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Life Sciences

Automation in Therapeutic Antibody Development: Current Trends, Challenges and Solutions

Introduction

Monoclonal antibodies (mAbs) are now considered a key component of the drug development landscape.[1] Their high degree of efficacy has been repeatedly demonstrated, with treatments such as nivolumab (anti-PD-1), dostarlimab (anti-PD-L1) and isatuximab (anti-CD38) making significant contributions to oncology treatment.[2] Likewise, ipilimumab (anti-CTLA-4) has received praise for treating advanced and metastatic cancer, as either a solo treatment or in combination with other mAb therapeutics such as nivolumab.[3] Therapeutics like adalimumab (anti-TNFα) have also shown success in autoimmune diseases such as psoriasis and rheumatoid arthritis, while sotrovimab has been an effective treatment for infectious diseases like COVID-19.[4,5] These examples are reinforced by the increasing market presence of mAbs; in 2023, pembrolizumab (anti-PD-1) generated revenue of $25 billion, a 19% increase compared to $20.9 billion in 2022.[6] This growth is forecast to continue, with the market predicted to reach $300 billion by 2025.[7]

mAbs represent a global success story and, as of 2022, more than 150 antibody therapies have been approved by at least one regulatory agency in the world.[8] With novel formats such as bispecific mAbs and antibody–drug conjugates (ADCs) entering the market, the mAb landscape will continue to grow, broadening the horizons of medicines and life-saving therapeutics. A combination of clinical efficacy, growing market share and global regulatory approval have established mAbs as a pillar of the pharmaceutical industry. As such, rigorous, consistent and cost-effective mAb development now represents the foundation for one of the most successful treatment modalities in the last century.

mAb development remains, however, a complex and challenging process. From preclinical development through to manufacturing, potential bottlenecks limit the speed at which novel mAb therapies can be brought to market. For instance, cell line development, clone screening and selection are labor-intensive and generate large volumes of complex data that must be collated and interpreted. Clinical development also involves extensive safety and pharmacokinetic profiling, which relies on extensive data management and often uses instruments integrated across multiple locations. Meanwhile, efficient manufacturing requires optimization and quality control in line with regulatory requirements. The need to meet these regulatory requirements, laid out by agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA), can create further bottlenecks, prolonging the time it takes to develop a safe and effective mAb therapeutic.

It has been almost 40 years since the first licensed monoclonal antibody treatment became available on the market in 1986.[9] Over this period, discovery and development obstacles have created a growing demand for cost savings through optimization and process intensification.[10] This has been driven in part by the inefficiency of current approaches to mAb development, where preclinical assessment can take at least 12 months and total development costs are more than $100 million.[11,12] It is unsurprising therefore that many developers are seeking methods to reduce costs and shorten development timelines. Automation offers a promising solution to achieve these goals and unlock the power of accelerated decision-making, enhance quality control and streamline manufacturing.

This whitepaper explores the latest progress in mAb development, focusing on the potential of automation to address existing challenges in mAb development, and shares insights into how automation can accelerate the translation of mAb candidates from bench to bedside.

Streamlining antibody production through automation

Antibody production

Advances in biotechnology have provided different methods to produce monoclonal antibodies, including hybridoma technology, phage display and single B cell technologies.[2] Hybridoma technology stands out as a long-established and commonly used method, first pioneered by Köhler and Milstein in 1975. Notable therapeutics generated using this method include rituximab (anti-CD20), used in the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukemia, and trastuzumab (anti-HER2), utilized for HER2-positive breast cancer.[13,14] This production method involves the fusion of antibody-producing B cells with immortal cancerous cell lines, such as myeloma cells, which leads to the generation of immortal hybrid cell lines capable of limitless antibody production.

