility is an option of increasing relevance and importance as the biopharmaceutical industry matures. Although an acquired facility is unlikely to have all of the desired facility attributes, this option allows companies to obtain greater control over development resources and timing and to do so with less lead time and generally less capital investment than is required to build a new facility. An acquired facility would in all probability need to be renovated and re-validated so it would not be immediately available for operation. The ability to acquire a suitable facility within the desired window of opportunity is very unpredictable and geographic options can be limiting. Nevertheless, as the industry matures, more facilities are becoming available, so it is advisable that companies scan acquisition options for suitability before committing to the construction of a new manufacturing facility.

Conclusion

Regardless of the stage of development, any company developing biopharmaceutical products should establish a manufacturing strategy that takes into account the multiple uncertainties, risks, opportunities, and technological challenges of manufacturing these products. The strategy developed should be lifecycle-appropriate, both for the product pipeline and for the company and should be reviewed on a regular basis as the company matures. Developing and maintaining a manufacturing strategy is an invaluable exercise that enables companies to more swiftly respond to both opportunities and threats as they arise that helps increase long-term organizational value. No organization, regardless of size or organizational maturity, should ignore it.

References

8. Kelley, B. Designing a 10 ton mAb process: Is conventional chromatography limiting? Presented at American Chemical Society Biochemical Technology Division; 2006 Sep 10-12; San Francisco, CA.


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