Early Scale Up Strategies

Preparing for scale up in the early phases of monoclonal antibody development

Monoclonal antibodies (mAbs) are a key part of the biopharmaceutical landscape. Although their manufacture is well established, the sensitive nature of biologic products continues to give rise to challenges. Efficient and reliable scale up is a key component of mAb production – and there are several considerations that need to be understood and reviewed early on in the process. In this article, we explore scale up in the earlier phases of the product lifecycle with Kristina Pleitt from Thermo Fisher Scientific.

What is your role?

I'm a Senior Manager in the Bioprocessing Collaboration Center in Thermo Fisher Scientific's R&D Innovation team. While we sit in the Bioproduction Group, our team is actually the interface between two business units, Bioproduction and Pharma Services (a CDMO for recombinant protein production via mammalian cells). This allows us to have good exposure to most of what Thermo Fisher Scientific offers, be that equipment, single-use products, or services for clinical and commercial drug substance development and production. Our role at the BCC is to operate between these two business units and help fill gaps with products and strategies that currently don't exist. We also have the task of refining our existing products to ensure we are providing the best end user experience. Our team members have extensive experience in mAb process development and scale-up for production, including full development and tech transfers for early and late phase molecules.

mAbs are well established in the industry, so does this mean that scale up is straightforward?

Scale up is viewed as straightforward, but this doesn't necessarily mean it is simple or easy. There is a great deal that needs to be considered. Of course, you need to determine the process itself, but you also must understand the at-scale requirements, such as the logistics of how it's going to be manufactured, the required equipment, the footprint of the plant, and any processing constraints or limitations that are introduced when you move from the bench into the production suite. You have to address many aspects in your development plan.

A few things to keep in mind as you consider the feasibility of scaling up, especially in the early phase, are time of development and process requirements versus equipment/facility capabilities. And cost is always seen as a major factor. I would advocate that, even at the earliest stages of development, it is important to remember the longer-term goal. Sufficient time and expense spent at the early phases will save both time and money in the long run once large-scale production begins. As you move into scale, cost savings and other aspects that have been identified and put in place at the early stages of process development are amplified. Building and applying process knowledge early in development and initial scale up batches becomes very valuable both short- and long-term. It plays a role in establishing more robust methodologies for your process through its lifecycle. It is essential to understand that the early phase work is a necessary part of building the process for the final, large-scale manufacture of the product. Being mindful of this will avoid focusing on data that is only relevant to these early steps in the larger process.

More broadly speaking, at the early stages of scale up, the focus should be balanced between essentials and on manufacturing robustness. It is important to gather as much knowledge as possible so that, when you reach the manufacturing stage, there will be less challenges related to scaling to overcome. Be mindful about the experiments you choose to perform, ensuring each one gives more knowledge towards the process space. Having an oversight of what will be needed at the next stage informs the choice of studies at this earlier stage, so it's important not to overlook experiments, such as stability, for example.

What are the biggest challenges during the early scale up stages?

When you are gathering process knowledge, you need to be as complete as possible, but this is time consuming and expensive – so there is a temptation to skip some of these steps. It is also tempting to cut back on data ranges within experiments. However, you must remember that any shortcuts could result in costly problems later as you scale! Issues can also be exacerbated by lead times; it is essential to plan far in advance to secure the appropriate supply chain. Sometimes his does not sit comfortably with those clients wanting to chase aggressive timelines and move their programs along at pace.

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In summary, simplicity is key. The simpler the process, the lesser the chances for errors as higher yields are sought through scale up. Consider, for example, manual processes; such steps carry a high risk of error because different operators may perform them differently, which adds complexity to your process. Time taken to reduce or eliminate these steps – steps that are seemingly benign at a small scale – will vastly improve your chances of having a more robust process for larger scale production. The object is to understand your system in as much detail as possible, while balancing the time and cost it takes to get there. With this in mind, it is also important to know what kind of facility you will be transferring the process into for manufacturing; it will also point to further key experiments that need to be conducted at small scale to facilitate the transition.

Are there any mistakes you see being made in early-stage development time and time again?

One mistake that can creep into early R&D is to ignore incorporating short experiments to improve the manufacturability of the process. By considering how the process will be performed in GMP, a few select experiments can provide insights on the design space and de-risk potential challenges at-scale. These could be simple studies to improve process ranges, reduce operator interactions, or removing process performance-based decisions.

Another common problem is neglecting to perform an engineering run at-scale. Yes, this is something that does take time and money, but it is a great way of de-risking the process – and can save you time and money later on in expensive investigations, held up lots, and burdensome change controls in full GMP systems.

What are your recommendations to save time and costs?

One of the easiest ways to condense timelines is to leverage an existing platform. There tends to be a great deal of similarity across processes providing a solid foundation of knowledge and standard practices. Attempt to use standard platform processes and practices wherever possible and leverage raw material stocks to avoid long lead times. Other ways to cut time are to be judicious in the studies you do and partner wherever possible. Ensure each development step is critical; ask whether you are adding to the process knowledge or de-risking the output. Much of these depend on you having full oversight of where you want to be and how you will reach that point – something only experience brings. Building on what's known allows you to focus effort on refining and optimizing critical parameters.

Cost is again a balance of the value from de-risking versus the cash spent. At the early phase, raw materials are particularly expensive and can have long lead times. Working with a trusted and experienced partner, can help where there are already existing stocks. It is also beneficial at this stage to consider both the immediate and longer-term view. For instance, how many cycles or batches do you anticipate producing with a specific chromatography column? Is it possible to use stock media rather than custom? While these may seem like more cost up front, a little additional knowledge to increase process robustness could help during production.

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How can Thermo Fisher Scientific's expertise help support early stage scale up?

Thermo Fisher Scientific offers a lot of expertise and experience in this sector and has been working with companies throughout their scale-up programs for many years. Within our Pharma Services Group, we have two specific programs: "Quick to Clinic™" and "Quick to Care™". These platforms focus upon the development of manufacturing processes and encompasses a wealth of experience. Similarly, we have a considerable range of products, from media to single-use products that can scale with your program, and that means you can consolidate your efforts within one dependable partner. Partnering or collaborating with clients is very much part of our ethos. Not only does this better prepare the supply chain, but it also helps us identify ways to meet the clients' needs and facilitate their processes – both now and in the future.

Through our collective bioprocessing development and manufacturing proven experience, we have a complete overview of the pathway from the bench to manufacture with good process knowledge at every scale. Our clients can feel confident that Thermo Fisher Scientific will use its extensive expertise and experience to fully support them at every step of their journey.