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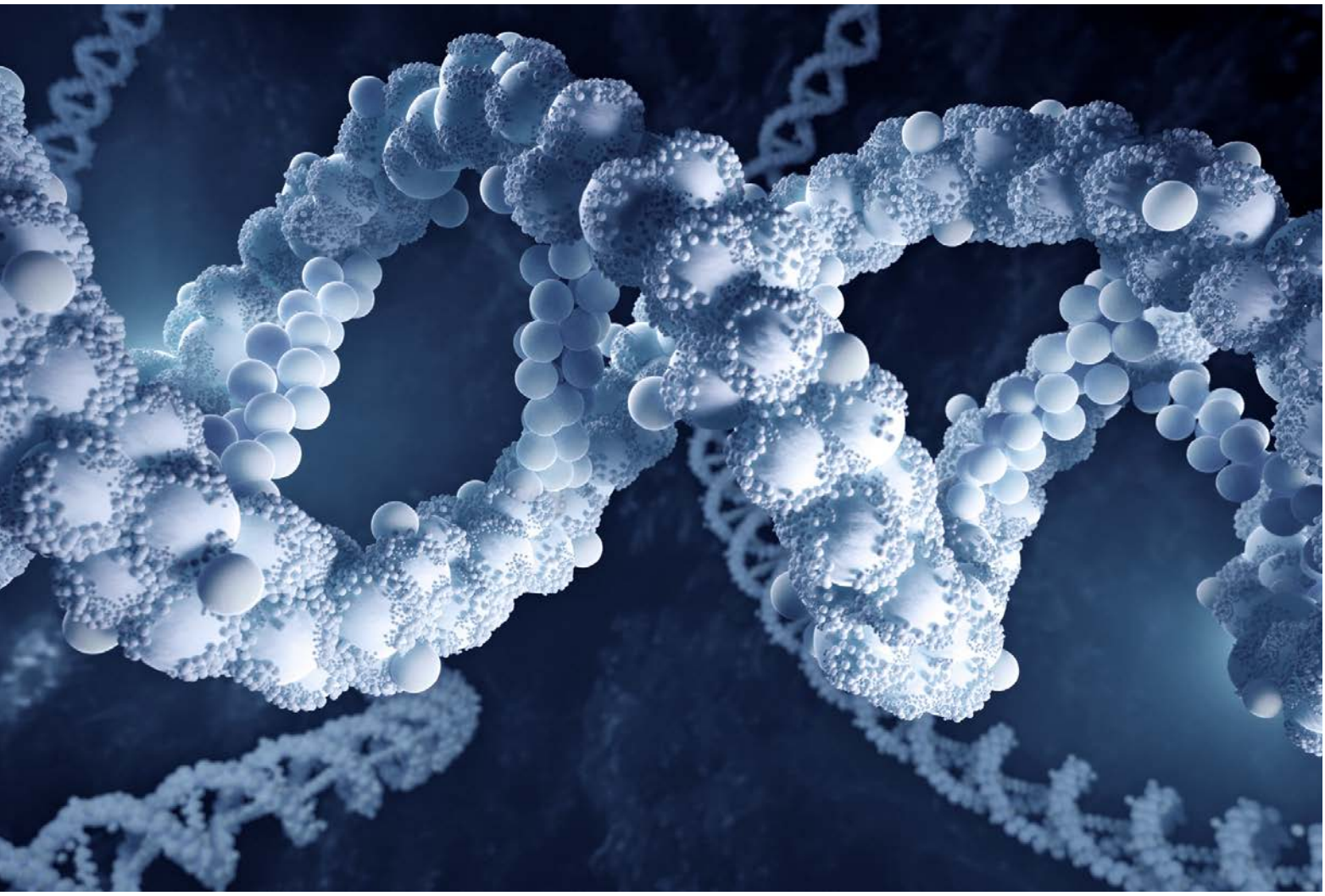

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# Challenges, risks, and strategies for biologic drug substance manufacturing

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# Abstract

Insights from pharmaceutical and biotechnology industry leaders make it clear that demand forecasting is a significant challenge when planning biologic drug substance production. The biologics development and approval process is typically long and complicated, increasing the risk of accurately forecasting demand. Overestimating demand can lead to higher per unit cost and disposal expenses, and underestimating it can result in missed market opportunities and negative reputational consequences for the company. Solutions like flexible capacity, modular and disposable technologies, continuous manufacturing, and options such as multiplexing can help biologics companies de-risk and avoid missed opportunities.

