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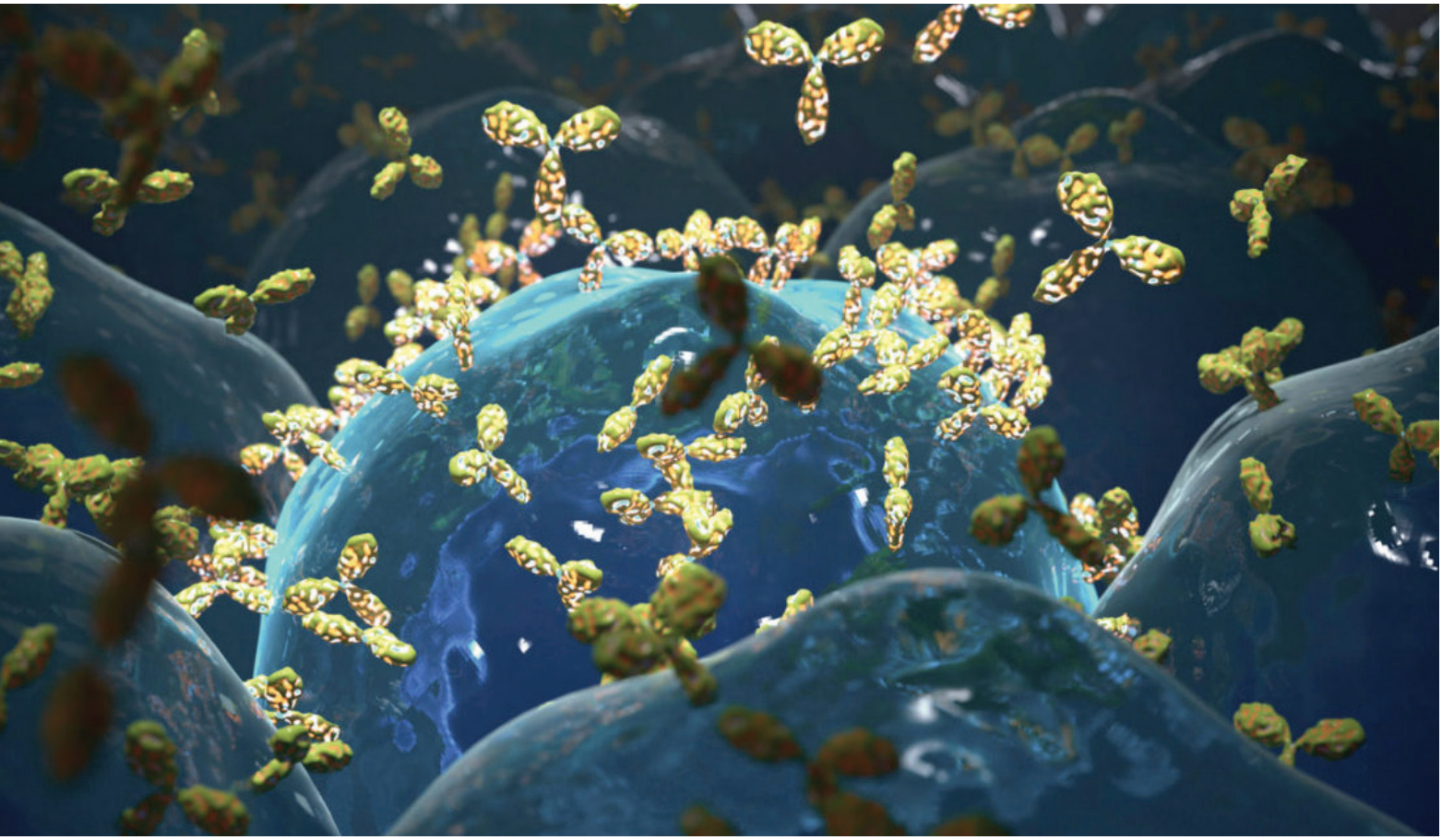

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WHITEPAPER

Targeting cancer with therapeutic antibodies: Solutions for every phase of mAb development

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Executive summary

Molecularly targeted therapies are formidable weapons in the fight against cancer. Monoclonal antibodies (mAbs), in particular, have emerged as a major targeted treatment strategy because of their ability to preferentially attack molecules responsible for cancer cell growth and survival while leaving healthy cells relatively unscathed. This high specificity staves off the severe off-target side effects associated with standard chemotherapy agents.

