BIOPROCESS TECHNOLOGY CONSULTANTS' ANALYSIS OF AN INDEPENDENT EXECUTIVE RESEARCH STUDY BY ORC INTERNATIONAL

The Right Partner Can Improve Flexibility and Mitigate Risks from Forecast Inaccuracy in Biomanufacturing

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ORC International's report "Implications of Inaccurate Forecasting on Biologics Drug Substance Manufacturing" explores the causes, consequences, and potential solutions to forecasting challenges specifically related to biopharmaceutical drug substance manufacturing.

Bioprocess Technology Consultants' (BPTC) following analysis provides further insight and perspective on the key themes that emerge from the report and offers additional solutions to companies to better prepare for the inevitable forecast inaccuracies for biopharmaceuticals.

While forecasts can never be 100% accurate, the goal for biopharmaceutical forecasters should be to minimize the degree of inaccuracies as much as possible.

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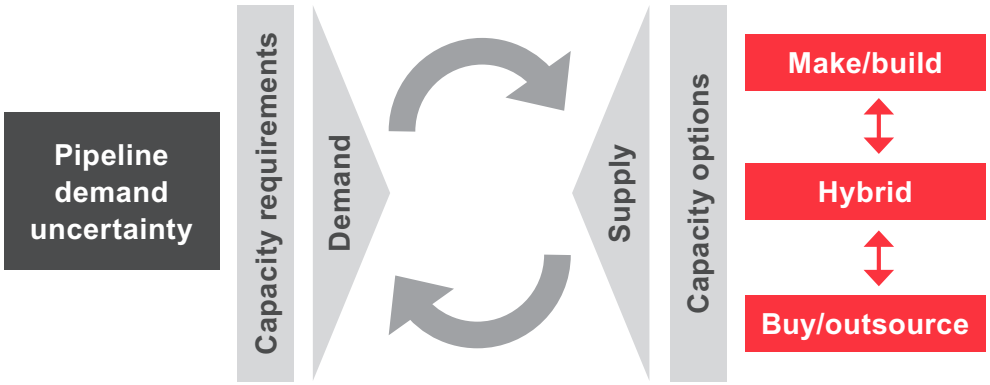
To reduce the impact of inaccurate forecasting over the life cycle of a product, companies need to focus on those variables that they have the most control over. As echoed by many of the participants in ORC's report, Figure 1 illustrates significant sources of uncertainty and variables when developing forecasts for a pipeline of products that extends many years into the future. Companies cannot exactly predict the number of products in the pipeline, their stage of development, or where a commercial product may be in its life cycle at a specific time.

When developing an effective and responsive forecasting platform, companies must understand the potential capacity options, i.e. in-house versus outsource, that can minimize the impact of uncertain and inaccurate forecasts for both clinical and commercial stage products. A forecasting platform should focus on optimizing flexibility and risk mitigation. For example, when evaluating whether to manufacture in-house ("Make") or to outsource ("Buy") to meet forecasts, the focus should be to optimize internal company opportunities, as there is always limited capital available for competing initiatives, such as manufacturing versus R&D activities. Several of the ORC report respondents acknowledged the make or buy dilemma is a difficult one. Building an in-house biopharmaceutical manufacturing facility can take up to five years to construct, commission, and produce supply; therefore, the decision to build a facility is often made at risk during Phase II/III clinical trials, well before definitive pivotal clinical trial results are available. The cost to build and commission can be in excess of $300 million. As shown, accurately forecasting and planning for capacity requirements years in advance is challenging and will have considerable financial ramifications. For these reasons, tying up scarce capital in a physical manufacturing facility is generally ill-advised for a small company.



Sources of uncertainty:

- Number of products in pipeline
- Timing of development stages
- Clinical plans
- Probability of success
- Development/manufacturing productivity and scale
- Outsourced capacity availability and quality
- Build capacity timing and scope
- In-licensing/partnering

Figure 1. Variables and uncertainties to consider in biopharmaceuticals forecasting

As a result, companies are increasingly relying on contract development and manufacturing organizations (CDMOs) as part of their overall supply chain to improve flexibility and mitigate risk given uncertain forecasts. However, CDMOs must rely on the relative accuracy of their customers' forecasts to plan for near term capacity scheduling as well as long term capacity expansions. CDMOs, like product based companies, look for approaches that enable facilities to be constructed in shorter time frames or with less capital to have flexible capacity available in the face of uncertain forecasts. ORC report participants agreed that uncertain manufacturing capacity has been and continues to be one of the major driving forces for adoption of single-use technologies and modular/flexible facility designs in the biopharmaceutical industry[1].

