SARTORIUS

Comprehensive Solutions for Optimizing ADC Development and Manufacturing

BioProcess International
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Marc Jenke

Antibody–drug conjugates (ADCs) are an innovative class of targeted cancer therapeutics that combine the specificity of a monoclonal antibody (mAb) with the potency of a cytotoxic drug using a molecular linker. Such a design enables selective delivery of chemotherapy: The antibody directs the toxic payload to cancer cells that express a particular antigen. ADCs thereby spare healthy tissues from off-target effects often observed with traditional chemotherapy, which is more of a "shotgun" approach. First-generation ADCs sometimes exhibited problems with instability and toxicity. For instance, Mylotarg (gemtuzumab ozogamicin), the first such product to receive regulatory approval (2000), had issues with premature drug release. However, the field has matured significantly to enhance product efficacy, safety, and manufacturability.

First-generation ADCs were susceptible to hydrophobicity-driven aggregation, off-target toxicity, and inconsistent pharmacokinetics due to heterogeneous drug:antibody ratios (DARs). Second-generation designs improved solubility and potency with hydrophilic linkers and stronger payloads, yet DAR variability and residual toxicity persisted due to random conjugation. Third-generation ADCs mark a paradigm shift, leveraging site-specific conjugation and hydrophilic payloads to achieve homogeneous DARs, reduced aggregation, and improved pharmacokinetics — resulting in safer, more effective therapies.

Since 2017, the pace of approvals has accelerated. A decade ago, only three ADCs had received marketing authorization in the United States, European Union, and Japan. By mid-2025, the US Food and Drug Administration (FDA) had approved 15 ADCs, including two approvals during that year alone (**1**). Novel conjugate modalities — e.g., radioimmunoconjugates and antibody–oligonucleotide conjugates (AOCs) (Table 1) (**2**) — are emerging to expand the concept of bioconjugates beyond conventional ADCs for traditional oncology indications. This report provides a deep dive into the ADC landscape, covering background technology, market trends, manufacturing processes, key challenges, and emerging solutions with a focus on single-use (SU) bioprocess innovations (**3**). The report also discusses future pathways and offers recommendations for stakeholders in this rapidly growing field.

ADC Market Landscape

The ADC therapeutics market is experiencing remarkable growth and investment. In 2024, global sales of approved ADC drugs tallied an estimated $16.1 billion, and analysts project sales to quadruple to $57.4–63.1 billion by 2030 (**4**). That implies a 15–25% compound annual growth rate (CAGR) over that period, which is one of the fastest growth rates in oncology (**2**). By comparison, the mAb market is expected to grow at a compound annual rate of 12% between 2025 and 2030. Drivers of rapid expansion in the ADC market include recent clinical successes and a robust development pipeline.

Rising Approvals: ADC approvals are rising rapidly. In the first half of 2025 alone, two new products received FDA approval: AbbVie's Emrelis (telisotuzumab vedotin) for MET-gene–positive lung cancer and AstraZeneca/Daiichi's Datroway (datopotamab deruxtecan) for hormone-receptor (HR)–positive breast cancer. Such approvals reflect growing regulatory confidence in improved ADC designs and successful clinical results (**5**).

Extensive Pipeline: The development pipeline has expanded in size and diversity. More than 1000 ADC candidates are in preclinical research and development (R&D), and >200 are in clinical trials globally (**6**). At least 24 candidates have reached phase 3 trials, suggesting many more approvals to come in the following years. Together, those investigational ADCs target >50 different tumor antigens, and often those candidates incorporate next-generation technologies. The breadth of programs spans both major pharmaceutical companies and specialized biotechnology companies, indicating widespread commitment to ADC innovation.