Although mAbs have been used in the treatment of cancer for more than 30 years, ongoing advances in the understanding of cancer biology and the emergence of next-generation sequencing technologies have accelerated the identification of molecular drivers of cancer and the search for antibody-based agents to block them.[1]

With an urgency fueled by the increasing prevalence of cancer globally and the lack of effective treatments for many types of cancer, these development activities are driving unprecedented growth opportunities in the oncology segment. From $49.81 billion in 2021, the oncology mAb market is projected to grow to $56 billion in 2022 (12.4% CAGR), and it is expected to reach $159.7 billion (11.2% CAGR) by 2030.[2]

While major technological advances have enabled great gains, the path to mAb commercialization requires navigating complicated manufacturing operations, intricate supply chain management, and scale and capacity limitations.

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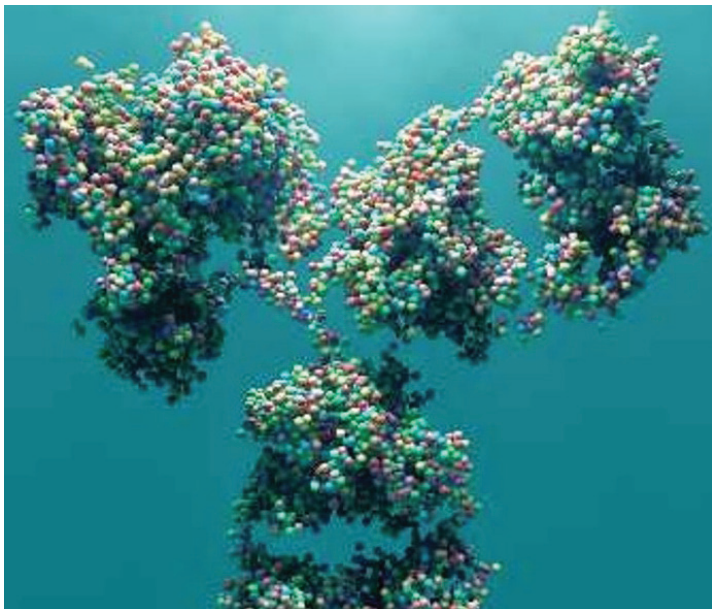


Marketplace pressures around development speed add another layer of complexity. The emerging biotech companies that own the majority of the preclinical and clinical mAb pipeline are racing to bring new therapeutic mAb candidates to IND/IMPD filing quickly in order to demonstrate progress and secure additional funding. And regulatory agencies have opened accelerated review and approval pathways to fill the unmet medical needs of cancer patients waiting for lifesaving therapies as quickly as possible. Yet, the process and product development complexities noted above constrain the speed at which a new therapeutic mAb can reach the market. To manage the opposing pressures, manufacturers must carefully and constantly balance cost, risk, and speed without sacrificing quality.

