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Managing demand uncertainty in biologics production

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Abstract

Forecasting demand and planning capacity is a critical component for all biopharmaceutical companies preparing to launch a new product. To create this forecast, it must factor in its estimate of the size of future sales, the timing of the launch, the dosage of the product, its strategy for building its market and a host of other variables. Variations in any one of those factors can lead to drastically different demand scenarios. If a company overestimates demand, it may end up investing in too much capacity, and therefore find itself paying more per unit of the product than it needs to, thus impacting its margins. If it underestimates demand, it risks not being able to satisfy demand, therefore losing revenue. This white paper provides best practices for building better forecasts, determining demand, and mitigating risk.

Why forecasting is so difficult

Forecasting demand is a complex endeavor. For instance, it's not unusual for the forecasted and actual dosage of a product to vary by a factor of as much as three. Obviously, that makes a big difference to a demand forecast. If a manufacturer has built capacity in anticipation of a new product and its clinical trial is delayed—for any number of reasons—that manufacturer's capital is tied up in a fallow facility. For a small company for which liquidity is critical, that can be catastrophic.

When planning for capacity, a manufacturer must consider both volume and scale.

When planning for capacity, a manufacturer must consider both volume and scale. Both are important, the effect of scale being to make costs non-linear with volume. For example, say a manufacturer makes a 2,000-liter subculture batch, at a cost of about $1.5 million to $2 million—including raw materials. For a titer of 1 gram per liter, that's about 1.6 kilos of active pharmaceutical ingredient (API), with yield losses, at a cost of $1,250 a gram. A 20,000-liter batch, which would cost $4 million, would yield about 16 kilos of product at $250 a gram. That's 80% less than the 2,000-liter batch. Much more cost effective.

However, at the 20,000-liter batch size, the sponsor could end up with too much product, some of which may expire before it can be sold. That's a loss. Further, the commitment to large-scale capacity is very expensive, whether in-house or via a contract development and manufacturing organization (CDMO). Large-scale plants cost hundreds of millions of dollars, and many CDMOs require long-term commitments for large scale.

On the other hand, the manufacturer could run a batch only every few years at large scale to guard against producing too much product. However, that might create scheduling issues and degrade the effectiveness of the manufacturing organization; changeovers in large-scale plants can be very expensive.

The manufacturer also risks losing inventory, not just due to product expiration, but also due to latent defects, issues that may only become apparent after several years. Plus, one would still need three to five validation batches, which being large, would be expensive. Of course, at a smaller scale of production, each unit costs more.

Large or small, the approach one chooses will have a ripple effect throughout the business, affecting hiring decisions, cash flow, schedule duration, available capacity, cost of goods and on and on. And the scarcity of outsourceable capacity at certain scales (for example, 20,000-liters) further complicates the process—all of which sometimes leads companies to choose a solution that is suboptimal.

An Rx for navigating complexity

It is possible though to mitigate forecasting risk so long as you start the process early in the product commercialization lifecycle. Here is our approach:

1. Determine a target cost per gram for the API

Too often, this conversation does not happen until it is too late. Companies fearful of overproducing often launch without enough capacity. Then, post-launch, they must scale up, and they get caught in a long pre-approval process.