Similarly, the single B cell method involves preparing peripheral blood mononuclear cells (PBMCs) from infected or vaccinated donors. B cells are then isolated from the PBMC samples using flow cytometry, and RT-PCR is used for further analysis to guide the generation of human monoclonal antibodies. Subsequently, these identified sequences are cloned into expression vectors and transfected into host cells, such as Chinese hamster ovary (CHO) cells, for purification and production. Treatments such as daratumumab (anti-CD38), approved for multiple myeloma, and ocrelizumab (anti-CD20), used in the treatment of multiple sclerosis, are produced using this approach.[15,16]

In the phage display approach, a phage-displayed human antibody library is used to select antigens of interest, after which DNA sequences are analyzed to construct and express human antibodies. Once the desired DNA sequence encoding human antibodies has been identified, it is then cloned into an expression vector and used to produce the full-length antibody. In this case, examples include atezolizumab (anti-PD-L1), approved for various cancers, and adalimumab (anti-TNFα), used in the treatment of autoimmune diseases.[17]

As interest in mAb development has grown, the industry has progressed from legacy methods, such as hybridoma and phage display, and has adopted more advanced approaches to mAb production instead. Recent advances that have the potential to optimize mAb development include the high-throughput engineering of antibody fragments, cell-free expression and screening platforms, and generative-based de novo design.[18,19,20] All of these approaches provide an opportunity to drive mAb development forward, especially as they engage with automated solutions which can further facilitate high throughput and push mAb development towards greater levels of precision and efficiency.

Cell line development

During mAb development, mid-scale top clone selection remains a challenge, due to clonal heterogeneity, productivity considerations and the identification of critical quality attributes (CQAs). As demand for mAbs continues to grow, there is a need to identify top-performing clones with precision and accuracy. This means efficiently evaluating clones for their ability to grow to high viable cell densities, produce high titers of antibodies and exhibit high levels of stability with low aggregation, all while retaining a high degree of therapeutic efficacy. This can complicate the selection process, as it requires careful evaluation and optimization to identify the most promising candidates. This process also typically requires extensive manual handling, including cell culture maintenance, clone screening assays and data analysis.

When selecting clones that perform well, clone screening presents specific challenges, including variability in clone productivity and the potential for clonal instability over time. Identifying clones that meet all desired criteria requires meticulous evaluation and often involves trade-offs with other CQAs (e.g., purity and stability), adding complexity to the development process and consuming significant time and resources.

The labor-intensive nature of cell line development and clone screening contributes to increased personnel costs and prolongs the time required to bring new therapies to market. The selection of subpar clones can also result in downstream issues such as low antibody titers, reduced product quality and the need for additional process optimization, further increasing development costs. Ultimately these factors have long-term negative consequences as prolonged development timelines and higher costs translate to higher drug prices for patients. Additionally, suboptimal clone selection may lead to the production of less efficacious or less stable antibodies, potentially compromising patient outcomes and necessitating additional treatments or interventions, further driving up healthcare costs.

In contrast to traditional methods, automation of cell line development provides a means to streamline the clone selection processes. With advanced screening and characterization capabilities, it is possible to efficiently evaluate a large number of candidates and identify top clones with greater precision and accuracy. By reducing manual labor and improving the clone selection processes, adopting automation can lead to significant cost savings and efficiencies during this stage of mAb development.[21]

Upstream processing

In recent years, mAb development has focused on *in vitro* methodologies, moving away from *in vivo* methods. There is a growing reliance on *in vitro* methods during preclinical safety assessments, including the use of human-relevant cell-based assays to investigate key pharmacological and toxicological characteristics of mAbs. This includes assessing key mechanisms such as antibody dependent cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) via complement activation and complement dependent cellular cytotoxicity.[22,23] There has also been increasing interest in *in silico* technologies that can be used to refine clone sequences and identify potential liabilities that may lead to the use of unstable or low-efficiency producers.

This shift has been fueled by the need to precisely control multiple production variables, including temperature, pH and nutrient concentrations. When implemented, these approaches can also reduce costs and decrease the time it takes to get a product to market. Despite their efficacy however, these approaches face challenges in scalability and efficiency, especially as demand for mAbs continues to grow. These challenges can be overcome with automation, which offers the ability to streamline processes and improve consistency.

Downstream processing

Resource-intensive processes, such as clarification and purification, require scale-up to meet market demands. Centrifugation, chromatography, fragmentation, conjugation with chelating agents and ultrafiltration are key steps, but all place heavy demands on resources. During this process, vast amounts of data are generated, requiring sophisticated data management solutions.