This whitepaper identifies the key challenges faced at each stage of mAb development and provides guidance for streamlining pipeline progress of therapeutic mAb candidates, focusing specifically on the following:

- Leveraging technology in the early stages to accelerate development while reducing risk
- Scaling processes and production to match clinical and commercial demands
- Integrating key regulatory considerations as a precursor to long-term success
- Accelerating the start-to-finish workflow

Introduction

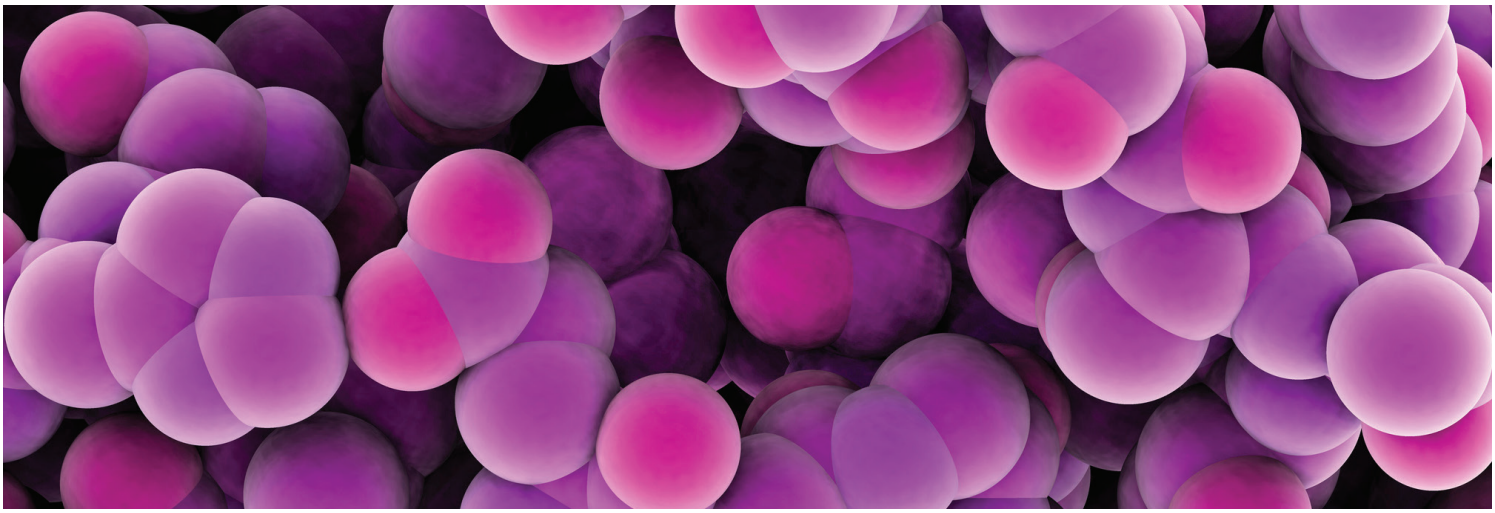
Antibodies are Y-shaped protein molecules produced as part of the body's immune response to identify and neutralize foreign objects. The "arms" of the Y bind to intruder molecules, while the stalk binds to other immune system compounds that attack the intruders, either directly or through a signaling cascade. Each antibody recognizes a specific antigen unique to its target. This high degree of specificity makes antibodies an excellent tool for detecting and quantifying a broad array of targets. Monoclonal antibodies, or mAbs, are immune system proteins created in the lab. They are derived from identical clones of B lymphocytes against a particular antigen.

