The ADC Era: *Bridging Innovation and Manufacturability for Precision Biopharmaceuticals*

Antibody–drug conjugates (ADCs) are at the forefront of targeted therapy, combining the precision of monoclonal antibodies with the efficacy of cytotoxic agents, delivering highly potent treatments directly to diseased cells while limiting systemic toxicity. The promise of ADCs to transform disease treatment since their inception in the 1960s is undeniable,[1] but so are the challenges for their development and manufacture.[2] As their clinical impact grows, so does the need to refine development economics and efficiencies as ADCs are inherently complex, requiring specialised payload handling with high containment environments. Historically, these difficulties have translated into extended timelines, elevated costs and operational bottlenecks. As the field advances, particularly in relation to the increasing volume of ADC-based therapies reaching clinical trials and the increased requirement for large-scale manufacture, addressing bottlenecks by selecting the correct equipment for each specific step becomes increasingly important, whether through purchasing equipment for use in-house or by working with a trusted CDMO partner.

Although the first antibody-drug conjugates (ADCs) were tested on animal models in the 1960s,[1] and the first ADC-based clinical trials conducted in the 1980s, the first ADC-based drug, Mylotarg (gemtuzumab ozogamicin), was only approved in the year 2000. However, Mylotarg had a rocky start; it required a black box warning to be added to the packaging a year after its first approval and was withdrawn from the US market in 2010 due to hepatotoxicity. Nevertheless, it was reintroduced in 2017 by Pfizer following further clinical trials.[3] Despite this initial setback for the field, it stimulated progress in the area, with several ADC-based therapies being approved in the 2010s, including the blockbuster Adcetris (brentuximab vedotin), heralding a new dawn in the field of ADC modalities and an explosion of interest in this class of drugs.

To keep pace with the rise in the number of ADCs approved as treatments for disease, advances in process design, manufacturability and integrated development have also seen great leaps forward. Furthermore, as knowledge and expertise around large-scale manufacturing have improved, so has the ability to streamline drug development programmes, ensuring predictability and cost-effectiveness. Organisations that take a holistic overview, for example by aligning early scientific decisions with scalable process design and informed equipment strategy, are uncovering opportunities to reduce costs without compromising performance or safety. This integrated approach strengthens data integrity, supports risk assessment and helps minimise deviations during scale-up and clinical submissions, creating a more predictable and efficient development pathway. Although many groups now hold specialised capabilities within the ADC ecosystem, it is the integration of these capabilities either through developing bespoke in-house solutions or working with a single CDMO, or even a series of highly specialised partners within a consortium, that shapes the most efficient and commercially viable development paths.

Rethinking ADC Complexity: Interdependence Drives Cost

The technical architecture of an ADC is well established with all three components, the antibody, linker and payload, bringing their own distinct manufacturing and regulatory requirements. For example, the antibody must maintain structural integrity through upstream expression and downstream purification; the linker, which can be prone to aggregation or unintended cleavage, must remain stable during storage and conjugation; and the payload must be handled under strict containment while delivering predictable drug-to-antibody ratios (DARs). Poor decisions early in a project amplify downstream inefficiencies. For example, unstable linkers may require additional purification, hydrophobic payloads may complicate conjugation control and marginally stable liquid formulations may necessitate costly cold-chain logistics. Understanding these interdependencies is the foundation of both technical and economic success.

The integration of biologics with synthetic chemistry is a key area of focus due to the requirement to manage the needs of each component alongside the breadth of expertise required. Each stage of the manufacture of ADCs requires specialised equipment, robust process control and keen analytical monitoring to ensure product quality and process reproducibility. Integration of these processes is essential to reduce risk, minimise product loss and ensure enhanced scalability to secure commercial and clinical supply:

- Bioreactors are used for mAb production and enable precise control over cell growth, nutrient feed, pH, temperature and oxygen content, with both stainless steel and single-use formats available to suit specific client needs. Advanced bioreactors support real-time monitoring through Process Analytical Technology (PAT), which allows rapid identification of any deviations that could negatively impact the manufacture.
- Tangential flow filtration (TFF) and chromatography are both used for mAb purification, with stainless steel and single-use formats available. During these processes, minimal shear stress alongside control of concentration and temperature are essential for antibody integrity. Crucially, TFF supports ultra, micro, nano and diafiltration operations, enabling gentle and efficient buffer exchange, concentration and impurity removal for ADCs, while preserving conjugate integrity and providing scalable, consistent purification from development through manufacturing.
- Control over the reaction conditions during conjugation is vital, with concentration, homogeneity and solvent removal all extremely important to ensure reproducible DARs.
- Modern isolator technologies and modular suites allow safe handling of potent payloads without the heavy capital

burden associated with traditional facility design. These modular solutions reduce downtime, simplify cleaning and allow facilities to adapt more easily to shifting project needs.