As the demand for therapeutic antibodies continues to rise, automation represents a pivotal solution to address the challenges associated with traditional production methods. Implementing automation, enhancing instrument connectivity, enabling real-time instrument monitoring, and utilizing advanced analytical tools can streamline decision-making, improve process efficiency, and facilitate scalability. These solutions pave the way for accelerated mAb development and can consequently improve patient outcomes.

The advantages of automation

Reduction in labor-intensive tasks

Automation can revolutionize the mAb development timeline by facilitating tasks that previously relied on manual intervention (Figure 1). Automated cloning systems, coupled with imaging techniques for real-time analysis, offer insight into the mAb production process. By automating labor-intensive tasks, such as repetitive pipetting and clone screening, resources can be reprioritized, optimized and re-allocated, improving cost-effectiveness and significantly reducing the time it takes to get a mAb to market.[24] Timed delivery of reagents during the capture and detection of antibodies also enhances efficiency and reproducibility. The result is a streamlined process that ensures consistent dispensing volumes and rapid identification of mAb variants, improving data quality and accelerating decision-making.

Interest in this automated approach to mAb development has been fueled by process intensification, which aims to increase productivity in terms of time, product yield or revenue. Advances in this area include the establishment of high-performing cell lines, high-density cell banks and a range of perfusion strategies for bioreactors.[10] These improvements aim to enable the fast and reliable setup of robust development processes, allowing for a reduction in both production cost and development times.

Figure 1. Key automation technologies in mAb development and the benefits they unlock.

Improved precision

Automation serves as a catalyst to shorten the traditional mAb development timeline, eliminating manual bottlenecks and reducing processing times, benefits that can be seen throughout the development pipeline (Figure 2). For example, during liquid handling, automated systems offer precise dispensing volumes and support rapid variant identification during screening and characterization. For instance, based on research and development data, high-throughput screening (HTS) reduces analysis time for a 384-well plate from 10 hours to 8 minutes, while plasmid library development accelerates gene assembly by up to 93% and colony picking efficiency by 4.75 times, compared to manual methods.[21]

By eliminating time-intensive tasks, these systems enhance throughput, maintain data quality and drive efficiency across the development pipeline. Likewise, early elimination of unsuitable candidates can be achieved through integrated data management systems that minimize resource wastage through data-driven decision-making. Automation also provides advanced quality control measures, integrated with regulatory compliance standards, to ensure product consistency and safety.

Reduced exposure and contamination risk

Automation can also minimize human interaction with cell cultures, mitigating the risk of contamination and increasing throughput. Automated platforms allow for the integration of culture vessels, reinforcing a hands-off approach to liquid handling. This can be particularly important during cell culture processes that require repeat access to cells, such as media exchange or cell passaging. This automated approach increases robustness, reliability and scalability, laying the foundation for accelerated therapeutic advancements.

Data integrity and traceability

Automated data systems provide advanced data management, data integration and data analysis capabilities, seamlessly managing the flow of data across multiple workstations and locations. This approach streamlines workflows, facilitates collaboration and enables real-time decision-making, further reinforcing efficiency and innovation.