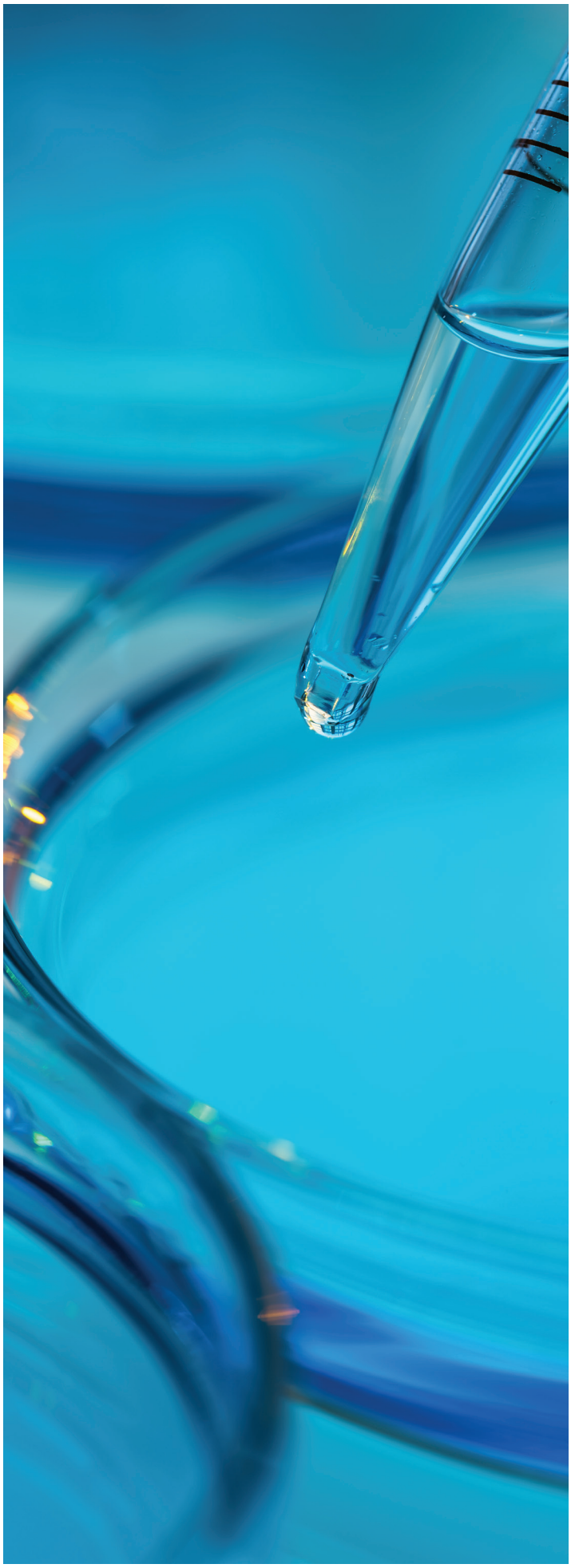
Today, mAbs are a major component of cancer therapy, attacking tumors through various mechanisms. Some mAbs target the cancer cell growth factor receptors that sit on the cell surface and signal the cell to survive and divide. Some act on the immune system, either by blocking proteins that stop the immune system from working or by attaching to cancer cells, making them easier to detect and target for destruction. Some block vascular endothelial growth factor (VEGF) proteins within tumors that trigger blood vessels, and thus the cancer, to grow. And some carry cancer drugs or radioactive substances directly to cancer cells. There also are other mAbs called bispecifics, which are engineered to recognize two different antigens and, thus, bring different target cells into close proximity of each other for an intended effect.[3]

The first mAb approved for human use was the immunosuppressant agent muromonab-CD3, which got the green light from regulators in the United States and Europe in 1986 to prevent organ transplant rejection. The first oncology-specific mAb approval came in 1997, when rituximab was approved for the treatment of low-grade B-cell lymphoma. Since that time, nearly 50 mAbs have received approval worldwide for treatment of a variety of solid tumors and hematological malignancies, and many are in the pipeline.[4]

In the decades since the first mAb reached the market, biomanufacturing processes for developing these therapies have matured substantially.

In the decades since the first mAb reached the market, biomanufacturing processes for developing these therapies have matured substantially. Steady improvements in cell lines, increasing expression titers, optimized culture media, modernized purification platforms, and new designs for flexible facilities and bioreactor configurations have enabled commercial-scale production with efficiencies that were previously unattainable.





Making mAbs: Phase-based challenges and solutions

Even with the many technology advances and process improvements in recent years, the development of therapeutic mAbs continues to be a complex undertaking that requires substantial knowledge and expertise in a wide variety of areas, including relevant biological pathways, creation and characterization of drug molecules, manufacturing, clinical research, and regulatory affairs. Progressing from target antigen identification to commercialization requires overcoming unique challenges across each phase of development: early discovery and research, upstream and downstream process development, clinical research, and scale-up for commercialization.