## The root causes of flawed forecasting

Clinical development of biologics lasts between 60 and 80 months on average with only 11%[1] of preclinical biologic products ultimately being approved. Thermo Fisher Scientific commissioned ORC International to conduct this research, which included phone interviews with 15 biopharmaceutical executives in North America and Europe who consistently utilize forecasts for drug substance and commercial manufacturing planning for biologics. According to the interviewed executives most biologic drug substance manufacturing decisions are made between Phase II and Phase III clinical trials, which builds in risk for the innovator companies because of the high clinical failure rates. The timeframe between the end of Phase II and biologics substance manufacturing can range from one to five years, according to the interviews. One executive noted that contract manufacturers are locking in biologic drug substance business seven years in advance. Moreover, cancellations can be costly. "Depending on how far in advance you cancel, you can lose up to 100 percent of the cost," said one executive.

With these extended timelines, biologics companies must make assumptions about patient populations, and plan years in advance of production to reserve capacity, either at company-owned facilities or with contract manufacturers. "Lack of commercial manufacturing capacity in the biologics industry is the biggest issue we face," said one executive. "It is hard to predict and build the infrastructure and assume the work will still be there in five years." This sentiment was echoed in every interview.

**"Being first to market is the primary reason companies are willing to risk making speculative demand forecasts and commit so early to commercial capacity."**

Market demand for a biologic is difficult to predict and companies are challenged by having to estimate the pharmaceutical characteristics of the drug when determining capacity requirements. "We look at the titer, and efficiency of the process, to make our decisions about commercial manufacturing," said one executive, adding that, "The clinical indication and the clinical need are very difficult to predict."

Being first to market is the primary reason companies are willing to risk making speculative demand forecasts and commit so early to commercial capacity. "Delaying signing a contract because you do not have the clinical results can delay launching a product," said one executive. Beating the competition maximizes market share, return on capital (ROC), and company valuation, which (in the minds of many managers) offsets the costs and inefficiencies of higher-than-needed plant production and inventory levels.

Indeed, most biologics executives interviewed said they err on the side of overestimating capacity requirements. One company routinely overestimated by about 75-100%. “We do that purposefully,” said the executive. “We will always make double of what we think we’ll need. And in every product situation that I’ve done that in, all the product has been used.”

Not every company has been so fortunate. For example, consider the circuitous and costly route one biotech company took to forecast demand for a new biologic drug. The company began construction of a new manufacturing facility based on an initial demand forecast of $50 million in sales for the first year.

Shortly after construction began, marketing doubled the estimate to $100 million, and within six months, doubled it again to $200 million. The company increased staff and made other moves to accommodate the new forecast. Not long after, marketing doubled the forecast yet again to $400 million a year, so the company expanded the plant.

A few months later, the FDA denied approval. A year after that, following further clinical trials, the FDA approved the drug, and the company ramped up production based on an updated demand forecast of $200 million a year.

Unfortunately, this company’s see-saw experience is all too common. Incorrect estimates for biologics lead to widespread frustration and a yearning among companies for greater flexibility in manufacturing to reduce risk and cost, as well as shorter time to market.

## De-risking the biomanufacturing process

Thermo Fisher has developed innovative capabilities, approaches, and business models that address many of the challenges raised by the executives that participated in the research study. Thermo Fisher’s new suite of biomanufacturing solutions provides both flexible and scalable capacity to pharmaceutical and biotech companies that can speed time to market while mitigating the risks and costs that come with uncertain substance manufacturing forecasts. These are customizable solutions that deliver high quality, robust process development and manufacturing, while accommodating capacity and demand fluctuations. The strategy does not solve the forecasting problem; rather, it makes forecast inaccuracies, and their implications for final supply, less painful and material.