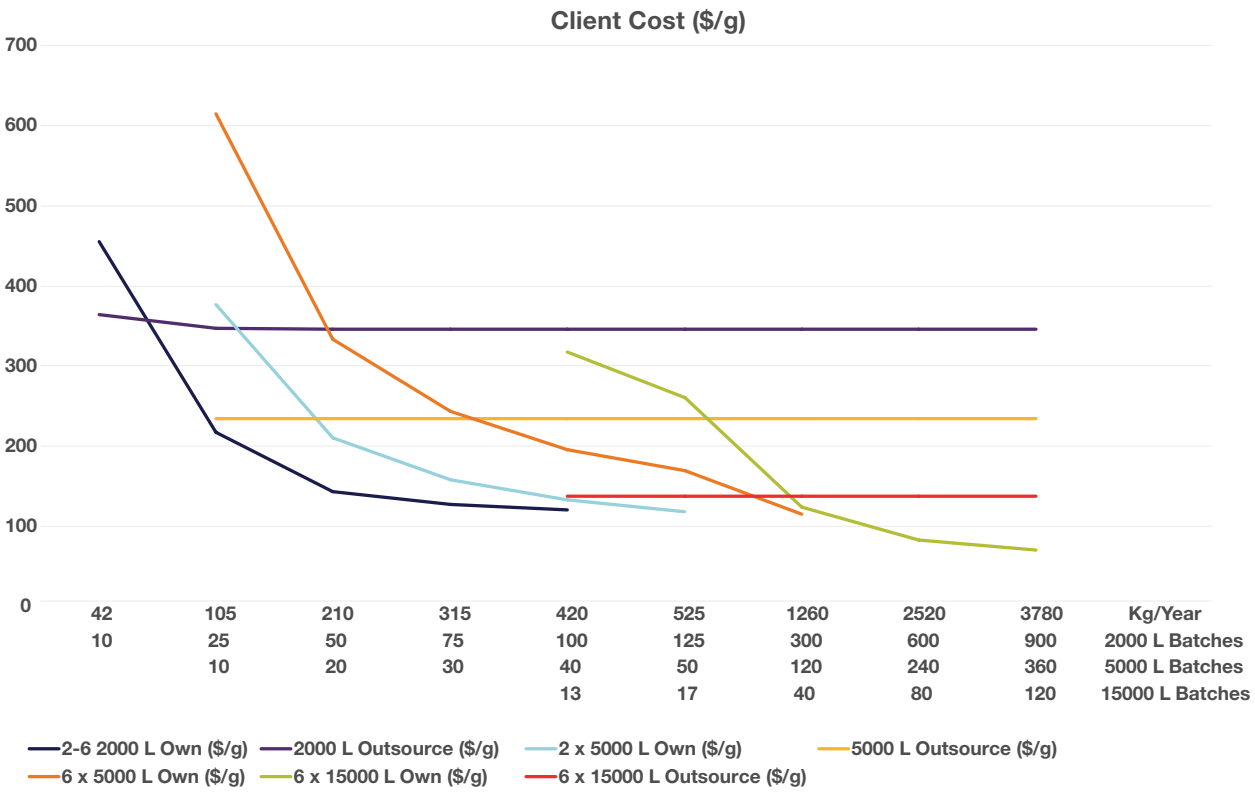


Exhibit 1: Scale, utilization and throughput have a significant impact on cost (based on a titer of 3g/l @ 75% yield)

That precludes them from meeting demand, and they lose revenue. Worse, it can lead to a permanent loss of market share to competitors whose products may not be covered by their patent.

The cost per gram of your API is a good place to start planning your capacity as it tends to be forecast-independent. It's primarily dependent on the titer, which you will know early on. Armed with that, you can determine your cost per gram of the API and check that it fits the projected price. If it does, your next step is to choose the manufacturing scale.

2. Choose the manufacturing scale

If you are a large manufacturer, you'll generally have the option to be in the $100 to $150 per gram band (Exhibit 1), and you can use capacity you already have for large molecule production. This will enable you to maintain a low cost and manage your risk. For a large company with a broad product portfolio, dedicated capacity allows it to flex to accommodate demand variations across the portfolio and to build its expertise in large molecule production.

For smaller production volumes, you will be on the left of the manufacturing scale chart, and the cost will be about $350 per gram if you outsource two to three 2,000-liter bioreactors.

It's in the middle, between small and large, where things get more complicated. For example, at 100 kilos per year, the cost would be about $35 million for an outsourced 2,000-liter process versus about $17 million for self-build.

"It's in the middle, between small and large, where things get more complicated."

