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Consultants' guide to flexible biomanufacturing solutions

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Abstract

Consultants play a critical role in ensuring the long-term success of small biopharmaceutical companies, though much of their work happens behind the scenes. From lifecycle planning to marketing advice, consultants help fill gaps in knowledge while having their fingers on the pulse of new production strategies that might be a fit for clients. Counseling clients on such solutions—especially those that may help to de-risk the increasingly challenging biopharmaceutical development process—can be a win-win for the industry and consumers alike. What follows is a guide to some key strategies that consultants can keep in mind for their smaller biopharmaceutical clients.

Need: Safer supply forecasting **Solution:** Flexible scale manufacturing

Timelines for developing biologics can be long and unpredictable, with financial resources often ebbing and flowing at the whim of market events. This creates a situation where companies are forced to predict production capacity for clinical studies—and even commercialization—that will occur years in the future. Such forecasting is not easy, and if it isn't exact, over- or underestimation can lead to increased costs and stalled timelines. When firms end up with a supply shortfall, they may learn the hard way that capacity for biologics is at a premium. In fact, securing an extra 2,000-L bioreactor run for a clinical study can take as long as a year or more. The other option—building one's own dedicated capacity—is almost always out of the question for a small biopharmaceutical company with budget and time constraints.

When firms end up with a supply shortfall, they may learn the hard way that capacity for biologics is at a premium.

Meanwhile, overestimating demand is not a good strategy either; unused supply capacity wastes valuable resources and cuts into the bottom line. In these complex situations, clients can benefit from partnering with a provider of flexible manufacturing solutions—one that can facilitate multiple production options and support the variable demands—while transitioning through clinical stages and eventual commercial product supply. One solution is multiplexing, which involves a CDMO adding several single-use bioreactors to a process to drive a larger downstream volume or shorter process cycle times. This flexible and scalable manufacturing option builds customization into what is normally an unpredictable and rigid situation.

At Thermo Fisher, there may be multiple avenues for us to partner with our customers as we learn more about process capability and product demands. If the product demands indicate a case where multiple 2,000-L bioreactors are necessary, we can provide a road map for how and when supply expansions are needed. With the proper technical approach for the process, the business options become more flexible and could include the establishment of dedicated capacity for a client and their products. The key parts for the business discussion are (1) to understand our scale-up options, and (2) to agree on realistic lead times for supply of additional capacity.

The modular multiplexing approach saves clients time in another important way: revalidation time and effort are not needed during scale-up. If we anticipate during our evaluation process that a client may need additional production capacity in the future, we will build that capability into the initial process design, thereby eliminating the revalidation process.

In the end, multiplexing lets clients focus on robust process development without having to be fixated on anticipating their bioreactor size. Focusing on scale before volume is an important message to carry to biopharmaceutical companies of all sizes, as it avoids the expense of validation batches and wasted supply.

Because firms know their titer early in the process, they can estimate their biologic API's cost in dollars per gram. Then, they can project their optimum production scale. Large innovators can usually produce mAbs at $100–150/gram with dedicated capacity. For smaller production volumes that cost $350/gram, outsourced production of two or three 2,000-L bioreactors is the best option. Multiplexing allows such production capacity to scale as needed. For costs in the $150–350/gram range, a combination of insource–outsource manufacturing may be an option.[1]

At Thermo Fisher Scientific, some clients may benefit from our use of a ballroom upstream production suite in which multiple processes are run in the same room and under closed conditions. In cases where larger product volumes are needed, we can stagger the run of up to four bioreactors in a single suite and then run them into a common downstream process.

The bottom line is that when biopharmaceutical clients work with a CDMO that offers multiple, flexible solutions, their supply production will be faster and more in sync with their end goals and project timelines.

Need: Faster tech transfer Solution: Better evaluation process

At its most basic level, the transfer of technology for scale-up is simply moving a project from one facility to another and sharing critical information about how a product is made. When tech transfer involves a knowledgeable CDMO, it can elevate projects to the next level—even those in mid-phase. CDMOs that employ cutting-edge manufacturing techniques can provide opportunities to build increased efficiency and strategic advantages into process development.

That statement may sound counterintuitive to firms that have gone through a time-consuming and laborious tech transfer, especially if communication wasn't forthcoming, the roadmap of procedures was muddy, or gaps in process data weren't filled.

Tech transfer doesn't have to be this way. We've seen that building customization into processes begins with a robust new-product onboarding process. At Thermo Fisher Scientific, we not only look at things like facility fit and scaling for later-stage projects, but also whether various flexible technology options are a fit and which of our geographic locations, specialized equipment, and scale options are best for each individual project.

Customized matching of flexible solutions to client projects should encompass everything from cell line work through the manufacturing scale and the scalability of the process. Within the perfusion space, for instance, we might make use of alternating tangential flow (ATF) for one commercial project, and then use a totally different harvesting technique for another project. Meanwhile, if additional development work is needed for an earlier-stage molecule, we build in ways to fill in the data gaps before proceeding.

When a fast technology transfer is required, a robust and efficient onboarding process can support technology transfers that occur as quickly as four to six months from project kickoff to first manufacturing run, in our experience. We believe that a more efficient transfer timeline can be a differentiator for CDMO selection.

