

INSIDE OUTSOURCING



BALANCING ACT: QUALITY VS. QUOTA

For biotechs, outsourced process development is a key strategy for bringing products forward quickly. But there's more to successful product development than speed....

BY CINDY H. DUBIN

When biopharmaceutical companies need to develop a manufacturing process, there are plenty of reasons why they often turn to contract manufacturing organizations (CMOs).

Process development is a big job—especially for a smaller company that is trying to juggle multiple projects and conserve resources. The numerous complex variables to be studied, along with their interaction in the process-development stage, can be tedious and time-consuming at a point in the company's life when speed is probably of the essence. Choosing an experienced manufacturer can potentially bring products to market a lot quicker.

What's more, the process itself is technologically complex and highly regulated. Unlike the small molecules created by chemical synthesis, the large, complex protein structures produced in biologics manufacturing are unstable and have a low tolerance for error. Even small temperature changes can have dramatic effects on the production process. Biologics manufacturing requires specialized capabilities, more planning, skilled staff, and more investment compared with small-molecule manufacturing.

(Of course, all of these are also reasons to be cautious in using a CMO.)

Many biopharm firms will seek out a process-development contractor for a soup-to-nuts project, handling everything from developing a process to commercial manufacturing. In other cases, companies already have their active ingredient, but want a third party to develop the process, identify the right dosage form, scale up the process, and perform the manufacturing; some already have their process, but need it optimized; still others just simply need another manufacturing site.

Whatever the reason for outsourcing, quality should be at the forefront of the project, agree the experts. But is it?

A NEED FOR SPEED

One company that feels it has the balance right is Artisan Pharma, in Framingham, MA. The biopharmaceutical recently announced a strategic relationship with the Singapore-based CMO A-Bio Pharma to handle the process development, scale-up and manufacture of ART-123, a recombinant protein for the treatment of disseminated intravascular coagulation (DIC) in sepsis.

A-Bio will undertake the various development and validation activities necessary to ensure further clinical development and commercial supply of ART-123 for Artisan, and, in return, Artisan will enter into a preferential and long-term supply agreement with A-Bio.

“Speed is important to us, and our relationship with A-Bio ensures that speed will be there,” says Jeffrey D. Wager, Artisan’s president and CEO. “But speed is second to quality for us. All of the work is for naught if a drug has to be pulled or suspended because of a quality issue.”

The process-development team at A-Bio identifies and develops production processes, as well as support for transitions and scale up from 2 liters to 500 liters.

Production of preclinical toxicology material is also carried out in this department at up to 500-liter scale.

“This agreement is important to us for two reasons. First, we are committed to ensuring a safe and consistent supply of ART-123 throughout our territory,” says Wager. “The relationship with A-Bio accomplishes this objective to a very high standard. Secondly, this alliance enables us to focus more of our financial and human resources on ART-123 clinical development through strategic outsourcing of ART-123 manufacturing.”

ART-123, Artisan’s lead candidate, targets both anticoagulant and systemic anti-inflammatory pathways, and holds promise as a self-regulating treatment of DIC in sepsis.

“We are very focused on clinical development, and we conserve and channel our resources accordingly,” says Wager. “Working with a CMO like A-Bio allows us to focus on that work exclusively and not invest in establishing a manufacturing capability ourselves.”

“Larger biopharms and Big Pharma typically outsource because they have more product candidates in their pipelines than they can

support internally. To maintain momentum, outsourcing offers an attractive—and, sometimes, the only—alternative,” says Wager.

WHEN IS ENOUGH ENOUGH?

Timeliness is much easier to tackle in the early phases of process development, where a development project can turn into a research project pretty quickly. That changes during Phase III, when process development requires several performance runs, process validation, and analytical testing.

Because many companies receive rounds of funding based on meeting promised milestones, “there is a business pressure for us to deliver a process on schedule—the clients want to get

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into the clinic as fast as possible to meet benchmarks and receive additional funding,” says Rich Hetrick, director of business development for QSV Biologics, a CMO that specializes in mammalian cell culture, microbial fermentation, and purification services. “This often creates conflict, as expectations may exceed reality.”

Allison Vernon, head of mammalian R&D services at Lonza Biologics, agrees. “The onus is on us for speed to produce materials for toxicological studies so that our customers can move into those studies quickly. We will not compromise the product quality for speed; we ensure the process is robust and not a result of hasty development. The client must remember that the ultimate objective is to create a process that is robust and repeatable and has longevity.”

Time constraints place added stress on the CMO and put pressure on the client to determine if time and money outweigh quality.



