mAbs: Making the Right Equipment and Process Decisions

How to identify the best equipment for your monoclonal antibody production

What is the best equipment for producing mAbs? What are the main key considerations? How do you decide between single use and stainless steel? We spoke with Matthew Zustiak, Director of the Bioprocess Collaboration Center at Thermo Fisher Scientific, to discuss the challenges of equipment choice.

What is your role at Thermo Fisher Scientific?

I am the Director of Research and Development for our Bioprocessing Collaboration Center. The Center and its team collaborate internally within different groups of Thermo Fisher Scientific as well as externally with other companies. My area of expertise is around upstream bioprocessing. During my career, I've spent several years in process development, covering everything from early to late stage development, and I have experience transferring those processes into manufacturing, which gives me a useful overview of the entire process. The Bioprocessing Collaboration Center is based in St. Louis, Missouri, adjacent to our pharma services group. We have a pilot lab, operating up to the 500-L scale, that we use to test new equipment and instruments at various stages of development to provide useful feedback on their development to increase speed to market and improve market adoption.

What specific equipment is needed for mAb production?

mAbs are primarily produced in mammalian cells, so for the upstream process – where you are growing cells – you require various culturing systems for small culture volumes out of cryopreservation with progressively larger systems used through the scale-up of the culture until a large bioreactor is used for the production stage. At the early stages of the seed train, you tend to see the use of shake flasks and rocker bags, which are single-use systems. In later stages, we generally see requirements in the 1,000–5,000-L range – the top end of this now enabled by Thermo Fisher Scientific's introduction of 5,000-L single-use products. However, as you scale the culture up, the demands of greater volume instruct the choice of equipment. A production scale bioreactor could be as little as a 500-L system, covered by single use products or all the way up to a 15,000 L production volume capacity using larger, stainless-steel bioreactors.

After the production phase, the supernatant needs separating from the cells, which requires a harvesting system, such as a centrifuge followed by depth filtration or a dual stage depth filtration system. From here, the product moves into equipment specialized for purifying the antibody out of the clarified culture fluid. This most often involves chromatography systems of various sizes, depending on the amount of material you are producing, along with the appropriate columns for your protein. From here, you will employ viral filtration, ultrafiltration and diafiltration steps, to provide buffer exchanges and formulate the product into a stable final formulation at the desired concentration.

For bulk drug substance, the product is often filled into bags or carboys and frozen or kept at 2-8 °C. For drug products, specialized filling equipment is required for sterile vial filling operations and, in some cases, lyophilization equipment as well.

How do equipment requirements change as development progresses?

The three main phases of bioprocessing, upstream (cell culture), harvest and downstream (separation, purification), and fill and finish, must all scale to meet a defined product output. How much material or product you need to produce is a critical question that companies should address early in the development process because it has a significant impact on equipment choice and requirements. It is not simply a matter of scaling the equipment in size; other choices can be made, such as stainless steel or single use. For anything sub 5,000 L, single use equipment can be employed, which brings discreet advantages to a process. Single use removes the need for certain steps (for example, cleaning and sanitizing), allowing manufacturers to swap between products efficiently and without the need for a host of analytical methodologies to ensure there is no cross contamination. However, single use is only cost-effective at lower volumes and, when production demands increase, stainless-steel vessels become the better choice. Stainless steel may also be the better option if the manufacturer is concentrating on a single product because cleaning and sanitation protocols are simplified.

At what stage of development do companies need to start thinking about equipment and processing needs?

One important question that should be asked early on is, is it commercially attractive to set up a full-scale production plant, or is it better to contract out the work to a CDMO? The choice of building in-house capacity or using a CDMO needs to be considered early in the development process. In the early phases of product testing, especially at the clinical trial stage, commitment to a full-scale processing facility may not be as attractive as engaging a CDMO. This is effectively a de-risking position until clinical confidence in the product is gained and when there is certainty that no further process changes will be required.

If you do opt to build your own plant – which can have long-term benefits – then the earlier this is considered the better. However, it is important to have thoroughly defined your entire process before committing to a plant, which may mean waiting until in vivo testing of your product is complete. For instance, as you learn more about the product in its clinical setting, late-stage changes in processes are often discovered and these can bring about expensive modifications to the equipment required as well as changes in the accompanying regulatory approvals.

What is your advice when it comes to making final equipment decisions?

Market size for the final product is a critical starting point. Are you looking at 2000 patients a year or two million? You must build your capacity from the start to meet your market estimation, and this, therefore, dictates the type of equipment (and size) that will be required. You also need to consider how many batches per year will be required, and ensure you have the appropriate profile of equipment to meet that demand.

Occasionally, you find yourself on the borderline between single use equipment and more permanent stainless-steel vessels. In this space, you may find that the costs of single use begin to outweigh their benefits. In such cases, if you go back and look at the early stages of the process, there may be changes you can make that would have an advantageous effect later and help with equipment decisions. For instance, upstream host cell engineering may be able to double or triple the titer, ultimately making single use the way to go.

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What about the vendor–client relationship?

To ensure you are choosing the right plant for your process from the beginning, it is crucial to work with a trusted partner that has experience with the complete system, including how systems scale from the early research phases through to production. At Thermo Fisher Scientific, our experience in the biopharma industry and continued investments in innovation means that we have extensive, important knowledge to share with our clients. We can engage early in the process and collaborate to plan the optimum system, which is how we prefer to work with our clients. In my experience, once a well-considered system is up and running – and properly validated – it should be very robust. At the early stage, it pays to ensure that the appropriate equipment is chosen to meet the exact specifications and output of the proposed process, as changes later down the line become ever increasingly expensive.

We also recognize that many of the process steps are common to most – if not all – systems; by providing standardized units for these steps, we can expedite process development. Recently, Thermo Fisher Scientific launched its "mAb Process Playbook," focusing on single-use technology recommendations for production up to 2,000 L. The idea here is that a package of single-use components can be sent out to clients that can be readily incorporated into a manufacturing process, providing an almost end-to-end solution.

How do you expect technologies to continue to advance in the future?

Every change in the biopharmaceutical area has historically involved incremental improvements. Right now, a key trend is process intensification, which is pushing titers higher and higher. There is also a shift towards greater product quality and consistency, especially during the upstream phases. This means that there is a growing focus on new analytical technologies, with different sensors and probes that can be inserted into different parts of the process to capture real-time data. This will eventually allow "real-time release," where manufacturers can have confidence on the quality of the final product without having to tap samples for assessment.

Designing and equipping a manufacturing process efficiently and cost-effectively requires extensive planning. Knowing the end market use, having realistic production requirements, and determining whether to scale up or scale out are all critical factors; once in place, a manufacturing plant is very expensive to change. Thermo Fisher Scientific has the right depth of experience and is continually working at the forefront of improvements to methodologies and equipment. We welcome any company, regardless of size, that would like to discuss its ambitions early in their decision-making process.