De-risking biologic drug development: strategic solutions for biotech companies

Biotech companies face unique challenges in developing increasingly complex biologic therapies. How can early de-risking, smart chemistry, manufacturing and controls strategy, and the right contract development and manufacturing organisation partnership help developers accelerate progress to the clinic without compromising on quality, regulatory readiness or long-term success?

By Megan Mason and Alice Harrison at Lonza

Biologic therapies continue to reshape the treatment landscape for a range of conditions including autoimmune diseases, cancer, metabolic disorders and rare diseases. Alongside the growing use of these therapies, the diversity and complexity of biotherapeutic proteins are increasing. Beyond conventional monoclonal antibodies, today's pipelines include bispecific antibodies, antibody-drug conjugates (ADCs), fusion proteins and other advanced formats designed to enhance therapeutic impact or address specific needs.

For biotech and pharma companies, these innovations come with significant pressure. Development timelines are often closely tied to funding milestones, investor confidence and partnering opportunities, making speed to clinic critical. However, greater molecular complexity also increases the risk of costly rework or poor process economics, particularly when manufacturability, stability or immunogenicity challenges surface too late to address efficiently. The pressure creates a fundamental tension: how to move fast, without taking shortcuts that compromise investigational new drug (IND) readiness or derail programmes altogether.

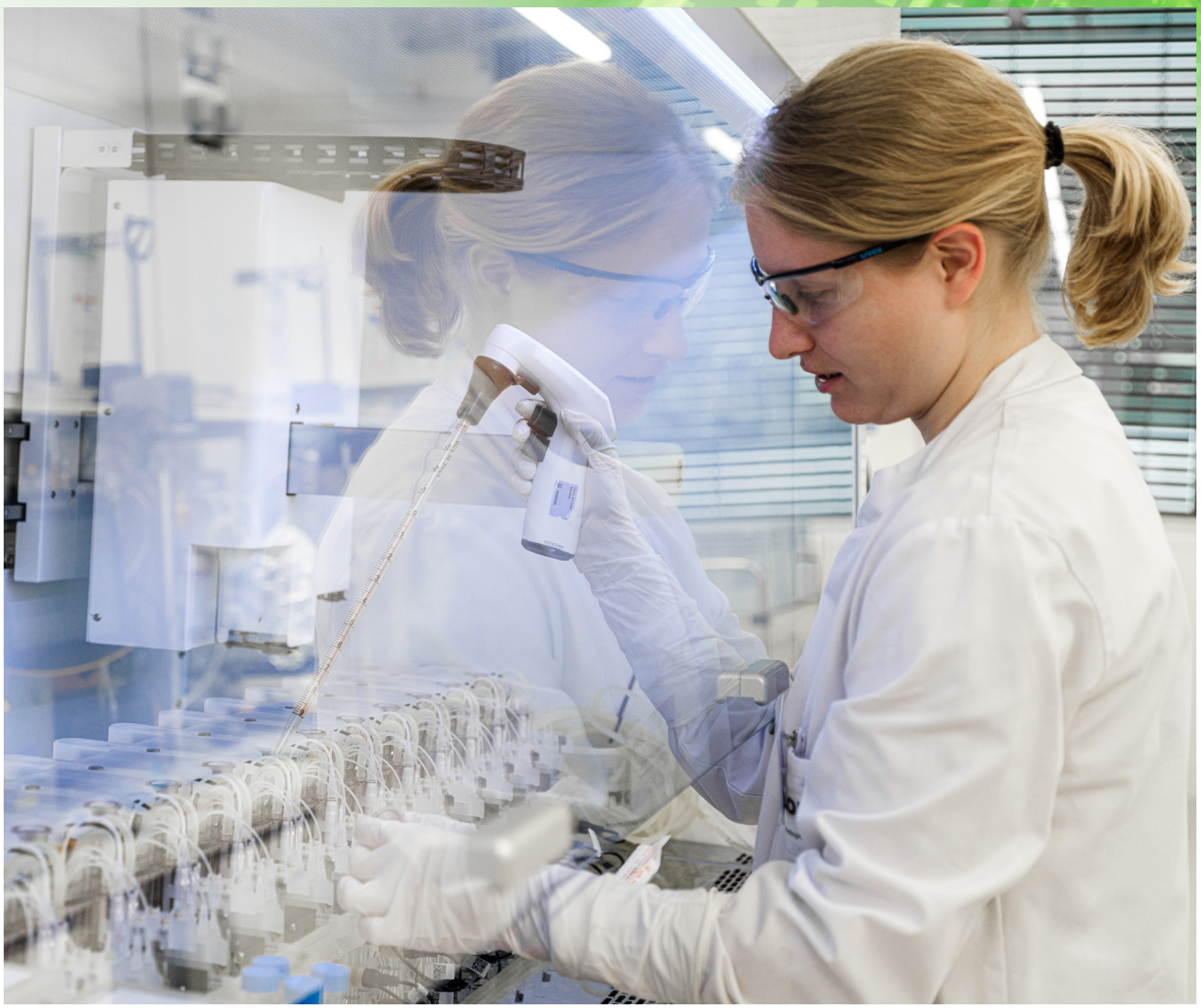
In early development, specialised expertise across diverse molecule types is essential. In practical terms, the strongest early foundation combines *in silico* developability screens with small-scale expression, purification and product quality assessment to evaluate manufacturability. These initial steps are followed by targeted sequence adjustment, if required, and development of a manufacturing process tailored to the molecule's needs. When combined with a strategic chemistry, manufacturing and controls (CMC) approach, such efforts enable a smoother path to IND and/or clinical trial application submissions. The challenge is particularly acute for small and emerging biotechs, which often lack the required resources, equipment and regulatory know-how to navigate an accelerated path to clinic for a more complex molecule. Partnering early with an experienced and well-equipped contract development and manufacturing organisation (CDMO) provides access to critical capabilities and knowledge. The right partner will help a biotech innovator advance its product across every stage of development, reducing risks that could hinder manufacturing or delay clinical trials.

