

Automation, modularity allow mAb biotech to cut scale-up time

Original developers of biosolutions and products, especially those facing the debut of biosimilars in core markets, have an urgent imperative to reduce manufacturing costs via increased productivity and yields. In turn, this drives a wide range of business decisions, including capital investment, process choices and design, and equipment selection.

An interview with:

Dr. Ting Xu, CEO of Alphamab Co. Ltd, a fast-growing biodeveloper and producer

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To this end, for example, biodevelopers are adopting more sophisticated processes, such as perfusion, to address low-titer cell lines and reduce raw material costs. They're also seeking more sophisticated and flexible research and development (R&D) and process development (PD) capabilities in several ways by deploying equipment to enable simultaneous development of multiple products; automate rapid experimental design and implementation; optimize processes; and gain better analytical insights, especially for PAT and regulatory compliance.

Introducing Alphamab, a fully equipped biodeveloper and producer

Alphamab Co. Ltd, a fast-growing biodeveloper and producer, is one such company looking for those kinds of capabilities. Founded in 2009 and located in Suzhou, a city about 60 miles northwest of Shanghai, Alphamab's R&D center consists of more than 60,000 square feet of offices and labs, fully equipped for investigating, commercializing, and producing the latest in biologic products.

Its BDS and FFP suites are built to meet the rigorous cGMP requirements of the CFDA, FDA, and EMA. After those facilities opened in 2013, the Jiangsu CFDA certified them for biologics manufacturing. The facilities also include a pilot plant, GMP production, and a fill-and-finish plant.

At Alphamab, over 100 scientists are engaged in a wide range of activities that include target validation, hit screening, H2L, PK/PD, pharmacology, cell line construction, process development, scale-up GMP manufacturing, and IND filing. Currently, the staff is involved in almost 60 projects including treatments for autoimmune diseases, blood clotting issues, diabetes, infections, tumor immunology, cancer, ophthalmology, and osteoporosis. Of these, nearly 20 are technology transfer projects.

Alphamab uses lab-scale bioreactors in 1 L, 3 L, and 15 L sizes, with antibody production projects in the 5 g/L to 10 g/L sizes, and sometimes more. While it still uses glass vessels in its R&D and PD labs, the company has adopted single-use bioreactors across all its cGMP manufacturing facilities, instead of the glass and stainless steel vessels it used before.

Many challenges of scale-up, especially across different projects

According to Dr. Ting Xu, CEO at Alphamab, the company facilities have quickly matured: “We now have a number of development platforms, including ones for prescreening as well as yeast and phage displays, so we can screen humanized antibody sequences plus nano antibodies, too. Our protein engineering capabilities include a patented mixture platform and an EI-specific platform. And our process R&D and pilot production platforms include DHDP production, in addition to our fill-and-finish platform.”

Xu points out that scaling up production from lab to pilot to full commercial production raises many challenges—especially across many different projects. “Mainly, the key difficulties are understanding the depth of process and the impact of parameters on process scale-up,” he says. “These must be known in order to guide how we set our parameters for consistency during scale-up, so we can ensure cell growth, viability and yield and, ultimately, product quality.”

Alphamab has been an early adopter of single-use technology to help boost productivity in its cGMP manufacturing, while also reducing scale-up cycle times and costs. The company used to favor stainless steel equipment, but migrated to a single-use model for many reasons.

“For starters, stainless steel is expensive and time-consuming to deploy,” Xu explains. “Once deployed, it has a high risk of cross-contamination, thus requiring time and resources to clean, sterilize, and validate. Then there's constant maintenance that commands even more time and money. The business case for single-use technology is compelling on many levels.”

What Alphamab found unique about the HyPerforma G3 Controllers for bioreactors is their versatile ability to scale up and scale down.

Automation, a bio-development and production accelerator

One complement to single-use technology is having a consistent automation platform across Alphamab's different upstream and downstream phases, which the company defines using a Quality by Design (QbD) approach.

"Because each process is special," Xu says, "it's difficult to have one common platform for all projects. But going from a small lab project to a complete process scale-up using one platform, especially the controller, can help to increase our success rate. Of course, this depends on the accuracy of sensors and the stability of the controller, which is what we were looking for."

Specifically, for Alphamab's glass-vessel, benchtop bioreactors in its R&D and PD labs, the company deployed a Thermo Scientific™ G3Lab™ Controller. This consists of a utility tower and a Thermo Scientific™ TruFlow™ gas manifold, which are sized to minimize the footprint while providing company researchers with maximum process flexibility.