Major Investments and Partnerships: The ADC boom has triggered high-value mergers and collaborations. In 2023 and 2024, pharmaceutical

companies announced over US$60 billion in ADC-related acquisitions and alliances. Notable examples include Pfizer's $43 billion acquisition of ADC pioneer Seagen in 2023 and AbbVie's $10 billion purchase of ImmunoGen in 2024. Companies also are investing in enabling technologies. For example, Johnson & Johnson acquired Ambrx and its site-specific conjugation platform for $2 billion, and Genmab bought ProfoundBio and its proprietary hydrophilic linkers for $1.8 billion (**7**). The wave of deals underscores the strategic importance of ADCs as big pharma secures pipelines and know-how while injecting capital to scale up manufacturing capabilities (e.g., new high-containment facilities) in anticipation of growing demand.

Commercial Success of Flagship ADCs: Several recently launched ADCs already have achieved blockbuster sales, validating the commercial viability of the modality. For instance, Enhertu (trastuzumab deruxtecan), a human epidermal growth factor receptor 2 (HER2)–targeted ADC, earned over $2.5 billion in 2023, its fourth year on market (**8**). In the same year, Kadcyla (ado-trastuzumab emtansine, approved in 2013) tallied sales of about $2.2 billion (**9**). Other ADCs, such as Adcetris (brentuximab vedotin) and Trodelvy (sacituzumab govitecan), have shown similarly robust revenue growth as their indications expand. Such successes are giving the pharmaceutical industry confidence in this modality's therapeutic value, encouraging further adoption and R&D investment.

Global Expansion: North America and Europe currently lead in ADC development and sales, but Asia — China in particular — is increasing its market presence rapidly. That country has dozens of ADC trials underway and is projected to expand its market at a rapidly accelerated pace (**10**). Regulatory bodies worldwide are establishing clear guidelines for ADC approval and manufacturing, helping to globalize access. Notably, up to 80% of ADC manufacturing is outsourced to specialized contract development and manufacturing organizations (CDMOs), reflecting such products' high containment and expertise requirements. That trend is likely to continue as more ADCs enter late-stage development.

Overall, the ADC market outlook is extremely positive. Analysts envision a bright future in which a growing roster of ADC therapies addresses unmet needs in oncology, potentially making ADCs a cornerstone of cancer treatment alongside immunotherapies (**11**). To realize such potential, the biopharmaceutical industry must develop and manufacture ADCs efficiently at scale. Thus,

Table 1: Emerging modalities in bioconjugate therapeutics (**2**)

Modality	Description
Antibody–drug conjugate (ADC)	Includes a full-chain monoclonal antibody (mAb), linker, and toxin
Radionucleotide–antibody conjugate (RAC)	Applies an antibody, peptide, or small molecule for precise targeting of cytotoxic and/or imaging factors (e.g., radionuclides and radioisotopes)
Small-molecule–drug conjugate (SMDC)	Comprises a targeting molecule, linker, and effector molecule (e.g., cytotoxins and E3 ubiquitin ligases)
Immune-stimulating antibody conjugate (ISAC)	Modulates immune stimulation and microenvironment to activate immune killing and therapeutic sensitization
Antibody–degraducer conjugate (AdeC)	Replaces a traditional ADC payload with a degradation molecule, minimizing systemic exposure and sometimes overcoming druggability problems
Antibody fragment–drug conjugate (FDC)	Replaces a traditional ADC antibody with an antibody fragment (e.g., single-chain variable fragment, scFv), opening up potential for higher drug:antibody ratios
Aptamer–drug conjugate (ApDC)	Leverages nucleic-acid aptamers as "chemical antibodies" to achieve antibody-like targeting and binding properties; holds advantages such as high stability, low immunogenicity, low production costs, and easy chemical modification
Virus-like drug conjugate (VDC)	Uses a viral capsid designed as a noninfectious protein nanoparticle (virus-like particle, VLP) for efficient delivery of small-molecule drug
Antibody–oligonucleotide conjugate (AOC)	Delivers therapeutic oligonucleotides — e.g., small interfering RNA (siRNA) and phosphorodiamidate morpholino oligomers (PMOs) — to specific cells or tissues using a targeting antibody, thereby reducing the required amount of drug
Degrader–antibody conjugate (DAC)	Combines a mAb with a proteolysis-targeting chimera (PROTAC) payload using some type of chemical linker

substantial investments are going into production infrastructure and technologies such as SU bioprocess systems and high-containment suites. The following sections delve into what makes ADCs unique and how their manufacturing processes can be optimized to sustain current growth.

