The Risk=Speed Equation

Balancing Risk and Speed when Time is of the Essence

Proven Strategies to Accelerate Drug Development

BioReliance®

Pharma & Biopharma Manufacturing & Testing Services

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Proven Strategies to Accelerate Drug Development

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For an early-stage biotech, the decisions made now will shape the future of the company and can determine long-term success or failure. From day one, the pressure is on to rapidly progress towards milestones and demonstrate value to investors and other stakeholders. You need to move quickly and use resources efficiently to advance a drug candidate into the clinic and ultimately onto the market. But while time is of the essence, this fast pace must be effectively balanced with risk mitigation.

Companies are faced with making a strategic assessment of how best to balance speed and risk and the impact of that decision. One extreme is to reach the investigational new drug (IND) or Investigational Medicinal Product Dossier (IMPD) filing stage at a slow and measured pace, with minimal risk; the other extreme is to get to IND/IMPD as quickly as possible but face an increased risk of failure. Fortunately, there are many options on the speed/risk spectrum between these two extremes that can effectively satisfy both the speed and risk imperatives.

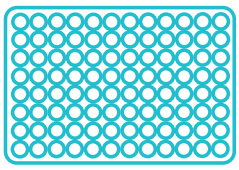
With an overarching strategy in place for development, additional decisions remain that are unique to each company, process and molecule and must also balance speed and risk. Small biotechs need to decide on how they want to structure their team and whether they have the experts to take them through the various stages of process development, as well as chemistry, manufacturing and controls (CMC), filing and regulatory affairs.

Next comes process development. At this point, the company must set goals for the productivity of the cells, the yield and the quality of the molecule. A master cell bank that will support manufacturing throughout the entire duration of the project must be created and its monoclonality, stability and viral safety confirmed and maintained.

Starting at the point of transfection and including all the components needed for production, researchers and regulatory authorities need to be able to trace the process of cell line development.

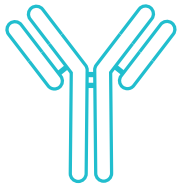
Additionally, the representativity of the preclinical material versus future clinical material must be ensured and patient safety must be guaranteed throughout the process.

Each of these steps in the drug development process offer opportunities to accelerate timelines while ensuring that risk is properly mitigated, and quality is not compromised. Below, we describe four areas of development where we have applied this strategy for customers:



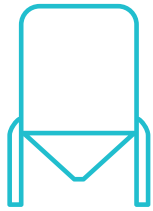
Identification of high-producing cell lines

1



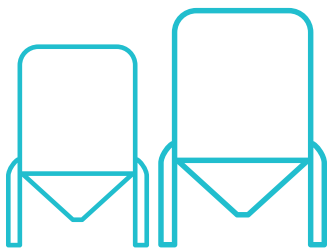
Development of analytical methods

2



Reduction of host cell protein in the bioreactor harvest

3



Scale-up of manufacturing to support clinical trials

4

A Fast-Track Approach to Accelerate Identification of High-Producing Cell Lines

The quest for a viable upstream process relies on generation of a cell line expressing the protein of interest. Unfortunately, finding the best-producing clone is often compared with looking for a needle in a haystack. Making this more challenging is the pressure to get it right the first time, quickly and while mitigating risk and keeping cost under control.

Our mini-pool approach consists of dividing a transfected cell population into many tiny populations in 96-well plates. This facilitates detection of high-producing cells as a result of the reduced diversity and reduced competition occurring within these mini-pools. Having a large number of mini-pools available for screening increases the probability of isolating a high producer.

To accelerate the timelines, process development using material from the mini-pools can be done in parallel with expansion, creation and characterization of the master cell bank. This is in contrast to conventional approaches in which creation of the process development cell bank, followed by expansion of cells and creation and characterization of the master cell bank, are completed prior to initiating process development.

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Conducting these activities in parallel, rather than sequentially, can save up to three months as generation of the master cell bank requires about one month and characterization can take between six and eight weeks. Parallel development of analytical methods at this point can also further reduce timelines.

A Streamlined Approach to Analytical Method Development and Implementation

The development and implementation of analytical methods are essential for success at all phases of a molecule's journey, from pre-clinical development, to clinical manufacturing and ultimately, commercialization.

Driven by the need for rapid advancement towards key milestones, an early-stage company must optimize the balance of speed and safety, while ensuring quality and gathering important information about the molecule. Ultimately, the analytical package must be designed to mitigate the risks for key milestones. Missing key milestones might result in failure at an early stage and the need for subsequent redevelopment and remanufacturing, which adds significant time and cost to the process.

Early-stage companies can, however, can leverage a streamlined analytical program that focuses on what is needed for IND/IMPD filing and for Phases I and II batches. The same analytical panel can be applied in characterization and comparison of drug substances (DS) in both preclinical and GMP batches with additional necessary safety controls to ensure GMP DS as will be dosed in humans the first time. This approach is time- and cost-efficient while delivering the necessary information for both the company and regulatory agencies

For an early-stage company, a basic analytical package should include content, purity, activity and safety controls. Establishment of analytical methods can be accelerated by starting from use of standard or platform methods, such as H/UPLC, CE-SDS and glycan profile analysis. Specific needs for, such as product degradation or process impurities can be addressed by further development. Potential post-translational modifications, aggregation or degradation of the product could have an effect on the efficacy or safety and should be assessed. If a molecule is sensitive to oxidation, for example, a method to characterize the oxidation is needed.

