A Novel Approach Holds Promise for Gaining Capacity: Blueprint Your Cell Lines Prior to Scale-up

Leveraging the Role of Cell Line Development in Biopharmaceutical Drug Development

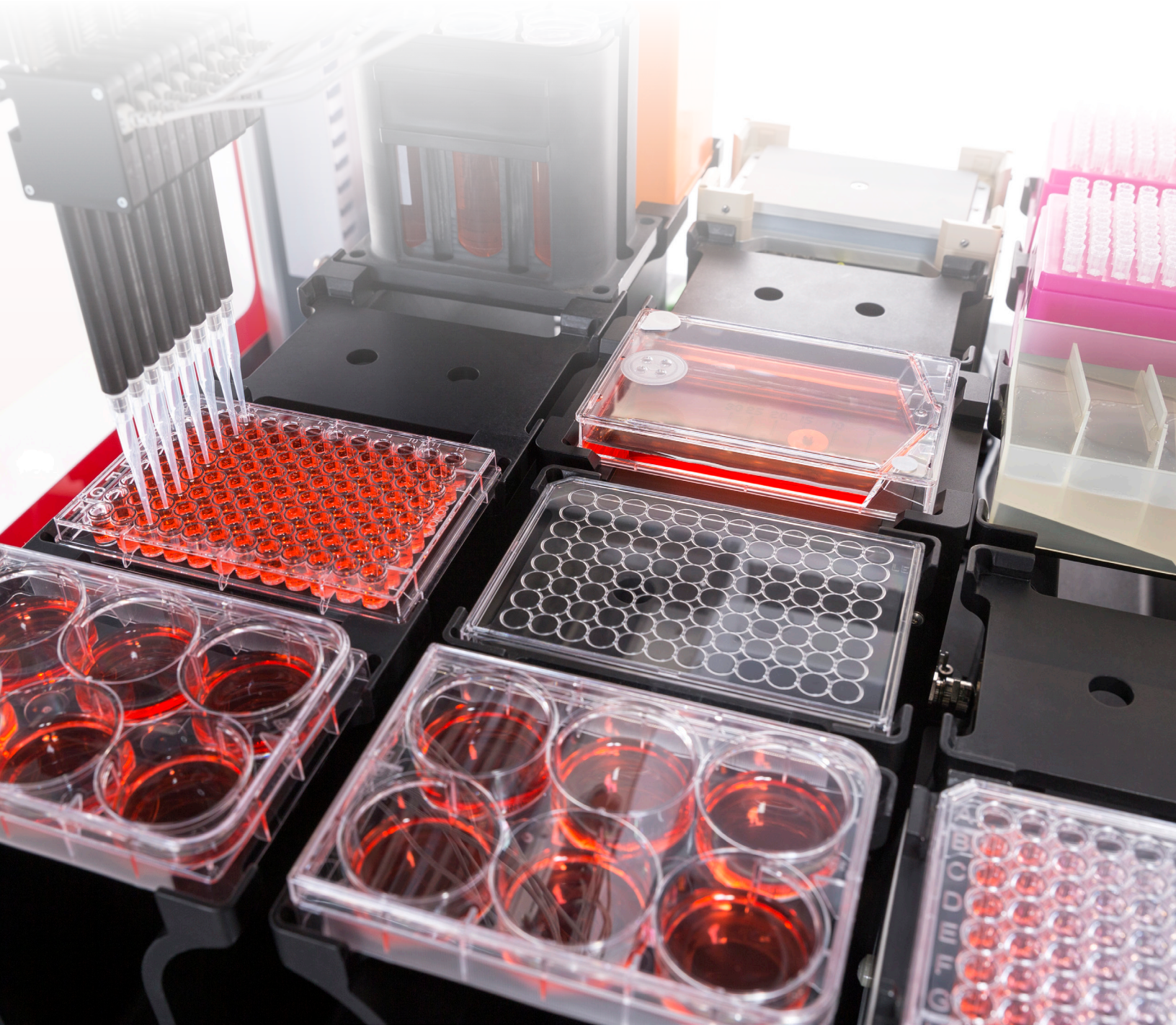
The landscape of drug development is undergoing a significant transformation. The pharmaceutical industry is now transitioning to include more biologically-derived therapeutics in their drug development pipelines, putting Cell Line Development (CLD) in the spotlight. This shift intensifies the demand for Chemistry Manufacturing and Controls (CMC) departments to deliver products faster without compromising quality.