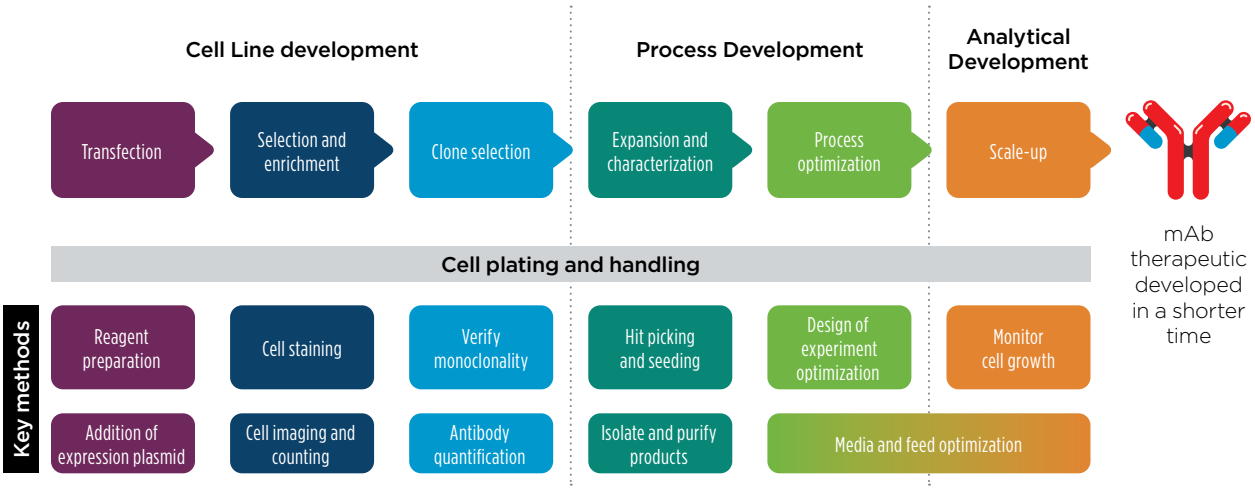

Figure 2. Tasks that could be eliminated during mAb development using automation.

Common challenges

Implementing automation in mAb development can be a daunting process, a viewpoint that has hindered widespread adoption. This includes initial investment costs, infrastructure requirements and labor-intensive incorporation into existing workflows. However, the latest automation tools offer solutions to overcome many of these challenges.

Cost

While initial costs may seem high, the long-term benefits outweigh the upfront expenditure; reduced reliance on resource-intensive processes leads to significant cost savings over time. Integrating automation into existing workflows can be time-consuming and disruptive, requiring careful planning and coordination to ensure a seamless transition. However, the latest systems are equipped with a full suite of tools that allow for simplified integration and minimal disruption.

Over time this will allow resources to be shifted away from the labor-intensive manual stages, allowing developers to focus resources on other aspects of the workflow, such as analytics and optimization.

Regulatory considerations

Regulatory considerations and compliance add another layer of complexity to the adoption of automation in mAb development. Ensuring that automated production methods comply with regulatory guidelines is essential for maintaining product quality and safety. Thankfully, automated systems enable better quality control, allowing developers to adopt a Quality by Design (QbD) approach. By proactively addressing quality and compliance requirements from the outset, organizations can ensure that their products meet regulatory standards. Additionally, the adoption of instruments that are enabled for good manufacturing practices (GMP) during discovery and development facilitates method transfer when progressing to manufacturing. This allows the development of high-quality products in line with regulations – such as those laid out by the FDA, EMA or International Council for Harmonisation (ICH) – which provide guidance on the biosimilarity, comparability and quality attributes needed in mAb products.[25,26,27] An automated approach to these regulations minimizes compliance challenges and potentially streamlines the approval process.

Large datasets: Management and analysis

With automation enabling high-throughput screening, precise control over cell culture conditions and streamlined downstream processing, the volume of data generated increases significantly. Managing and analyzing this data requires robust data management systems and advanced analytical tools capable of handling complex datasets. Additionally, ensuring data integrity, accuracy and consistency across multiple automated systems poses further challenges. Addressing these challenges is essential to harness the full potential of automation in mAb development and leverage data-driven insights to optimize processes and accelerate therapeutic discovery and development.

Equipment compatibility

Integrating automation systems with existing equipment and infrastructure can be a hurdle for many developers seeking to adopt automation. Ensuring compatibility between platforms and different instruments, bioreactors, purification systems and analytical devices requires careful planning and coordination. Rigorous planning reduces the risk of resources being wasted during setup.

While the adoption of automation may present initial challenges, the long-term benefits allow organizations to accelerate the development of successful mAb-based therapeutics, allowing them to bring products to market more efficiently.

Conclusion and future perspectives

The development of mAbs has laid the foundation for groundbreaking therapeutic solutions across various disease areas, with a focus on oncology and autoimmune diseases. Looking forward, the mAb therapeutic market is predicted to generate $300 billion in revenue by 2025, emphasizing the increasingly pivotal role mAb development will play in the therapeutic landscape.[7]

Automation offers the opportunity to enhance the entire mAb development process. By streamlining workflows, optimizing efficiency and improving quality control, automation will allow mAb developers to remain competitive in a rapidly evolving market. From accelerated decision-making to reduced development timelines, automation provides the tools needed to bring life-saving therapies to patients more efficiently. With faster access to innovative therapies, patients can benefit from improved treatment outcomes and enhanced quality of life.

Discover the latest automated tools for monoclonal antibody development

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