“When a client comes to Baxter, we can’t possibly know all there is to know about its compound,” says Gregory Sacha, research scientist at Baxter. “There can often be surprises, such as instability in a dosage form, that alter timelines. The client needs to decide how much revamping a process will set them back, both from a financial standpoint and a time-to-market standpoint.”

“Unpredictability is a big challenge,” agrees Hetrick. “In formulating a development plan, we have to project forward how much time and resources it will require to develop a compliant, robust process, but we cannot foresee all the technical issues that may negatively affect process development and scale-up.”

Vernon says, however, that saving time and money does not have to entail a sacrifice of quality. “We can condense the critical path and revisit something later in the process so that things do not need to be held up.” In the case of Lonza, which performs mammalian process development, this might mean moving forward initially with a cell line that has not undergone a formal round of cloning, only to swap in that fully cloned cell line later in the development process, hence making significant time savings on the critical path.

Ensuring that quality is not the sacrificial lamb is the notion behind Quality by Design (QbD). The objective is to develop a process that can be scaled, robust, reproduced, and meets regulatory requirements, but its adoption is not yet widespread, according to Sacha. “Not having a real guideline to support or define QbD puts the onus on the contractor to explain the

benefits and necessity of it.”

Doing its part, Baxter has purchased a LyoFlux mass flow monitor and tunable diode laser absorption spectroscopy-based sensor, for monitoring water vapor concentration and flow velocity between the freeze-drying chamber and condenser. Baxter is using the equipment to evaluate the effect of process parameters on water vapor flow rate during lyophilization. The data will be used to develop a product-specific process design space.

In a similar vein, Lonza recently purchased Aggresolve technology, a comprehensive in silico protein analysis platform that is being used to screen proteins to predict protein aggregation problems, to determine sequence changes likely to reduce aggregation, and to design aggregation inhibitors and stabilizers. “In other words, we assess the product for aggregation before we create the cell line, making suggestions for product reengineering if necessary,” says Vernon.

P.A.T. AND PLATFORM TECHNOLOGIES

According to John Curling, president of John Curling Consulting of Uppsala, Sweden, and senior adviser to ProMetic BioTherapeutics of Gaithersburg, MD, the axiom that “quality cannot be tested into products but should be built-in or should be by design” is being applied to reduce failures and mitigate deviation during manufacturing.

Two tools help to speed the process of technology transfer into manufacturing: Process Analytical Technology (PAT) and the development of platform technologies.

Curling says the use of online process



monitoring in the biopharmaceutical industry forms the foundation for development of corrective measures in manufacturing and the adaptation of at-line and offline analytical procedures to PAT. Together with trend analysis and other computational methods, PAT is expected to contribute to process understanding and reduce risk associated with the impact of seemingly small process changes.

Platform technologies are manufacturing operations that should be applicable to more than one biopharmaceutical, with the desired effect of eliminating process re-invention for each new product and reducing manufacturing investments.

The combination of platform technology development and implementation of comparability protocol supported by PAT should facilitate change for the better, as well as the introduction of the new technologies.

EYES WIDE OPEN

When the time comes to transfer the process, quality and integrity must be maintained, say the experts. For instance, once QSV delivers a product ready for clinical studies, it remains in contact with the client until the customer returns for commercial manufacturing. In the case of Lonza, which transfers most of its processes internally, the R&D team remains in the loop during GMP for consulting. “We might be asked to optimize or the upgrade the process,” says Vernon.

Being at the ready is just one trait a CMO should exhibit. According to research conducted by Corinne Chao and Jayant Lakshminathan of Deloitte, an effective CMO should also:

- ▶ have access to significant amounts of capital—of the same order as the large biopharma companies
- ▶ build a reputation to help attract top talent in

- all aspects of biologics manufacturing
- ▶ have access to top research, with a goal of being on the cutting edge in its field
- ▶ absorb financial shock associated with losses from initial products
- ▶ effectively collaborate with drug development companies to manage operational risk. This relationship should facilitate process development and the effective transfer of the drug from clinical development to large-scale production.
- ▶ be well-versed and experienced in advanced risk-management techniques. The risks inherent in biotech products require tight risk management through contracts and appropriate selection of customers and products.

Industry insiders advise biopharms to understand that just because a CMO is an expert in process development does not mean that speed comes along with the territory. “It is unrealistic to expect a CMO to develop a GMP-compliant process in a time frame that is solely determined on attaining a financial milestone or clinical trial window,” says Hetrick. “Biopharmaceutical companies must understand that process development is somewhat unpredictable and that it will likely cost more and take more time than originally projected. Go into process development with eyes open wide and plan ahead.”

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