Early discovery and research: Selection and screening

The objective of the early discovery and research phase is to identify a candidate mAb molecule that is suitable to enter first-in-human trials. The goal is to optimize the R&D efforts at the bench, while trying to find ways to stretch the investment dollars and accelerate the development timeline. This is where the hard science is done. Not all mAbs behave as well in real life as they do on paper, and the implications of each molecule's inherent scalability, predictability, and stability will carry over into the subsequent process development phase.

Some opportunities to overcome the challenges in this phase include leveraging new and emerging technical innovations to improve precision, increase throughput, and expand parallel processivity and the use of automation.

For example, liquid chromatography technology can be used to automate purification, which is the process used to identify mAbs with ideal specificity, affinity, and binding kinetics. Hundreds of candidates must be purified and screened in downstream functional assays. Achieving the ideal purity and state can create a screening bottleneck. The availability of fully automated processing technology can streamline the process, purifying each therapeutic mAb candidate in 30 to 45 minutes.

Comprehensive gap assessments during the early phase are also extremely valuable, particularly for the transfer of technology to a contract development and manufacturing organization (CDMO). These assessments can provide important insight into raw material and capability concerns that may uncover the need for further technical evaluations. Digitizing data transfer at this early stage is also recommended, as it can improve accuracy while reducing human error and effort. Lastly, leveraging platform cell lines and/or platform processes can help get new molecules to and through the proof-of-concept phase more quickly.

Development phase: Mastering the recipe

The development phase is all about mastering the mAb recipe and ensuring that the upstream processes for developing healthy mAb-producing cells will be scalable, compliant, and economical for large-scale cGMP manufacturing.

The main challenge at this stage is to conduct the full range of design of experiment (DOE) efforts that will ensure the production of a product that meets quality and regulatory requirements relative to safety, purity, potency, identity, and immunogenicity. It is also important at this stage to think about the kind of facility that would be best suited for producing the mAb. To avoid unnecessary switches in sites or suppliers stemming from capacity limitations, a facility's capacity, quality systems, total capabilities, and availability for clinical trials material and beyond should factor into the decision.

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The important work of this phase benefits from a hyper-focus on critical platform knowledge to ensure a clear understanding about which variables can and should be adjusted. In addition, leveraging the various technically advanced high-throughput automation systems that are available can dramatically accelerate key steps in the development process. Lastly, it's important to identify and characterize key ranges for manufacturing at this stage to avoid deviations that would cause failures down the line.

Clinical trials phase: Does it work? Is it safe?

The trials phase is when the effectiveness of the candidate mAb molecule is determined. During this phase, it is critical to consider the realities of scaling production to meet potential dosage and resupply demands without compromising quality. The question of how much material is needed should be front and center, as this information will guide decisions related to manufacturing capabilities and capacity to match potentially changing clinical demands.

Having a responsive manufacturing partner that can coordinate raw materials via exceptional communication and forecasting can be a critically important way to safeguard the success of your product.

Having a responsive manufacturing partner that can coordinate raw materials via exceptional communication and forecasting can be a critically important way to safeguard the success of your product. The right partner can leverage its buying power and scale to ensure continuity of critical supply. Also, a partner that has bioreactors, total bioreactor capacity, and distribution of bioreactors in various geographies can provide the ability to adjust production based on clinical demand or changes in demand due to dosing requirements. Lastly, a reliable and integrated partner can be an invaluable resource for clinical trials and logistics support, which encompasses patient recruitment, patient management, distribution, and clinical packaging.