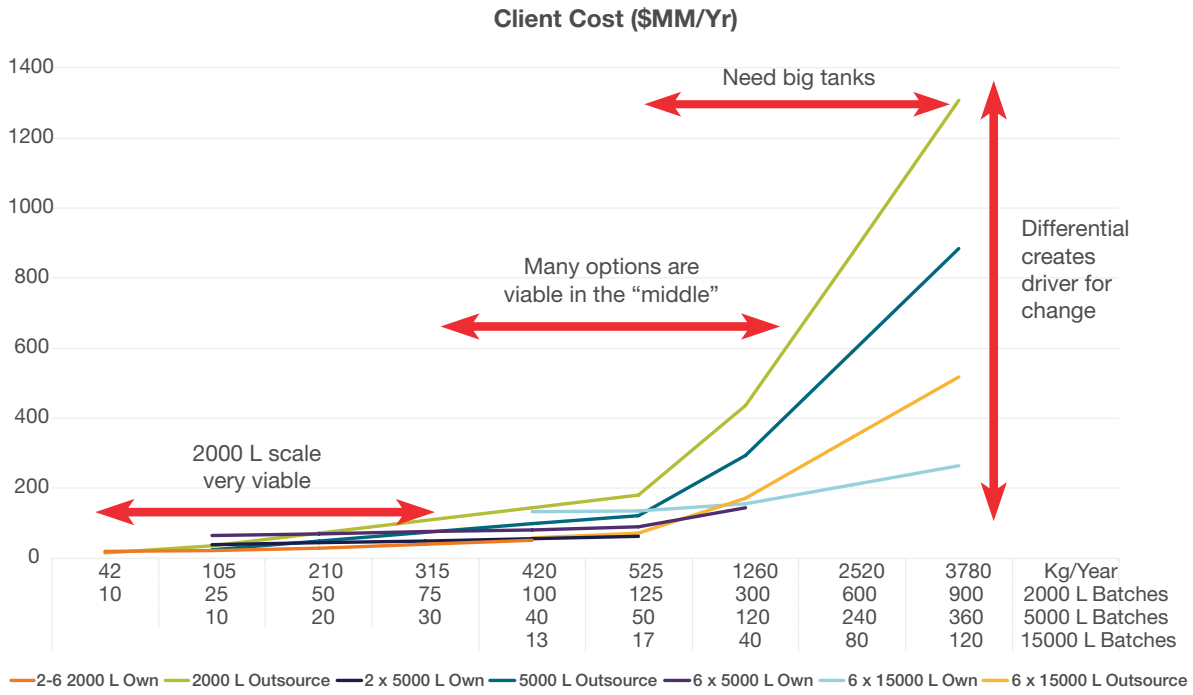


Exhibit 2: Total cost expended identifies driving force for change

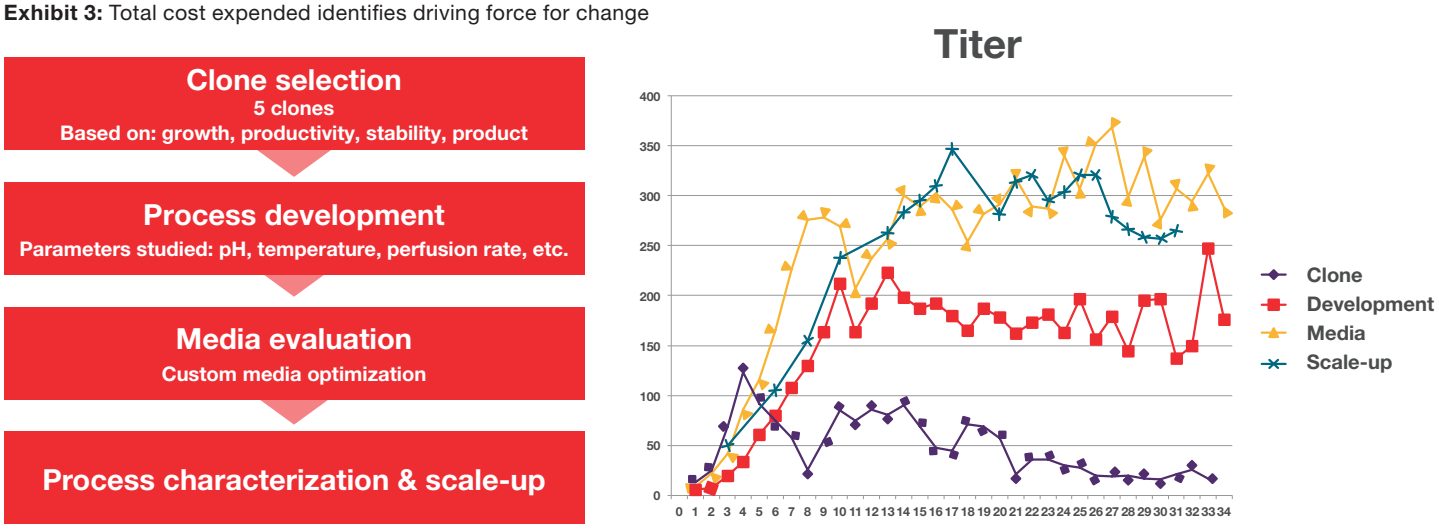
Alternatively, the solution might be to develop the process to improve the yield. That might cost say $20 million with all the development work and regulatory refiling required. Improving the process often makes sense once the volume is in the range of 20-50 batches per year.