Validation efforts will first focus on the purified product to ensure that the analytical method is fit for purpose (release and stability), meaning that it is able to detect what is it intended to detect with sufficient sensitivity. Following product characterization (i.e., identification of post-translational modifications and glycosylation) and production of the first GMP batches, the analytical methods will be refined as needed. The panel will then be capable of following characteristics of the molecule (including parameters that assess stability) to ensure batch-to-batch consistency.

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An Innovative Combination of Precipitation and Filtration to Reduce Host Cell Proteins

Host cell proteins (HCPs) are an inevitable by-product of biologics manufacturing and can have a negative impact on product quality, efficacy and patient safety. Processes designed to remove HCPs from the bioreactor harvest must not only be successful in achieving acceptable limits, but also be scalable.

We recently developed a process to reduce HCPs in a bioreactor harvest for a customer who needed to supply drug substance for a Phase 1 clinical trial, which was scheduled to start in one month. The high level of HCPs (1,000,000 ppm in the harvest and 700 ppm at the end of purification) unfavorably impacted the planned clarification process and subsequent downstream steps. The goal was to reduce the level to a maximum of 300 ppm at the end of process purification and ensure the entire 2000L harvest could be processed.

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HCP levels can be reduced using mixed-mode and hydrophobic interaction columns, but these approaches are more complex and would not have allowed an optimized solution to be delivered within the compressed timeframe. Further, these options would not solve the problem of filterability of the 2000L using a conventional clarification filter. A reduction in bioreactor size to 1000L, which would allow for this clarification, was not feasible due to the amount of drug substance needed for the trial.

The approach selected to drastically reduce HCPs and increase filterability was caprylic acid precipitation followed by filtration using Clarisolve® filters. Design of experiments (DOE) was used to identify the optimal conditions for precipitation with a focus on two key parameters, the concentration of caprylic acid and temperature. Use of DOE enabled us to reduce the number of experiments required to evaluate these parameters, which was crucial as we had a limited number of time and cells available for the study.

The combination of caprylic acid precipitation and Clarisolve® filters enabled a reduction of 80% of harvest HCPs to reach a target of less than 100ppm at the end of process purification and clarification of the entire 2000L harvest. Incorporation of the Clarisolve® filters also had a positive impact on downstream steps including reducing the number of filters needed, the volume of water needed to wash the filter and the dilution of the material after the wash. With a reduced dilution, the capture step following the filtration required less time.

This solution was developed within the one-month timeframe and strategically combined innovative Clarisolve® filters with a conventional approach to precipitation.

Scaling a Process Directly from 3L to 2000L

Being able to quickly produce a batch at the right time and at the right size is essential to support development and get to the finish line faster.

Once a robust upstream process established, scalability is critical to support demand for drug substance during clinical development. A typical scaling initiative takes a 3 liter process and increases it to 2000 liters with intermediate volumes and pilot runs in-between. This stepwise approach can require up to three months and can slow progress towards important milestones. We explored strategies to accelerate this scale-up process while ensuring safety, efficiency and robustness.

We developed a strategy to enable a direct, efficient and robust tech transfer of a monoclonal antibody production process from a 3L bioreactor to 2000L without the need for any intermediate volumes. The knowledge generated during process development, as well as a specific model designed to keep the oxygen mass transfer coefficient (KLa) stable in any bioreactor, were key factors in our success. In addition, we conducted a clone stability study and defined process tolerances for volume, gas level, pH, feed and other parameters as all system characteristics must be considered. Mixing efficiency, sparging efficiency and fluid movement and gas/liquid interaction can all vary among bioreactor sizes and were modeled and evaluated.

Our approach allowed us to achieve similar conditions for production at the 2000L scale as were developed for the 3L bioreactor. By leveraging our deep understanding of process dynamics and sophisticated Mobius® bioreactors, process scale-up from 3L bench scale bioreactors to 2000L becomes faster, more predictable, and consistent. The need for intermediate scale steps at 200L and 1000L, for example, along with pilot runs become obsolete. Elimination of these intermediate steps can significantly shorten the scale-up process – accelerating the time to market and delivering a competitive advantage.

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Choose a Partner to Help Balance Speed and Risk

As an early-stage biotech company, you face uncertainty but need to move quickly. Success is measured in sustained progress towards milestones and risk looms in all directions. At this stage, many small biotech companies decide to outsource some or all of process development and manufacturing.

Identifying the right outsourcing partner can increase the odds of success for your company, your investors and ultimately, patients with unmet medical needs. A trusted contract development and manufacturing organization (CDMO) can help guide you through the different stages of drug development and to bring the necessary expertise and infrastructure to the table. But how do you find the best CDMO?

- Look for a partner with the expertise and experience to support the decision-making process and become a valuable advisor to the company.
- Ensure the CDMO has the flexibility to adapt to specific project requirements and the ability to handle surprises that may arise during process development.
- Choose a partner with experience engaging with regulatory agencies; one who can help answer questions and explain processes and control strategies.
- Select a partner with specialized, in-house experts readily available when urgent matters arise and one project manager to ensure the process and communication is centralized, coordinated and transparent.

Move Quickly and Stay in Control

While the drug development journey is long and challenging, there are many ways to accelerate progress towards the clinic and the market, and at the same time, control risk and maintain quality. A trusted, experienced partner can help identity those opportunities and implement proven strategies, such as those described above, customized for your company, program and molecule.

About BioReliance® End-to-End Solutions

We are an integrated contract development and manufacturing partner, offering adaptive solutions for small and mid-sized biotechs needing to develop and commercialize biologics. We do this by balancing speed, risk and cost through custom solutions, by leveraging our bioprocessing technologies and process development expertise, and by allowing our clients to transfer their process and knowledge to their end point at any step of the way.

To learn more, please visit
EMDMillipore.com/adaptive-CDMO

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