Commercial production: Meeting patients' needs

Launching a commercial product that can effectively meet patients' needs requires understanding and fully addressing the challenges associated with achieving and maintaining commercial quality at scale. Any production process must be stress-tested, and critical parameters must be fully characterized, validated, and controlled at production scale and in a sufficient number of batches to support filing of a biologics license application (BLA). Also, post-BLA continuous process verification must be supported to ensure ongoing quality and compliance and enable continuous improvement.

Some strategies for managing these challenges include using standardized templates and approaches, standardized training regimens, sitewide alignment across sites for documentation, controls, and standard operating procedures to reduce timelines while improving cohesiveness. It is also helpful to leverage surrogates instead of actual product or process solutions.

Regulatory considerations

Because of the complex pharmacokinetic and pharmacodynamic properties of mAbs, safety outcomes, including those related to unwanted immunogenicity, are highly variable, and many mAbs are considered to be high-risk medicinal products.[5] Developing a strategic regulatory plan early on can provide a crucial framework for minimizing risk across the overall development project. By giving all stakeholders a complete picture of the nonclinical, technical, and clinical testing requirements for registration, the regulatory strategy establishes clear expectations and enables the proactive evaluation of potential hurdles. It can also prepare sponsors for interim conversations with regulators in advance of a first-in-human trial submission. Early communication with regulators provides an opportunity to gain formal feedback on chemistry, manufacturing, and control (CMC) strategies and future development plans. These early insights and advice can help sponsors identify and avoid unnecessary development studies, CMC clinical holds, and costly delays along the path to development milestones.

For novel products and new manufacturing processes, good communication is critical to get early buy-in and approval. Regulators know the science, but they don't know each product or process. Proactively creating a well-vetted CMC strategy, particularly for first-in-human dossier preparation and clinic entry, ensures that CMC regulators will be an early and engaged partner in all aspects of drug development discussions, from preclinical to clinical, and facilitates progress through the subsequent phases toward licensing and marketing.

To be optimally effective, the CMC dossier should include detailed justifications for specifications and purification steps. The dossier should also be written to fit the broadest possible audience and the jurisdiction should be kept neutral to facilitate future life-cycle management flexibility.

Many of the oncology mAbs in the development pipeline are targeting large groups of rare and less common cancers where the unmet need is very high. From a regulatory perspective, these indications are less likely to have development guidelines and precedents; therefore, the development of a thorough regulatory strategy is critical. These programs often require the development and validation of new endpoints and biomarkers, and the smaller patient populations mean smaller phase 1 clinical studies, where early safety and clinical efficacy evidence is required for the design of accelerated phase 2/3 clinical studies. An early understanding of all the registration requirements can add efficiencies throughout the development program.

Accelerating the start-to-finish workflow

In recent years, acceleration of development timelines has become a major focus within the biopharmaceutical industry to more quickly bring innovative therapies to patients. The COVID-19 pandemic increased the pressure to identify the quickest path to regulatory approval, and the industry responded through a combination of technical advances and an increased tolerance for business risk, without compromising product quality or patient safety.[6]

A framework for acceleration can be built around three main principles. These include leveraging advancements in bioprocessing technology, including higher-expressing cell lines, improved bioreactor performance, increasing single-use capabilities at higher scales, and higher throughput screening tools; careful construction and parallelization of drug substance– and drug product–related activities and timelines, as well as prequalification of common vial formats; and integration of prior process experience, proven platforms, established protocols, and templated processes to reduce time while ensuring that risks taken are relative to actual rewards.

Some of the specific steps that can be taken to achieve an accelerated development timeline include:

- Pulling forward analytical method establishment as early as possible and using transient material
- Using a strategic mix of platform analytical methods
- Co-qualifying drug substance and drug product sites during analytical development, thereby enabling concentration and ID assays to be done together rather than separately
- Executing upstream process development and cell-line development in parallel
- Performing confirmation runs and toxicology batches simultaneously to understand robustness of the process while generating tox material
- Coordinating shipments between drug substance sites and drug product sites

Avoiding development pitfalls

As the largest and one of the fastest-moving therapeutic areas, the oncology market is highly competitive, but a misguided focus can derail even the most promising development program. Maintaining a laser focus on the end goal—getting safe, effective, potentially life-saving therapies to patients—can help keep programs on track, as can avoiding these mindset pitfalls.