CLD, the first stage of CMC, aims to produce stable, high-yielding cell lines which can be used for the production of biotherapeutics of interest, such as monoclonal antibodies and other recombinant proteins. The process begins in small-scale cell culture and involves multiple stages, ranging from initial target gene construction and cell transfection to selecting of clones expressing the target protein most efficiently, through to stability testing to ensure selected clones produce the target biologic at a stable rate. Once these steps have been implemented, this master cell bank (MCB) is selected, serving as a source for future scaling during Process Development (PD). Therefore, establishing a high-quality MCB is becoming a priority. The emergence of complex therapeutic molecules, such as bi- and trispecific antibodies and antibody-drug conjugates, impose significant challenges on CLD labs to meet capacity and regulatory requirements while managing an increasing number of candidates.

CLD is the foundation of successful drug development. Variations at genetic, genomic, and metabolomic levels within a single cell line can lead to differences in productivity (how much of a particular biotherapeutic can the cell line produce), product quality (the efficacy and safety of the drug), and behavior in the bioreactor (how well cells expand and function in the bioreactor environment). Consequently, the quality and characteristics of the cell line developed during CLD directly influence the success of subsequent stages of biomanufacturing, including PD. Over the past six years, significant improvements have been made in cell line development, including the introduction of better screening and imaging tools to confirm monoclonality, which is a regulatory requirement. However, CLD still requires screening numerous clones to identify those that produce high levels of the protein of interest, making CLD a very complex, time-consuming, and resource-intensive process.

CLD is followed by upstream PD, which optimizes and scales up production processes to ensure the successful transition from small-scale development in a laboratory setting to large-scale

manufacturing for preclinical validation, clinical trials, and commercial production. CLD and PD are closely intertwined. Thus, data gathered during CLD processes will directly influence the subsequent steps of upstream PD. This underlines the need to improve the CLD workflow through automation, analytical capabilities, and digital/data solutions to accelerate the speed at which a drug candidate moves through the pipeline and ultimately reaches the market. Adapting a forward-thinking and more holistic approach, which entails considering PD aspects during the CLD stage, could potentially streamline CMC within the drug development process. However, the sheer volume of candidates and parameters typically screened for in CLD each process makes a comprehensive merger of methods and data analyses between PD and CLD complex at a minimum. Consequently, most CLD labs still select clones based on a fixed set of traditional parameters and accept the risk of overlooking good candidates.



Navigating Through the Challenges of CLD

Despite the benefits that successful CLD brings, navigating the associated challenges within the workflow is not an easy task. One of the current bottlenecks of CLD workflows is the need for further automation of existing processes. Of course, there are several instruments already embedded within this workflow that can help increase capacity and levels of consistency, such as automated liquid handlers. There remains a pressing demand to incorporate automation into other crucial parts of the process, such as sample preparation for analytical methods, bringing consistency to processes, and increasing laboratory associate capacity to handle more specialized tasks during drug development.

Increasing analytical capabilities by incorporating screening assays early in the workflow can offer valuable insights into the robustness of cell lines and clones against certain parameters, potentially predicting further stability within the process. Consequently, introducing analytical tools earlier in the development process and better integration and feedback between equipment can accelerate the process facilitating more informed decision-making.

Miniaturization, which mimics large-scale processes, is another key aspect as the industry matures. At present, many stages of CLD are performed in well plates where certain relevant variables, such as pH or dissolved oxygen, are not controlled. Therefore, investing in developing suitable small-scale models that accurately replicate the bioreactor environment holds promise to make the overall process more cost-effective.

Another significant challenge is associated with data management. CLD generates a vast amount of data from numerous sources and about many clones. Additionally, it can be challenging to identify the best candidates based on the results obtained from different instruments (e.g., high-throughput screening systems and analytical equipment) due to the lack of data capture methods and standard formats for data reporting. Thus, there is a need to develop innovative solutions that allow for better integration and interoperability between equipment and labs. This will improve communication and data sharing between CLD and PD labs, making the decisions on candidates for the MCB more informed and effective.