ADC Fundamentals: Structure and Components

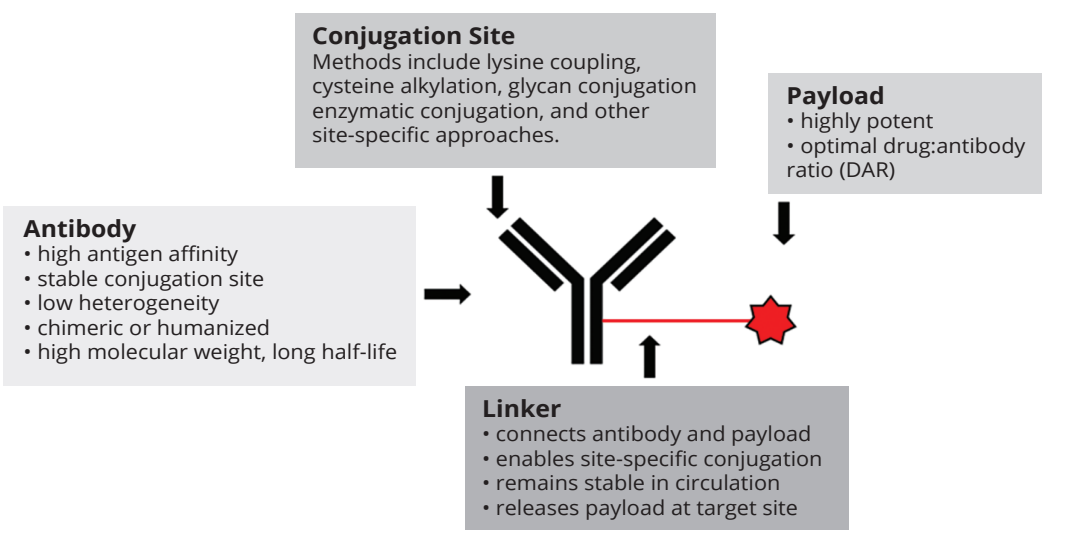
An ADC comprises three main molecular components: an antibody, a linker, and a payload (Figure 1) (**12**). Each component must be engineered carefully because it critically influences the safety and efficacy of the final conjugate (**13**).

The **mAb** component provides targeting specificity. Manufacturers typically choose a humanized or fully human immunoglobulin G (IgG) for high affinity and specificity to an antigen that is highly expressed on cancer cells but not on normal cells. Such a strategy ensures that ADCs will bind primarily with tumor cells. The chosen mAb should have minimal immunogenicity and sufficient stability to withstand harsh solvent-based conjugation processes. Traditional conjugation chemistries attach drugs to certain amino acids on the antibody (e.g., lysines or reduced cysteines), yielding a mixture of conjugates with different DARs. For example, conventional methods might produce a distribution of zero to eight payloads per antibody, leading to heterogeneity that can complicate pharmacokinetics.

Next-generation conjugation techniques address shortcomings of traditional methods by engineering specific conjugation sites or adding unique amino-acid handles (**14**). Manufacturers now can produce relatively homogeneous ADCs with well-defined DARs, which improves product consistency and often widens a product's therapeutic window with less off-target toxicity. For example, AstraZeneca's experimental anti-HER2 ADC ARX-788 uses engineered attachment sites to ensure a DAR of 2, enhancing stability and performance (**15**). In summary, a selected antibody must combine high tumor-targeting ability with compatibility for conjugation, and modern antibody engineering provides precise control over where and how many payloads are attached.

A **linker** connects drug molecules to antibodies and controls when and where those drugs will be

Figure 1: Components of a conventional antibody–drug conjugate (ADC)



released. An ideal linker is stable enough in a patient's bloodstream to prevent premature payload release and systemic toxicity, yet pliable enough to release drug molecules efficiently into target cells when they reach them.