- Single-use systems continue to gain traction, particularly in early clinical production. Their ability to minimise cleaning validation, reduce cross-contamination risk and enable rapid changeover allows companies to move faster with fewer operational overheads.

Variability in any single element can cascade across the process. The whole manufacturing sequence from bioreactor to purification, conjugation, lyophilisation and aseptic fill-finish behaves as a tightly coupled system, as shown in Figure 1.

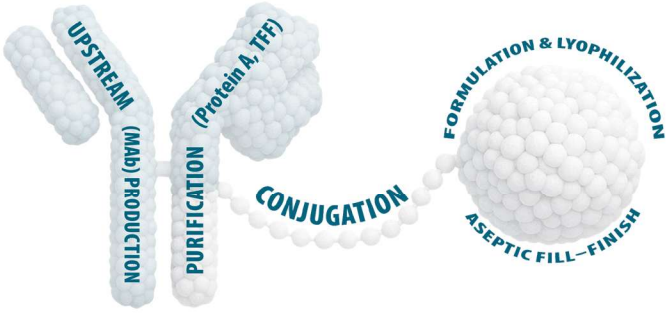

Figure 1: The five critical stages to ADC preparation, where TFF is tangential flow filtration.

Designing for Manufacturability: Preventing Costly Challenges Early

R&D choices determine how simple (or how burdensome) the manufacturing path will be. Companies that intentionally design for scalability and manufacturability experience shorter timelines, fewer surprises and significantly lower costs than those that don't. Investment in and development of in-house capabilities, especially in relation to the purchase of specific equipment and instrumentation, is of increasing importance. In addition, investment in personnel and paying attention to key processes early can pay dividends, for example, by inclusion of manufacturability evaluations, early risk assessment and guidance on how formulation behaviour, conjugation strategy and downstream processing will interact at scale. If an in-house solution is not possible, then working with a single CDMO or a series of highly specialised partners within a consortium can also be a viable route forward, allowing ADC developers to capitalise on the specialist knowledge and expertise within niche CDMO providers. Put simply, knowledge is power.

CASE STUDY

Working with Clients to Optimise ADC Manufacture and Remove Bottlenecks

A mid-stage oncology ADC programme faced significant challenges during Phase II clinical development due to instability in the liquid formulation. The molecule exhibited linker hydrolysis, aggregation and loss of potency, resulting in limited shelf life and an over-reliance on cold-chain storage. These issues risked delaying pivotal studies and increasing both material use and manufacturing cost.

To address these challenges, the development and manufacturing process was re-engineered by working with the client to develop an integrated approach that aligned upstream production, conjugation control, solvent management, formulation optimisation and lyophilisation strategy.

Key elements included:

1. **Consistent monoclonal antibody production**
   High-yield upstream expression was achieved using a 50 L single-use bioreactor, followed by tangential flow filtration (TFF) for buffer exchange and concentration. This provided a stable, well-characterised starting material for conjugation.
2. **Safer, efficient solvent removal**
   Vacuum evaporation supported controlled solvent reduction while minimising operator exposure to high-potency intermediates.
3. **Optimised formulation and freeze-drying cycle**
   Pre-lyophilisation characterisation, including thermal analysis and controlled nucleation studies, enabled the design of a reproducible pilot-scale freeze-drying cycle. This improved cake structure, reduced variability and supported a robust stability profile.
4. **Contained aseptic fill–finish**
   The final drug product was filled under isolator conditions, ensuring sterility and operator protection while supporting efficient turnaround of high-potency batches.