Pitfall 1: Speed at all costs—Despite the emphasis on speed to clinic, speed shouldn't be prioritized over other critical success factors. Time pressures can result in missed opportunities, poorly considered platform selection, inadequate material for scale-up or clinical trials, and even unsatisfactory analytics data for IND/IMPD applications. Each of these risks can become significant financial, time, regulatory, or logistics problems at the point of application or beyond.

Pitfall 2: IND/IMPD over everything else—Filing the IND/IMPD quickly shouldn't mean putting the blinders on to future issues concerning scale-up, scope, analytics, practical costs, or logistics. These may seem like far-off factors irrelevant to early decision-making, but they can make or break the success of a drug product during clinical testing or commercialization. To reduce risk of future platform changes or forced cell-line reevaluation, scalability should be considered sooner rather than later.

Pitfall 3: Focus only on phase 1 trial needs—Focusing only on phase 1 trial needs to the neglect of adherence to proper testing and documentation can be an obstacle to swift IND approval. It also can limit the potential product knowledge gained from early research studies. Early-phase clinical work has very different requirements than late-phase development and commercial use. What's sufficient for small-scale pharmacokinetic/pharmacodynamic studies and first-in-human proof-of-concept studies may not be practical to scale or maintain in future clinical development stages or after marketing authorization. Identifying critical requirements for filing and phase 1 initiation and recognizing how production needs will change as the molecule advances allows for early planning to provide an advantage for approval, transfer, future research, and commercialization.

In addition to these strategies for accelerating early development phases, there are also strategies for moving a product more quickly through late-stage development to commercial launch.

Today, pharma companies are increasingly looking to integrated providers that have the ability to manage the full process, from early development through late-phase clinical supply and on into commercialization.

Historically, innovators have hopped from vendor to vendor looking for the best phase-specific partners. That approach means multiple service and quality agreements to review and negotiate as well as multiple invoices to reconcile. It also means that no single entity is accountable for the overall program. Further, the time, effort, and resources needed to facilitate technical transfers between companies, manage the flow of regulatory information, and transport materials between various sites introduces additional risk, expense, and time to the development program.

Today, pharma companies are increasingly looking to integrated providers that have the ability to manage the full process, from early development through late-phase clinical supply and on into commercialization. This "start here, stay here" approach can save time, lower costs, streamline communications, provide more reliable access to materials, and ensure accountability for the sponsor.[7] More importantly, however, it can accelerate patient access to potentially life-saving treatments.

Conclusion

Therapeutic mAbs play a critical role in the global oncology pipeline. Together with a greater understanding of the immunomodulatory properties of antibodies, advances in antibody engineering have enhanced the safety and efficacy of these therapies and paved the way for the next generation of new and improved antibody-based drugs for the treatment of cancer.

As the demand for mAbs grows, the pressure on pharma companies to bring new products to market more quickly is growing as well. But streamlining the development of therapeutic mAb candidates requires overcoming some of the unique challenges associated with antibody production. Some key considerations include finding ways to decrease the time it takes to get to human trials by leveraging technology to accelerate the early development stages and pursuing careful construction and parallelization of drug substance and drug product activities.

Early and detailed communication with regulatory entities is also important, as is the need to avoid a "speed at all costs" mentality that can jeopardize IND/IMPD. For late-phase development, careful consideration of such issues as clinical supply strategy, transportation management planning, and the coordination of communications between a network of vendors and suppliers is essential. Adopting a "start here, stay here" strategy can eliminate some of the technical, logistical, and communication challenges associated with a more distributed approach. This can be achieved by aligning with an experienced partner that can support early-phase through commercial development.

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