Linkers come in two major designs. **Cleavable linkers** are designed to disengage in tumor cells by exploiting intracellular conditions, such as low pH, specific enzymes, or a reducing environment. Common designs include acid-labile linkers that cleave in acidic endosomes, protease-sensitive peptides that are cleaved by cathepsins and other lysosomal enzymes, and disulfide bonds that are reduced inside cells.

For example, valine–citrulline (Val-Cit) dipeptide linkers such as that used in Adcetris (brentuximab vedotin) remain stable in circulation but are cleaved by cathepsin enzymes within lysosomes, in turn releasing monomethyl auristatin E (MMAE) toxins. Cleavable linkers also can facilitate bystander effects, through which released drugs (if membrane-permeable) diffuse to neighboring tumor cells and kill them. Such effects can be useful against heterogeneous tumors.

However, cleavable linkers must display robust stability in blood circulation. Early generation linkers such as hydrazones were too unstable and caused off-target toxicity. Newer, more robust cleavables — e.g., Val-Cit or glycine–glycine–phenylalanine–glycine (Gly-Gly-Phe-Gly) systems — strike a better balance, remaining intact in the bloodstream and releasing payloads only inside target cells.

Noncleavable linkers do not break apart under physiological conditions. Instead, they rely on an entire ADC being taken into a target cell. Drug is released only upon full antibody degradation (usually in the lysosome) after attachment — e.g., through an amino-acid remnant. A classic example is the succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) thioether linker in Kadcyla (trastuzumab emtansine), which is stable in circulation and releases the cytotoxin mertansine (DM1) only after ADC internalization and antibody degradation, yielding a toxin amino-acid adduct that kills the cell. ADCs with noncleavable linkers tend to exhibit high stability in circulation with minimal off-target release and relatively longer half-lives. However, the trade-off with stable linkers is that bystander killing is limited because drug remains attached until the target cell dies. The choice between a cleavable or noncleavable linker depends on the cancer indication and payload properties; each linker type has distinct advantages and disadvantages.

Linker hydrophobicity is another critical design factor for ADCs. Extremely hydrophobic linkers, especially when combined with hydrophobic payloads, can cause ADCs to aggregate or stick to proteins, leading to rapid clearance or nonspecific uptake. The latest generation of ADCs tend to use hydrophilic linkers, such as polyethylene glycol (PEG) segments or polar amino acids, to improve solubility. For instance, the anti-CD19 ADC Zynlonta (loncastuximab tesirine) uses a hydrophilized peptide linker to counter its extremely hydrophobic pyrrolobenzodiazepine (PBD) payload, thereby extending the conjugate's half-life. Likewise, Enhertu (fam-trastuzumab deruxtecan) includes a short hydrophilic peptide in its cleavable linker to facilitate high DARs (≈8) without compromising pharmacokinetics. Optimizing the hydrophilic–lipophilic balance of the linker–payload combination is essential; too much hydrophobicity leads to instability, whereas too much hydrophilicity reduces the cell permeability of released drug.

ADC **payloads** are most often small-molecule cytotoxins intended to destroy target cancer cells. Such drugs tend to be extremely potent — 100–1000× more toxic than conventional chemotherapy agents — because only a few molecules can be delivered per cell. Common payloads fall into a few classes defined by their mechanism of action (MoA):

- *Auristatins* inhibit microtubule polymerization, causing mitotic arrest and apoptosis (e.g., the Adcetris ADC uses MMAE)
- *Maytansinoids* are microtubule inhibitors (maytansine derivatives) that induce mitotic arrest (the Kadcyla and Elahere products use DM1 and DM4, respectively)
- *Calicheamicins* are enediyne antibiotics that cause double-strand DNA breaks (e.g., the Mylotarg ADC uses a calicheamicin derivative)
- *Duocarmycins* are DNA alkylators that bind to DNA's minor groove and form covalent adducts, leading to cell death (several duocarmycin-based ADCs are in clinical trials, such as trastuzumab duocarmazine)
- *PBDs* are ultrapotent DNA crosslinkers that prevent separation (the Zynlonta product uses a PBD dimer)
- *Camptothecin derivatives* inhibit topoisomerase I, leading to DNA breaks during replication (the Enhertu and Datroway ADCs use deruxtecan, a camptothecin analog).

