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WHITEPAPER

Multiplexing: Managing risk with proven, single-use solutions

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Abstract

When pharmaceutical companies introduce a new drug to market, they invest enormous amounts of capital, and assume equally enormous amounts of risk. As it usually takes three to four years to prepare manufacturing capacity for the large-scale production of a new product, the decision as to how much volume a company will need often must be made before Phase III trials are completed.

At that point, it is difficult for developers to forecast demand. Therefore, deciding how much manufacturing capacity they will need is problematic. Underestimating or overestimating demand can have a devastating impact on the bottom line. If companies set their estimate of the demand for a new product too low, they will under-produce, and miss out on never-to-be replaced revenue. If they set it too high, they will invest in too much production capacity, and drastically cut into profits.

Introduction

For too long, pharma companies and contract development manufacturing organizations (CDMOs) have tried to solve this capacity conundrum in the wrong ways. Either they have spent time and money trying to improve their forecasting, or they have focused on protecting potential revenues by building excess capacity—just in case. Neither strategy has decreased the incidence of forecasting inaccuracies or wasted investments.

Instead of trying to make better predictions developers and CDMOs should seek manufacturing flexibility.

In biologics manufacturing, for example, full production-scale reactors are traditionally 10,000-20,000L. These are expensive to build, and take three to four years to commission. But if we look at the aggregate global capacity for biologics today, it is less than 70% utilized, with the majority of the excess capacity held by big pharma companies.

While this excess capacity certainly helps ensure supply, it's also a drag on return on capital that large pharmaceutical and biotech companies naturally would like to avoid. Still, when we speak with most clients about preparing capacity for an upcoming launch, the starting point invariably is 10,000L reactors.

Typically, demand forecasts for drugs prior to launch reflect a huge range of expectations. This illustrates just how hard it is to forecast accurately. And though marketing departments may be loath to admit it, the bottom line is that when their products launch, they just don't know what demand will be.

Instead of trying to make better predictions—which will never be wholly accurate nor truly able to remove risk—or erring on the side of overcapacity (which is a drag on ROC), developers and CDMOs should seek manufacturing flexibility. With sufficient flexibility, there is less need to predict demand for a product that does not yet exist. That flexibility can be achieved through 2,000L single-use bioreactors. Single use and perfusion technologies provide nimbler, more cost-effective (i.e., expandable) solutions to the demand forecast/excess capacity puzzle.

The modular approach for reproducible, scalable expansion of capacity

The best approach for developers is to plan for a scale that is big enough to yield an acceptable unit cost, but modular, so that it can be expanded should the market require. Multiplexing, a modular approach to manufacturing for biologics, allows reproducible, scalable (i.e., low risk) progress from smaller to larger capacities (e.g., 2,000L to 10,000L).

Two thousand L single-use reactors are a good fit for modular, multiplexed solutions. When further reactors are added, there is no need to revalidate the process because it is the same as the one that already exists. The process can be replicated in-house, with a CDMO or with more than one CDMO, without the need to revalidate.

Essential features of a flexible facility—for several products or lines—should include:

- 2,000L single use bioreactors for clinical and commercial production
- Multiple bioreactors in one ballroom-style suite
- Capabilities for mammalian cell culture in perfusion or fed batch
- Support for media and buffer preparation, cell culture and downstream purification operations

The modular approach offers developers security by reconfiguring already validated technologies and processes based on open-architecture principles, rather than on unproven, new technologies. Multiplexing affords flexibility, adaptability and configurability. Combined with the growing trend toward continuous manufacturing, it offers an efficient option for meeting diverse demands and production needs with state of the art upstream and downstream processes.

For example, a client developing a biosimilar for a major disease indication began thinking seriously about production just two years prior to launch, while the drug was still in Phase III trials. The developer's challenges included: 1) a short timeframe—they wanted to be the first biosimilar to launch in a crowded market; and 2) an uncertain forecast—large scale mammalian cell production capacity was needed in case product sales took off, but there was a fourfold difference between low and high demand forecasts.

Thermo Fisher Scientific proposed a multiplexing solution based on utilizing two modular plants (one in The Netherlands and the other in Australia) to accommodate the aggressive launch schedule and the hugely varying volume forecasts.

For this client, the schedule flexibility associated with modular manufacturing could become a significant competitive advantage, especially in a crowded therapeutic market where competing biosimilar products are in a race for regulatory approval. One additional, less obvious advantage of a compressed project timeline and flexible capacity may be the ability to delay manufacturing investment in order to analyze market conditions and potentially revise and/or scale back launch plans.

The benefits of a multiplexing solution—a case study

Speed

Manufacturing can be up and running in four months

Scalability

Capacity can ramp up based on demand

Redundancy

Two validated production sites builds in a backup plan

Flexibility

Capacity can be adjusted by adding or subtracting 2000L reactors

Global reach

Two sites allow for an agile response to geographic demand

Embracing flexibility

For most drugs, especially those for which demand is not yet known, it makes sense to use a multiplex solution, either in-house or outsourced. Outsourcing often will reduce risk further as a vendor with a large portfolio of biologics in production will be able to amortize the demand risk of any single product.

This is a message the market seems to be responding to. Each year, the relative proportion of in-house reactor capacity declines by about one percent. That's not a steep decline, but it's significant enough to drive growth in the CDMO industry three to five percent annually, and we expect that rate of growth will accelerate as the benefits of outsourcing become clearer.

Single-use benefits include:

- Less capital investment due to less infrastructure investment and less utilities
- Lower operational costs with fewer employees and faster turnaround between batches
- Greater flexibility allowing greater speed to market, the ability to scale up more quickly and lower cross-contamination risks
- Easy capacity additions

The demands of drug development—from discovery through regulatory approval to market access—have grown so complex that developers need to focus on those challenges, not on formulation or manufacturing. Managing uncertain production demand is a distraction developers don't need. It is a problem they can solve themselves by building their own flexible capacity, or they can hand it off to a supplier that already has it.

Combined with the growing trend toward continuous manufacturing, [multiplexing] offers an efficient option for meeting diverse demands and production needs with state of the art upstream and downstream processes.

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.

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