Early de-risking: setting up the programme for success

According to a 2025 US Food and Drug Administration (FDA) analysis of biological products between 2020 and 2024, 40% of IND programmes on clinical hold were due to CMC deficiencies.[1] Making informed decisions about a drug candidate as it enters the pipeline sets the stage for future clinical success, and therefore early de-risking becomes a strategic necessity. By proactively identifying a molecule's potential liabilities, addressing sequence- or structure-related risks, and ensuring manufacturing strategies are scalable and robust, biotechs can avoid costly rework later, such as changing cell lines, redeveloping processes or even re-engineering constructs.

Advanced *in silico* assessments can uncover product liabilities, such as unintended immunogenicity or adverse post-translational modifications, which may impact a drug's efficacy, safety or pharmacokinetics. These insights inform rational DNA construct design and optimisation, allowing sequence-related risks to be addressed before committing to cell line development. Identifying these potential problems early allows for targeted mitigation strategies, which can include implementing bespoke purification processes, optimising cell line development approaches and tailoring molecule-specific formulations.

Early formulation assessments are key first steps in selecting a formulation that enables long-term product



stability. Selecting an appropriate formulation is especially important for more complex biotherapeutic proteins such as ADCs, bispecific antibodies and Fc-fusions, because these molecules are inherently more fragile, prone to aggregation and sensitive to environmental stress than traditional antibodies. A tailored molecule-specific formulation helps ensure the therapeutic product remains stable, potent and safe, whilst enabling suitable patient delivery.

The foundation of biologic therapies is the expression platform, and choosing the right system is a critical early decision in terms of optimising yield and quality. Using an advanced platform such as Chinese hamster ovary cells ensures the manufacturing process can reliably achieve the desired critical quality attributes aligned with the drug developer's goals. Early cell platform selection enables a development pathway tailored to the expression host and the product, helping ensure attainment of quality and yield targets. An expression system that allows flexible design and optimisation of the DNA expression construct plays a key role in reaching those targets. For example, careful refinement of the construct in the relative gene order and use of high-performing promoters can significantly boost protein expression levels and stability, leading to higher yields and robust product quality. Choosing an established, well-characterised system helps ensure product consistency, while providing a validated path for development and regulatory approval.