Such payloads are far too toxic to administer on their own, but ADC formats enable their use by targeting delivery to tumor cells. Notably, ADC payloads often push the limits of solubility and stability. That is because they are chosen for potency, which further underscores the importance of a well-designed linker and antibody to keep them soluble in the bloodstream.

Evolution of ADC Design

Figure 2 depicts the evolution of ADC design. First-generation products (developed in the late 1990s–2000s) often struggle with hydrophobicity and instability. Linkers and payloads in such designs can cause aggregation or premature release, leading to off-target toxicities. For example, Mylotarg (gemtuzumab ozogamicin), which in 2000 became the first approved ADC, uses a hydrazone linker. It proved to be insufficiently stable for the initially approved dosing schedule, creating safety issues, and the product was approved for administration at a lower dose in 2017.

Second-generation ADCs from the 2010s introduced comparatively more stable linkers and more potent payloads, improving efficacy. However, many such products are manufactured using conventional conjugation techniques, resulting in heterogeneous DARs and some toxicity due to DAR distribution and bystander effects. The Kadcyla drug, approved in 2013, exemplifies this second generation. It features a stable noncleavable linker with an improved safety profile, but the product formulation contains a mix of species with DARs of 0–8 that require careful control.

Third-generation ADCs from 2019 to the present incorporate advanced linker designs and site-specific conjugation. Such products often use hydrophilic linkers or payloads to mitigate aggregation and to achieve homogeneous DARs and improved pharmacokinetics. The result is greater potency and less toxicity compared with what earlier designs can offer. The Enhertu drug, approved in 2019, is a case in point. It uses a topoisomerase-inhibitor payload attached by a cleavable, peptide-based linker that is relatively polar, allowing for a high DAR (≈8) while remaining tolerable to patients.

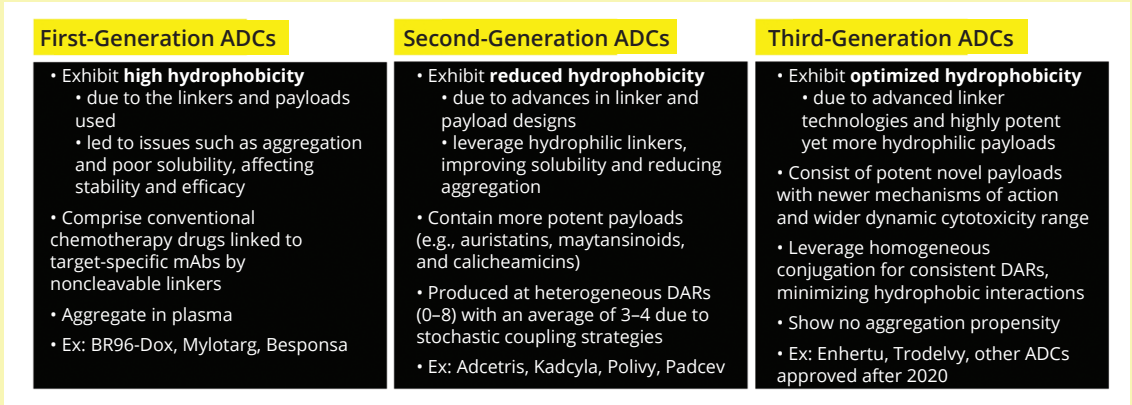
Manufacturing Process Overview

ADC manufacturing is a complex multistage process that combines antibody bioprocessing with high-potency small-molecule conjugation for the linker–payload. The process bridges biologics and chemistry workflows under stringent quality and safety controls across all of the following steps.