Forecasters should consider the Goldilocks principle when planning for biopharmaceutical capacity, too. If too much capacity is built, a company, both product and CDMO focused, will be left with an underutilized asset and forced to recoup wasted investment dollars. If too little capacity is built, the company or CDMO may lose substantial product sales, or service revenue and/or time in getting the product through the clinic due to delays in manufacturing. Similarly, because outsourcing strategies are increasingly being pursued, the product focused companies must secure the right amount of capacity at the right time. This is not always easy given the uncertainty of the product demands and the inability of any CDMO to be completely flexible to meet all companies' demands because of competing customers' demands. A solution most companies are employing early in development, is to have a well-controlled and predictable process. This can significantly reduce scale-up, technical transfer, and process risks in the supply chain planning and forecasting process and can be particularly important in a CDMO strategy scenario. Companies usually must pay a CDMO a capacity reservation fee far in advance of the actual manufacturing date – often more than one year. Additional fees apply if the reserved manufacturing slot is canceled or postponed, which is sometimes necessary to prevent excessive underutilized capacity at the CDMO due to inaccurate forecasts from the customer. However, for early phase development, there is a rush to complete process development and start manufacturing to get into the clinic as quickly as possible, sometimes before the process is really ready for manufacturing. Companies often take the risk to start manufacturing before the process is fully developed to avoid a costly penalty for rescheduling a reserved slot. Alternatively, some respondents in the ORC report indicated they delay scheduling the manufacturing slot altogether in order to avoid paying a reservation fee, only to find themselves later unable to secure a slot when the process is ready. Working with CDMOs that have multiple production scales and multiple locations can increase flexibility and reduce risk regarding when and where to access capacity.

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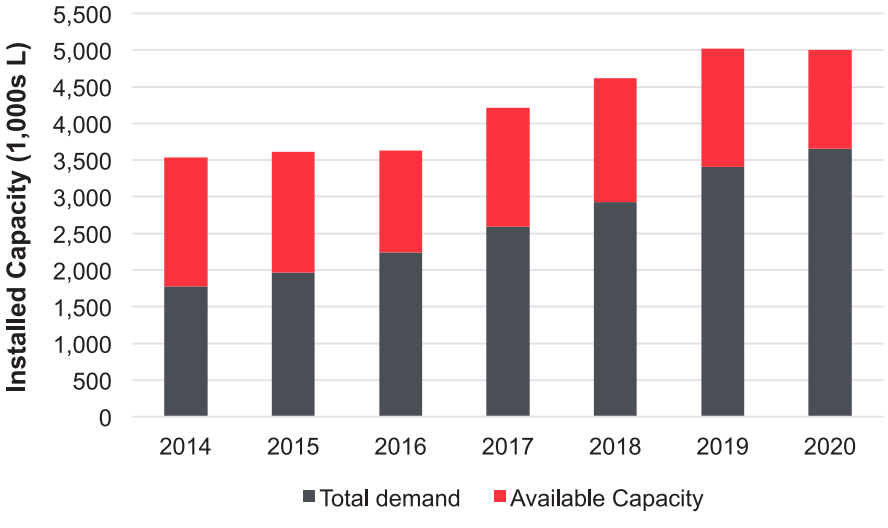
Figure 2. Forecast of industry supply and demand balance for biopharmaceuticals manufacturing capacity



Furthermore, the success or failure of clinical trials, additional indications in a trial or additional geographic territories for a given trial affect the forecasted quantities of product needed for any given product as it progresses through development.

Reacting to changes in clinical plans can be stressful on an organization. A well accepted approach that companies employ to build flexibility into product forecasts is applying a delayed differentiation approach to clinical supply. This maintains inventory in a somewhat undifferentiated state, such as formulated bulk drug substance. Companies can convert drug substance to drug product relatively quickly compared to the time required to manufacture a drug substance lot. In the case of labeled supply for global trials, retaining unlabeled drug product containers allows conversion of bulk drug product to country cluster SKUs (stock keeping unit) very quickly by applying the appropriate labels. CDMOs that have drug substance and drug product manufacturing capabilities, and even labeling and packaging capabilities, i.e., one-stop-shop, can offer significant flexibility in managing the many uncertainties with product forecasting and supply chain planning.

