Preparing Biologics for Commercialization

Understanding Strategies to Reduce Risk and Optimize Outcomes in Drug Development

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INTRODUCTION

Within the drug development process, there are several steps that occur between the laboratory and final manufacture of the drug product. Different players step in during each point, so keeping a program with many moving parts on track requires planning and time-tested execution approaches. An integrated Contract Development and Manufacturing Organization (CDMO) with the ability to carry out the late-stage development can ease the pain at each point.

LATE-STAGE DRUG DEVELOPMENT

As a drug moves into late-stage development, there are several considerations for the developer to minimize risk and have efficient time to market the product. The major concern is having sufficient material in time for the pivotal clinical trials and later commercial launch. It is also prudent at this point to develop a plan for commercialization of the product and its manufacturing process.

To be successful requires a solid Chemistry, Manufacturing and Controls (CMC) strategy. This strategy, which is part of the license or market applications, has key components that when done properly can minimize false starts. Some of the components of a good CMC strategy include process optimization, information on both process characterization and analytical characterization of the product, a robust controls strategy, and comparability data across various points in the manufacture and development. This data lays the groundwork for the commercial process and includes the process & method validation, specification setting, and stability strategy. Planning for process control strategy and process validation proactively makes certain that you are minimizing the inherent risks along the commercialization process.

It is important to engage with the regulatory agency early and work with them through the process to avoid pitfalls. A solid CMC plan provides a road map to move ahead in the development, assuring all the important points are addressed.

The plan also shows where you might be able to speed up a step or where you must be more thorough.

At this stage in development, demand uncertainty is a risk, and the scale at which you choose to produce the asset is going to be important. Selecting the right scale for the process can minimize this risk but requires an understanding of the cost of goods (COGS) and of the demand from clinical trials through commercialization.

Another consideration is building out the material stock. This requires accurate forecasting but forecasting only goes so far. Additional capacity or flexible capacity is the key to navigating these risks. For example, jumping from a 2000 L single use bioreactor (SUB) to a 15,000 L stainless steel bioreactor comes with added overhead such as increased costs for materials and additional validation work and turnaround time that may not be appropriate for the product demand. It may assure that you can meet optimistic demand but may require significant capital investment and operational costs for the process validation campaign which is typically conducted before the pivotal trail readout. It is risky to invest too early because the product may not succeed in the pivotal trial or the forecasted commercial demand may not be realized. Using reactors that have a 5000 L scale allows a scale-out approach that is more gradual scale-up than jumping to a 15,000 L vessel.

The benefit of a 5000 L scale-out approach can also be illustrated with a simple example of a typical demand scenario. Assume that you need 400 kg of drug substance per year. You can achieve that in a 5000 L scale by running twenty-one batches at a cell culture titer of 5 g/L or eleven batches per year at a titer of 10 g/L. According to the 2022 BioTrack Report, 80% of monoclonal antibody class commercial products have annual demand no more than 400 kg/year. Through utilizing the 5000 L scale, there is significant improvements in flexibility to meet demand. How you decide to support your scale up can provide adaptability during the program's lifetime and more efficiency for the overall operation.

In the past, the approach to increasing capacity or planning for a new product was to either build a new facility or retrofit an old one. With the current need for adaptability, the trend is to follow a platform approach where equipment can easily be adapted to a new product or facility. When working with a CDMO, the standards and structure put in place by the organization makes this flexible approach much more viable.

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BEST PRACTICES

Even with a plan, there are roadblocks that can set back the program. One of the most frequent obstacles is the desire to move faster than prudent. This may generate a roadblock later, such as rapidly moving into process performance qualification (PPQ) with a process that is not robust or well characterized. An example is a program that started without recognition that there was an undefined hold time. In one facility there was no defined hold point and in another, an uncontrolled hold point that was held longer. This led to product quality failures and the need to go back and examine the entire process. Another example is a parameter that was believed to be non-critical, proved to be critical based on a PPQ campaign. That led to a failure and restart of the PPQ campaign, along with timeline delays. Both could have been avoided by critical examination of the process and performing a robust process characterization.

Another roadblock is comparability. Even if a PPQ campaign is operating in the normal range, you need to understand the data used for comparison. An example is a new site where the PPQ being done was executed with a hold time that was lower than historically used before. That difference in hold time led to

differences in the Critical Quality Attribute (CQA) and even though everything was within specifications, the differences were flagged and had to be understood and explanation documented.

There are approaches to de-risk the product life cycle by focusing on technology transfer, process characterization, and process validation. It is best to standardize the procedures and set best practices across sites. This creates "guard rails" and helps build organic cross-functional and cross-site expertise that can help prevent some of these issues.

Some examples of this strategy include having a standard technology transfer process that has global standard operating procedures (SOPs) and is applied to all sites. The global subject matter experts (SMEs) support all sites and ensure everyone is working off the same templates. Having SME's that have seen similar situations before has real value in the implementation of a campaign. Following a robust business process will ensure the risks are identified early and all the questions are answered before proceeding to the next step. This is key to making sure you never inadvertently overlook something important to check on, like hold times or column sizes.

One of the best practices used at Thermo Fisher, especially in a late-stage project, is providing a CMC lead who helps with the overall picture of the program and advise on risks that may crop up. The functional area staff do the day-to-day work, and the CMC lead keeps the big picture in mind to assure the program keeps to targets and schedule.

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The final aspect that needs to be considered is the transition from drug substance to drug product manufacturing and how to optimize the process for the drug product. If you consider the CMC activity, it is not just a drug substance or a drug product but both and coordinating the two processes is necessary. There should be a plan of how to feed the drug substance into the drug product. Optimizing the testing for the drug substance and drug product stability makes it a more sustainable approach. In addition to the coordination, having both processes under one roof while using one quality system generates efficiencies and can shorten the timelines.

DIGITAL TOOLS

Digital capability impacts nearly every industry. As a service provider, Thermo Fisher believes examining data is extremely valuable and we can look at the trends to enhance robustness. Building a system that allows easy visibility into the process with milestones and risks with color coding shifts focus to discussions with the client.

One widely used digital tool is Skyland PIMS, a web interface that provides process data visibility to the manufacturing team on the floor as well as the outside team. The tools are set up with audit trails where you can examine historical data and conduct statistical analysis to assure everything is on track. Thermo Fisher has worked with external vendors to set up globally standardized approaches and tools to give customers visibility and provide consistent worldwide information. It is a value add for all involved.

CONCLUSION

Given the high stakes in late-stage drug development, strategies to maintain flexibility, adhere to timelines, minimize risks, and provide successful outcomes are critical. Working with a partner organization who has navigated these pitfalls, with strategies and tools in place, can deliver numerous benefits to these programs. An experienced CDMO understands how to reduce the risks, maintain flexibility to cope with the hidden unknowns, and provide the customer with the most up-to-date tools and approaches.