By combining integrated decision-making with high-performance analytical platforms, tailored analytical strategies, high-throughput screening and customised process solutions, each candidate can follow a designed phase-appropriate development pathway, maximising the likelihood of success.

Scaling toxicology material production

For most biotechs, a reliable CDMO partner brings robust quality systems, established platforms and advanced, scalable technologies to the table. Designing manufacturing processes with commercial viability in mind helps ensure consistency and control, paving the

way for a successful transition from clinical to commercial stages. This expertise is key when supplying material for toxicology (tox) studies, which can be a bottleneck but are essential to assessing the safety and efficacy of new therapies before they advance to first-in-human trials. Tox studies not only protect clinical trial participants, but also provide valuable insights into biological mechanisms of action while boosting the scientific credibility of the candidate molecule. Early tox material supply provides companies additional time to complete tox assessments, reducing the risk of filing delays. This benefit is crucial to the success of many biotechs, for whom robust early data enhances investor confidence – a factor that can secure further funding and accelerate the programme's path towards the clinic and commercialisation.

Scaling up production from tox material to clinical product can present challenges, such as maintaining strict quality control, ensuring process consistency, and navigating supply chain logistics and regulatory requirements. Experienced CDMOs help biotechs strike the right balance between speed, compliance and product quality, ensuring that tox material is representative of the final clinical product – an essential requirement for regulators – whilst keeping timelines on track. One way to accelerate early development timelines is through an integrated rapid tox approach, designed specifically for advanced biologics, including bispecifics. Use of high-efficiency expression technologies and connected upstream, downstream, analytical and formulation workflows can enable delivery of tox-grade drug substance and drug product within a compressed timeline. This accelerated pathway combines pool and clone-based tox material generation with robust comparability assessments to ensure that early, pre-good manufacturing practice material remains representative of the final clinical candidate. For developers of bispecifics, for instance, this approach helps mitigate risks associated with complex chain architectures and formulation challenges.

Building a strategic CMC plan for IND success

IND readiness is the result of ensuring alignment across product definition, manufacturing strategy, analytical readiness, tox execution and regulatory foresight. Navigating the regulatory landscape is a major challenge for small and emerging biotech and biopharma companies, especially as guidelines evolve and accelerated approval pathways become more commonplace for advanced therapies. An experienced CDMO partner – particularly one with integrated end-to-end solutions – can develop and implement a strategic CMC plan that ensures regulatory readiness without sacrificing speed and quality.

No two biotech companies are the same; even those with similar profiles may require different development approaches. By integrating molecule-specific insights, advanced technologies, early risk mitigation tools, fit-for-purpose analytics and regulatory foresight, a CDMO can help position a biotherapeutic protein to move confidently from DNA to IND and beyond. With the right partnership, drug developers can accelerate their development timelines and lay a strong foundation for successful commercialisation. Given the abundant and urgent unmet medical needs of numerous patient populations – particularly among those living with various rare diseases – forging these effective early-stage partnerships is essential for enabling access to potentially life-saving and life-enhancing treatments for patients.

Reference:

1. *Visit: fda.gov/news-events/press-announcements/fda-embraces-radical-transparency-publishing-complete-response-letters*

Alice Harrison, director of Global Technical & CMC, Analytics at **Lonza**, provides scientific and technical leadership to benefit customer programmes. Alice studied chemistry at Queen Mary College, University of London, UK, and earned her DPhil in molecular immunology from the University of Oxford, UK. She has over 20 years' experience in large molecule analysis within industry, and founded and led businesses supporting the development of antibody and complex protein therapeutics. Alice has an in-depth understanding of the bioanalytical challenges of complex molecule programmes.

Megan Mason is currently acting as implementation manager in the Global Process Development team at **Lonza**. She is responsible for overseeing the rollout of new process and technologies across the Lonza Integrated Biologics network. Megan holds a PhD in Chemical Engineering from Rensselaer Polytechnic Institute, US, where she studied the impact of primary sequence mutations on monoclonal antibody expression. She has over 15 years of experience in the development and manufacturing of biotherapeutics, with a focus on cell culture development and associated technologies.