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Thermo Fisher’s capabilities encompass a spectrum of production services that span both biologic development production and substance manufacturing. Experience with a drug during its development can help ensure a smoother transition to substance manufacturing, which translates into time and cost savings.

Moreover, the fact that Thermo Fisher has biologics facilities in Australia, Europe, and the U.S. ensures global coverage, and the ability to locate manufacturing to improve service to local markets. (Manufacturing in Australia also includes certain tax advantages.)

Because of the need for flexible capacity, biologics companies increasingly are demanding modular and disposable technologies, and continuous manufacturing. Thermo Fisher's perfusion and single-use technologies, together with the option of multiplexing, offer flexibility in both batch size and cost.

Because multiplexing is modular, reproducible, and scalable, biologics production can progress from smaller to larger capacities—2,000 to 10,000 liters—with lower risk and cost.

Thermo Fisher offers a variety of business models for delivering capabilities and services that accommodate flexible volume and the aggressive product launch schedules essential for success in biopharmaceuticals. These range from a dedicated facility, or line, to fractional ownership of a facility, a flexible network of facilities in local markets, or a fully customized suite of services that includes end-to-end production.

For companies that have production facilities, Thermo Fisher is well positioned to optimize the management of day-to-day operations. (See sidebar: Flexible business models.) Locking in production capacity years in advance of launch is a strategy fraught with risk. Biopharmaceutical companies can mitigate that risk with a flexible and versatile manufacturing solution. In that way, companies can speed time to market without rolling the dice on capacity.

## Flexible business models

Thermo Fisher's flexibility extends to offering five customizable biologics manufacturing models, depending on the needs of the company. These five options are points on a spectrum. Thermo Fisher can customize solutions to match specific client needs.

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### Dedicated capacity

Companies that have two or more products with similar bioprocessing requirements launching within 18 months, need a dedicated facility, or line, so they can modify their manufacturing schedule until they can understand the exact market demand for each product. Within the dedicated facility, a customer can determine how much is used for each product and can transfer technology in and out of the line without additional fees.

### Fractional ownership

For companies that don't have the budget—or volume—for a dedicated facility or manufacturing line, Thermo Fisher builds a single CMO facility or line for two or three clients, providing flexible capacity for each. This model is less expensive than the dedicated line, but still provides flexibility and scalability.

### Flexible network access

For regulatory purposes, global companies often need manufacturing capabilities in both North America and Europe. Or they simply may want on-demand access to capacity without preference for location. Flexible network access assures the client anytime access—within a specified period—to a specific type of capacity within Thermo Fisher's global network. Clients can adjust the product mix with the assurance they will have the right type of capacity when they need it.

### Condominium capacity

This is a fully customized solution for a company introducing a new product with unique characteristics (for example, unique product types or platforms) that cannot be manufactured on a conventional manufacturing line. Thermo Fisher provides design services, works with equipment suppliers, validates the process, builds the line, and manages operations on behalf of the client. Overhead is shared, and the line can operate as needed to meet demand.

### Enterprise

This is a solution for companies that own facilities in need of operational improvements. Some facilities may need to repurpose existing equipment; some should be closed. Thermo Fisher Scientific can manage these facilities to accomplish these goals, allowing companies to focus on their core competencies.

## References

1. “PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2015/2016,” PAREXEL, 2015

Thermo Fisher Scientific commissioned ORC International to conduct this research, which included phone interviews with 15 biopharmaceutical executives in North America and Europe who consistently utilize forecasts for drug substance and commercial manufacturing planning for biologics. This research is an extension of the ORC International research paper “Impact of Incorrect Forecasts on New Product Launches,” published March 14, 2016, which included 50 interviews with biopharmaceutical executives.

## About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we’re rapidly turning pharmaceutical possibilities into realities.

### John Foy

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John Foy is Vice President of Business Management for Thermo Fisher’s Biologics Business. Foy is a senior leader with 27 years’ experience, having worked primarily at Diosynth/ Fujifilm DiosynthBiotechnologies in sales positions ranging from program planning to chief business officer. He earned a Bachelor’s degree in Mechanical Engineering from Lehigh University. Prior to earning his MBA from University of North Carolina at Greensboro, John spent four years in the United States Air Force as an Aircraft Maintenance Officer.

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