Finally, understanding the potential variability in forecast assumptions, such as the number of products in development, their timing, etc., and the range of possible manufacturing requirements based on these variabilities is a critical aspect of effective forecasting and supply chain planning. To provide companies making forecasting decisions with better market information and to improve understanding of the industry-wide dilemma of balancing forecasted demand and supply, BPTC has built the proprietary bioTRAK® database. This database tracks existing and planned biopharmaceuticals manufacturing capacity (clinical and commercial), along with forecasted demand from biopharmaceuticals products in development, products awaiting approval, and products approved for commercial sale in the US and EU markets. Figure 2 shows the balance between demand for mammalian cell culture biopharmaceuticals manufacturing capacity based on product forecasts and total available industry-wide capacity[2]. The blue band in each bar represents aggregate forecasted commercial product demand for each year while the green band represents the remaining available capacity after that commercial demand is met. This analysis assumes an average capacity utilization of 18 batches per bioreactor per year. The demand for manufacturing capacity has been adjusted forward one year to account for the fact that bulk product is typically made well ahead of actual sales, on which demand calculations are based in the database. For the majority of products sold in 2014, for example, bulk drug substance was manufactured in 2013.

Our analysis shows there is currently sufficient mammalian cell culture capacity world-wide to meet the total industry forecasted demand, even accounting for the inherent variabilities in the forecast, and that in 2014, only 50% of industry-wide cell culture capacity was utilized.

This analysis of capacity utilization also indicates that while manufacturing capacity in general is projected to grow in the coming years, the demand for capacity will grow at a slightly greater rate so that by 2020 industry-wide capacity utilization will increase to 73%. At this anticipated level of utilization in 2020, some companies are likely to be challenged meeting the demand forecast for specific products or gaining access to capacity at CDMOs. The challenge of accessing the right amount of capacity to fulfill forecasts may be even more difficult for companies that do not have their own manufacturing capabilities. In 2016, 67% of the mammalian cell culture capacity is controlled by 10 companies, only three of which offer contract manufacturing services. By 2021, we predict that 61% of the mammalian cell culture

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capacity will be controlled by 10 companies, four of which will offer CDMO services – this, however, is not exactly a huge redistribution.

A capacity utilization rate of 50% may give the impression that the industry is not currently operating at "full utilization." However, manufacturers often consider "full utilization" in the range of 70-80% (or in some cases even lower) rather than 100% to account for change-overs, preventative maintenance, and facility upgrades. Product company manufacturers often take a proactive approach in protecting unused capacity to be able to respond to product demand surges and additional product indication approvals that had not been captured in forecasts. Furthermore, a 50% utilization rate can be deceiving because it does not completely reflect the (in)ability to access the right capacity size at the right time.

Given the risks (and opportunities) inherent in drug development, choosing the right forecasting and manufacturing strategy to sufficiently mitigate risks while remaining flexible enough to take full advantage of opportunities, such as expanded clinical indications, when they arise presents a major and significant challenge to companies developing and commercializing biopharmaceutical products. Overall, the ORC report and BPTC acknowledge that demand for biopharmaceutical products will continue to grow over the next several years, and biomanufacturing capacity will likely become constrained as this demand continues to increase. To ensure product companies have access to the right capacity and to ensure CDMOs can offer the right capacity, all parties must work closely together to improve forecasting accuracy over the next several years. In light of the rapid growth of development of biopharmaceutical products, regulatory changes, and tightening capacity access, choosing partners who can offer greater flexibility to respond to inevitable changes in demand is among the best strategies to mitigate risk.

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1 Ransohoff TC, et al. Forecasting industry-wide biopharmaceutical manufacturing capacity requirements. In: Langer E, editor. Advances in Large Scale BioManufacturing and Scale-up Production. New York, NY: ASM Press; 2004 p. 619-68

2 Seymour P and Ecker DM. Global biomanufacturing trends, capacity and technology drivers: Industry biomanufacturing capacity overview. Am Pharm Rev. 2016 May-Jun;19(4):22, 24, 26, 28-29.

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