The resulting lyophilised ADC demonstrated >95% reconstitution recovery, retained potency through 12 months of ambient storage and no longer required frozen or refrigerated distribution. This provided significant logistical advantages and reduced storage and transport costs. The integrated development strategy also supported seamless transition into GMP manufacture at multi-kilogram scale, reducing risk and improving regulatory readiness.

Equipment Choices:
Lyophilisation as a Tool for Long-term Stability

Lyophilisation is emerging as one of the most important cost-shaping technologies in ADC development; in fact, over 80% of commercially approved ADCs to date are formulated as lyophilised forms.[4] The reason for this is that many ADCs degrade rapidly in aqueous form, for example, through linker hydrolysis, deamidation and payload-induced destabilisation, often rendering liquid formulations unsuitable beyond short-term storage. Freeze-drying provides a route to restore shelf life, reduce reliance on cold-chain distribution and support more flexible global supply. However, achieving the benefits of lyophilisation depends on precise cycle design, industrial expertise and having the infrastructure that can work with highly potent active pharmaceutical ingredients (HPAPIs) that are classified under Occupational Exposure Band 6 (OEB 6), the highest safety classification for hazardous substances.

During the lyophilisation process, the freezing behaviour determines both the ice morphology and sublimation pathways, and there are many aspects to consider. Rapid cooling may protect product integrity in some cases, whereas controlled nucleation,[5] in which the freezing process is conducted at a higher temperature and therefore slowed, enables larger crystal formation and reduced randomness in crystal structure, which may deliver more uniform cake structures overall. Controlled nucleation has several other benefits, including more reproducible product quality and consistency, faster reconstitution during end-use, improved mechanical stability and reduced costs. Primary drying must balance heat input and chamber pressure to avoid collapse, while secondary drying must achieve the residual moisture content necessary for long-term stability without damaging the antibody, linker or payload.

Working with an organisation that has world-leading expertise and access to state-of-the-art equipment across both ADC manufacture and subsequent drug product preparation, such as lyophilisation, can be invaluable. Insights into the design and validation of the freeze-drying approach that can streamline cycle development can be offered, strengthening process control and reducing the risk of scale-up challenges.

Developing In-House Expertise or Using a CDMO Partner?

As ADC programmes progress towards more advanced stages, the practical value of developing in-house expertise becomes clear, although the breadth of expertise required, from handling high-potency materials to conjugation chemistry, purification, analytical characterisation, formulation development, lyophilisation and aseptic processing, can render it impractical for many organisations to build complete internal capabilities. In this case, enlisting a partner with technical expertise in a specialised area can significantly accelerate development and remove the need for large capital investments.

The ADC field is continually evolving, with more complex constructs, more potent payloads and more ambitious clinical targets constantly being developed. Rather than building capabilities indiscriminately, the most efficient organisations choose targeted equipment investments, purchasing instrumentation and equipment alongside specialist training that amplifies flexibility, supports scalability and complements their in-house capabilities for use on subsequent internal R&D

projects. If this isn't possible, then working with a trusted CDMO partner with expertise in a specific area, such as lyophilisation or formulation development, can be a valuable alternative.

REFERENCES

1. Fu, Z., Li, S., Han, S., Shi, C. & Zhang, Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct. Target. Ther. 7, 93 (2022). https://doi.org/10.1038/s41392-022-00947-7
2. Beck, A., Goetsch, L., Dumontet, C. et al. Strategies and challenges for the next generation of antibody–drug conjugates. Nat. Rev. Drug Discov. 16, 315–337 (2017). https://doi.org/10.1038/nrd.2016.268
3. Ali, S., Dunmore, H.-M., Karres, D. et al. The EMA Review of Mylotarg (Gemtuzumab Ozogamicin) for the Treatment of Acute Myeloid Leukemia. The Oncologist, 24, e171–e179 (2019). https://doi.org/10.1634/theoncologist.2019-0025
4. Wen, L., Zhang, Y., Wang, S. S. et al. Fundamental properties and principal areas of focus in antibody–drug conjugates formulation development. Antibody Therapeutics, 8, 99–110 (2025). https://doi.org/10.1093/abt/tbaf005
5. Geidobler, R. & Winter, G. Controlled ice nucleation in the field of freeze-drying: Fundamentals and technology review. Eur. J. Pharm. Biopharm., 85, 214–222 (2013). https://doi.org/10.1016/j.ejpb.2013.04.014

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