While each cell line development lab employs unique workflows based on specific applications, addressing these common challenges will lead to the introduction of general process improvements while still allowing for customization.

Solutions for CLD and PD Challenges from the Life Sciences companies of Danaher

With CLD and PD becoming closer workflows, critical stages of CLD will affect PD success. Clone screening is one such process step, and has become more vital for overall success than ever before. The accuracy of clone screening determines the selection of the most viable candidates for further development while discarding the less promising ones. This ensures that not only that the following steps in CLD and PD are efficient and cost-effective but also provides a smoother transition to the MCB. Incorporating technologies like fingerprinting early in CLD enables us to pinpoint high-performing clones and efficiently weed out less-promising ones. This strategic approach reduces unnecessary efforts not only during the initial stages of CLD, which include crucial phases like scale-up and bioreactor studies but also after the handoff of the MCB to PD. It ensures that only the most viable, robust clones are carried forward. Ultimately, this streamlined approach fosters a more time and cost-efficient drug development process.

In response to the complex demands of CLD and PD, Danaher Life Sciences has introduced three pathways to boost successful outcomes:

- Laboratory Automation: The Life Sciences companies of Danaher use the power of advanced technologies to increase workflow reproducibility and standardization. The integration of cutting-edge tools streamlines and automates processes, reducing the potential for human error, optimizing resources, and improving overall efficiency and productivity.
- Analytical Tools: The Life Sciences companies of Danaher promote the use of scalable solutions to gain critical insights during earlier stages of CLD. These robust, technologically advanced analytical tools are designed to enable rapid, accurate assessments, facilitating timely and informed decision-making during every crucial step of drug development.
- Digital Solutions: The Life Sciences companies of Danaher acknowledge the importance of enterprise-level workflow management, data handling, and analyses. By incorporating digital solutions, customers can manage and interpret the vast amount of data generated during the drug development process effectively and efficiently, ensuring data standardization.

One specific example of a solution is ValitaTiter IgG assays, an analytical tool from Beckman Coulter Life Sciences used for high-throughput quantification of Immunoglobulin G (IgG) in the process of quantifying monoclonal antibodies (mAbs). The Beckman Coulter Life Sciences ValitaTiter IgG assays provide rapid analytical data on IgG titer in under 15 minutes with an easy-to-follow and user-friendly workflow. Furthermore, these assays can be fully automated when combined with Molecular Devices SpectraMax microplate readers, offering a rapid and cost-effective platform for IgG quantification in drug discovery and development.

Danaher Life Sciences emphasizes the importance of laboratory automation and digital solutions by providing tools that encompass simplicity, speed, and scalability. By introducing these novel technologies, the Life Sciences companies of Danaher aim to speed up successful drug development from vector construction to the final development of the MCB, aiming to reduce costs and enhance sustainability.

Streamlining CLD and PD: the future of CMC

The future of CLD is exciting. The Life Sciences companies of Danaher stand at the forefront of this exciting revolution, anticipating significant developments occurring at various stages of the workflows across multiple disciplines. We foresee the introduction of techniques that quickly provide comprehensive assessments of candidate cell lines. By deploying assays that give fast turnaround for identifying protein variants or mimic bioprocess stressors occurring in a bioreactor environment, we can discover ideal candidates for efficient drug production. Utilizing these assays earlier will speed time to scale-up or manufacturing, thereby enabling the miniaturization and screening of multiple clones to minimize costs and maximize production value.

Other areas of development in the foreseeable future include a more advanced, integrated approach to data management. The goal is to consolidate data into a single, accessible source across multiple labs, irrespective of their geographical locations. This would promote data sharing between facilities, improving communication and automating databases. Along the same line, there is momentum for incorporating AI and ML technologies to improve real-time data integration and analysis, enabling data-based decision-making.

As biologics development is booming, the ability to leverage technological advancements becomes indispensable. It's crucial to thoroughly understand the current limitations and challenges associated with CLD and PD. Recognizing this, Danaher Life Sciences consistently invests in robust research and development to help the biopharmaceutical industry navigate these obstacles, aiming to speed up the development and delivery of successful biologics in a cost-effective manner.

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