In its cGMP facility, Alphamab installed Thermo Scientific™ HyPerforma™ Single-Use Bioreactors (S.U.B.s), each with Thermo Scientific™ HyPerforma™ G3Lite™ Controllers using the Emerson™ DeltaV™-based Thermo Scientific™ TruBio™ control platform. The system consists of a control tower featuring Thermo Scientific™ parts, transmitters, and actuators, the latter controlling four mass flow controllers.

The Thermo Scientific parts are intelligent, modular, plug-and-play hardware building blocks for measuring and controlling bioprocesses. They have built-in diagnostics and factory calibrations, can be auto-detected by Alphamab's network, and provide optimized local control of its various bioprocess functions.

"Previously we were using glass bench-top bioreactors from Applikon and Sartorius, but chose the Thermo Fisher Scientific platform because they offer proven performance, stability, and reliability, plus good service and support," Xu says.

Scalability and flexibility

What Alphamab found unique about the Thermo Scientific™ HyPerforma™ G3 Controllers is their versatile ability to scale up and scale down. "The scalability of the G3 control platform helps us facilitate process transfers from 0.5 L to 2,000 L," says Xu. "This enhances the quality, productivity, consistency, and reproducibility across our processes, whether we're using batch, fed-batch, or perfusion."

Another distinction that sets the HyPerforma G3 Controllers apart is their adaptability to third-party systems and peripherals. For example, in addition to the HyPerforma S.U.B.s that Alphamab deployed, the HyPerforma G3 Controllers are compatible with single-use, glass, and rocker systems from GE, Sartorius, and Eppendorf.

This enables customers to automate a wide range of both legacy and new-build infrastructure using what they determine to be best-of-breed solutions.

In combination with the HyPerforma G3 Controllers, Alphamab has found the Thermo Scientific™ TruBio™ Software extremely useful in controlling the bioprocesses of its cell culture operations. This hardware-independent software system was developed based on the Emerson™ Process Management DeltaV™ control platform. "Having the DeltaV automation control engine in the TruBio Software was an important factor in our selecting the Thermo Scientific automation platform," says Xu. "It really gave us confidence we were making the right choice."

What's more, he notes, the Thermo Scientific automation controller platform is proven globally, with more than 1,500 lab-scale and nearly 500 large-scale bioreactors installed and operating across more than 60 customers. "This helped reduce any sense of risk in choosing HyPerforma G3 Controllers for use in our R&D and PD labs as well as for use in the single-use bioreactors we use in our cGMP manufacturing," he says.

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TruBio Software, preconfigured and ready to use

The cGMP-compliant TruBio Software comes pre-configured with algorithms for controlling bioprocess parameters such as pH, dissolved oxygen, temperature, and pressure. With tridundant sensor loops as well as unlimited gas and liquid addition capability, the software can be used with glass vessels, wave rockers, and, like the HyPerforma G3 Controllers, most brands of single-use bioreactors.

Xu reports that his staff especially likes the flexibility, easy operation, and precision control of Alphamab’s Thermo Scientific automation control system. “In particular, they like the ease of configuring parameters for DO and pH control. This has helped them more easily and quickly define and then use the same scale-up standards for the same projects,” he says.

Executing scale-up standards for one project—or many projects simultaneously

“In the scale-up process, you have to find the key control parameters that affect your critical quality attributes, but each project has its own characteristics,” Xu explains. “For example, some may be more sensitive to speed, some to pH, some to the concentration of CO₂. By finding your own control range of key parameters, you can conduct a successful scale-up process. The Thermo Scientific platform is a huge help in accelerating the technology transfer phases of our operations by enabling us to execute a scale-up standard across an entire project.”

By migrating from glass to single-use bioreactors while also automating with the same scale-up standards using the TruBio software with HyPerforma G3 Controllers, Alphamab achieved two key goals: it reduced its scale-up cycle times to as little as 12 months, and it upheld its QbD standards, which ensure the quality of its process.

The Thermo Scientific solution is also helping Alphamab to manage the scale-up and technology transfer of as many as 20 projects at a time.

“Doing multiple scale-ups, each with their own technology-transfer standards, without an automation platform would be nearly impossible, not to mention error-prone,” says Xu. “But with the Thermo Scientific solution, we can cut out the errors along with a lot of time and cost to ensure faster time to market and, ultimately, greater profitability and competitiveness.”