Need: Simplified supply chain **Solution:** As one-vendor approach

Whether a biopharmaceutical company is large or small, supply chains are complicated and difficult to manage. A typical multi-vendor development plan might have as many as 10 different potential sources of time and cost inefficiencies. These areas may include everything from sourcing materials from multiple vendors, working out the various project details and timelines, negotiating numerous vendor contracts, coordinating tech transfers for scale-up, revalidating numerous steps of the process, documenting drug product testing from early stages and more.

When clients consolidate their supply base and use one vendor from drug substance through drug product, it can transform the entire drug development process into a more efficient system with cost and timeline advantages as well as potentially create an even better end-product.

Let's use the example of Thermo Fisher OneSource™, a systematic approach in which numerous vendors—including raw material vendors, manufacturing experts, packaging suppliers and others—are brought together within our network. Customers not only can access full drug substance manufacturing capabilities, but can also take advantage of drug product fill–finish services that exist under one umbrella and a common project management structure.

When multiple vendors are brought under one roof and the hand-offs and revalidation work are eliminated, we've seen our seamless approach shave 14–20 weeks off development timelines for large molecules. That's a significant time savings.

Moreover, when one CDMO is part of the development process from early- or mid-stage through later stage manufacturing, a one-network approach gives companies access to a large pool of experts that can easily share information and knowledge about products to properly guide clients every step of the way to commercialization. At Thermo Fisher Scientific, we believe the technical team that initially brought in the project should always be a resource as a project progresses into later manufacturing stages.

Need: Better cost-of-good metrics **Solution:** Flexible cell-culture harvesting options

As increasingly complex biologic molecules occupy a larger piece of the pipeline at biopharmaceutical companies both big and small, a CDMO's ability to respond to client demand is strongly tied to its cell-culture platform offerings.

During the evaluation process, CDMOs should consider a variety of factors in a molecule's development pathway and have the in-house capabilities to offer a solution that best fits the project, be it perfusion, high-density fed batch or another format. As opposed to a one-size-fits-all approach, we believe having the flexibility to offer numerous different platforms helps ensure a better cost-of-good metric for diverse projects.

For instance, we might evaluate a product's stability and determine that perfusion is the best choice. Perfusion cell culture helps increase yield at a lower production scale, which has a positive cost-of-goods impact for customers. With this technology, high cell densities operate at high productivity. As cell-culture fluid is continually replaced and added to the bioreactor and harvest removed, highly viable cultures are grown.

This is especially beneficial for cells prone to degradation from exposure to potentially toxic byproducts. In addition, we feel that perfusion builds a very consistent end-product because of the steady-state conditions inherent in this technique[2].

A final benefit is that perfusion also allows us to use smaller bioreactors to produce the same biomaterial as a much larger bioreactor, which reduces costs and gives us the space to add additional bioreactors as needed.

Need: Better foundation for IND filings Solution: Regulatory and CMC expertise

Virtual biotechs often operate with a lean, nimble staff. While this model is attractive from a financial point of view, it often leaves gaps in Chemistry, Manufacturing and Controls (CMC) and regulatory expertise. Without detailed knowledge in these areas, companies may not know they should collect adequate data early in the development process. The more complete information available for Investigational New Drug (IND) filing, the more likely that the CMC element can be kept off the critical path through the regulatory timeline.

Consider the teams your client will be working with at their CDMO. Is it mainly a project manager? Or, will several experts devote time, energy, and know-how to ensuring the project is a success?

We're a strong believer that clients are best served when the CDMO understands how to incorporate cGMPs into process design and has a network of capabilities to make that a reality. If we have a client with a product that requires heavy process development, for instance, we assign the project to either our Princeton or St. Louis location for the initial work. These sites are part of our Centers for Excellence and have extensive facilities and people devoted to process development. All told, we have approximately 140 total engineers and scientists at these two locations; a considerable amount of bandwidth is devoted to process development.

Biopharmaceutical clients also benefit from having a strong program management approach in which procedures are in place that carefully lead projects through important transitions. We feel it is key for each project to be assigned several subject matter experts (SMEs) who can shepherd the product through the various stages of its lifecycle while collecting adequate CMC data for an IND filing. At Thermo Fisher Scientific, we operate with a global project management organization that provides expertise to lead the cross-functional SMEs with a common approach focused on delivery for the customer.

As a solutions provider, this approach is invaluable from a regulatory perspective. No matter the problem, we want to have solutions available that enable projects to move forward successfully. In the end, as we go through the development pathway with a customer, we have a responsibility to prepare them for success in our support of their CMC strategy.

The path forward

As consultants prepare their clients for the challenges that surface during tech transfer and process scale-up, it is critical to help them select a CDMO partner that offers much more than machinery availability. Rather, deep technical and regulatory expertise is critical for ensuring the success of molecules as they progress toward an IND filing, through the clinic and into commercialization. At the same time, such a partner should bring numerous flexible options—e.g., multiplexing bioreactors, a streamlined vendor network, and even manufacturing site options—to the table that keep their clients' projects on time, on budget and on track for regulatory and market success.

References

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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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John Foy is Vice President of Business Management for Thermo Fisher's Biologics capabilities. Foy is a senior leader with 27 years' experience, having worked primarily at Fujifilm Diosynth Biotechnologies 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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