Then the lower API cost can often pay back the initial investment within a few years while releasing capacity for other products. Process development is often a lot less expensive than building a plant, although the outcome is less certain.

Or the right answer might be to outsource at first and then, if the volume meets or exceeds expectations, look at the cost-benefit of changing from outsourced to insourced, or of improving the process, or both. You can always improve the process in parallel and implement the new one when it's ready.

In Exhibit 2, the vertical gap between the lines is the financial driver for change. For instance, at 1,000 kilos per year, that's about a $300 million incentive to switch from 2,000L outsource to 15,000L outsource.

Exhibit 3: Total cost expended identifies driving force for change



3. Determine campaign size and frequency

Plan the campaign to meet the expected annual demand and make sure this will scale up at launch to meet peak projected sales. If the campaign volume is in the range, but your cost per unit is not, consider how you might improve the yield. Conversely, if the volume is too small, then consider a smaller scale for product launch, and either how to scale up post-launch or how to improve the yield.

4. Build flexibility into the scale

One way to achieve flexibility is through multiplexing. For example, one company recently validated its process in 2,000 liters stainless. It intends to obtain full approval for a multiplexed arrangement of six times 2,000 liters via a license variation.

Another way to acquire flexibility is to combine solutions. For example, you could outsource to a CDMO while working on improving the process or combine outsourcing with production from your own large tanks.

In fact, in the early stages, it is sometimes a good idea to make capacity variable—for example, several 2,000-liter tanks—and then consolidate as forecasts become more certain. Combining multiplexing with a future increase in downstream scale may simplify future technology transfers and regulatory strategies. By engaging in these discussions earlier in the commercialization timeline, you can develop multiple scenarios and test them against financial, regulatory and commercial success factors.

You can also use this time to discuss your potential strategies with regulatory agencies during the clinical development process.

5. Improve the yield

There are various new ways to improve API yield. One client asked Thermo Fisher Scientific to conduct a full perfusion development program on a complex recombinant protein to lower their cost of production. We went back to the cloning step and selected the best of five options. We then tested 20 media combinations and created an inexpensive custom medium.

And then we scaled up the process. The result was a 6-fold improvement in titer and a 10-fold improvement in volumetric reactor productivity. You can see the improvement due to each step in Exhibit 3.

The early planner contains the uncertainty

Ask any planner, and they will tell you that the only thing they know for sure about the forecast is that it will be wrong. The question is by how much. We recommend that you create a manufacturing strategy that can accommodate a forecast range and that you can adapt as better data becomes available.

Biologics manufacturers have many potential paths to accommodate demand forecast uncertainty, but once one is chosen, it can be difficult—and expensive—to switch. The earlier you start to plan, the more time you have to arrive at an option that's best for your company. Even outsourcing can have lengthy lead times, even longer if the process is complex and the desired volumes are high.

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There is no reason not to begin planning early. By the end of Phase I, a company will have a good idea of the dosing range and process yield. That means you can think about what cost band is optimal for each demand scenario and how best to maximize margins while reducing risks.

The best advice is to start early, build options into your process, understand the lead times to make the changes and continue to evaluate your strategy during the commercialization process. In this way, you can reduce the uncertainty in your plans.

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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As the VP of Engineering, John oversees engineering across multiple sites and business units within Thermo Fisher Scientific. John has more than 30 years of experience in the design, construction, and operation of API, sterile dosage, and biological production systems for both pharmaceuticals and alternative fuels utilizing both single use and stainless-steel systems. His experience includes implementing over 300,000 liters of mammalian cell culture systems successfully in multiple countries and locations, and managing multiple corporate and site operational functions, across multiple locations, in multiple countries. John is a pioneer in the use of modular construction, gray space and large-scale mammalian systems. He has delivered multiple "green technology" systems and programs, as well as managed major construction programs which ranked in the top 75 of ENR owners ranking. Prior to joining Thermo Fisher, John worked at Flour, Biogen, and Joule Unlimited (a Flagship Company). John holds an A.B. in Physics from Hamilton College, Clinton, NY, a Bachelor of Engineering and Master of Engineering from Dartmouth College, Hanover, NH and an MBA from the Ross School at the University of Michigan.

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