Antibody Production: The base antibody is expressed in cell culture and purified chromatographically, as with any therapeutic mAb. For ADCs, a frozen mAb drug substance must be thawed and exchanged into a conjugation-compatible buffer, often using tangential-flow filtration (TFF), at the correct concentration. Antibody solutions also can undergo filtration to remove precipitates before conjugation.

Linker–Payload Preparation: In parallel, manufacturers chemically synthesize the linker–drug combination. That compound often arrives at a biomanufacturing facility as a highly potent cytotoxic powder that requires handling in contained isolators. The material is dissolved into an appropriate neat solvent, such as dimethyl sulfoxide (DMSO) or dimethylacetamide (DMA), and prepared to the correct concentration for conjugation.

Figure 2: Advances in antibody–drug conjugate (ADC) design from constructs with hydrophobicity challenges to homogeneous, highly efficacious conjugates; DAR = drug:antibody ratio, mAb = monoclonal antibody



Conjugation Reaction: Next, manufacturers chemically conjugate mAbs with linker–payloads. Depending on the associated chemistry, conjugation might involve partially reducing antibody disulfide bonds or modifying specific amino-acid residues, followed by mixing with linker–payloads so that the components covalently attach. Manufacturers typically perform this step in a controlled reactor. For example, if using a maleimide chemistry, antibody cysteines are reduced before the reaction step with a maleimide-activated linker–drug. Time, temperature, stir rate, stoichiometry, and other reaction conditions are controlled tightly to achieve the intended DAR.

Quenching and Initial Purification: After conjugation, a manufacturer must quench or remove unreacted linker–payload molecules before the crude ADC mixture can undergo purification to separate complete ADCs from unconjugated antibodies, free drug, and by-products. Manufacturers often use TFF here for ultrafiltration/diafiltration (UF/DF). That approach can buffer-exchange the conjugation mixture and remove small-molecule impurities from the drug–solvent mixture while retaining and concentrating larger ADC molecules. Additional chromatography steps, such as hydrophobic-interaction or size-exclusion chromatography (HIC, SEC), can be used to purify ADCs further, enriching molecules with the target DAR.

Aggregate Removal and Polishing: ADC preparations are often prone to aggregates (e.g., antibody dimers), which must be removed because they can affect product safety and efficacy. Membrane chromatography enables removal of aggregates and residual linker–drug molecules from ADC mixtures while improving separation based on DAR. To isolate molecules with specific DARs, manufacturers can perform two-dimensional (2D) chromatography using solutions such as Sartobind S and Sartobind Phenyl membrane technologies from Sartorius.

Formulation and Fill–Finish: Manufacturers formulate purified ADCs into a final buffer with excipients added as stabilizers or bulking agents. This formulation step sets the correct ADC concentration for bulk filling (**17**). Formulated ADCs then undergo sterile filtration and aseptic filling into vials or syringes. Finally, vials often are lyophilized so that the products can be stored as freeze-dried powders for increased stability and longevity. Alternatively, they can be frozen.

Key Challenges in ADC Development and Manufacturing

Producing ADCs at commercial scale presents unique complications because they are hybrid products containing both biologic and cytotoxic chemical components. Key difficulties include handling **highly potent toxins**; thus, operator containment and safety are critical (**5**). ADC payloads are extremely cytotoxic, and even trace exposures can endanger production staff. Manufacturing must include strict high-containment measures. Facilities often use isolators or closed SU systems during conjugation and purification to protect operators and prevent cross-contamination. Personal protective equipment (PPE) and engineering controls need to be at the highest level, as is the case when handling a hazardous chemotherapy. Contaminated waste streams such as TFF flow-through must be deactivated, collected as hazardous waste, and transported off site. Maximizing worker and environmental safety is essential, so ADC handling requirements will influence facility design, equipment selection, and operating procedures.

Unlike standard mAb production, ADC processing involves **organic solvents and reactive chemicals**. Solvents such as DMA, DMSO, and acetonitrile are used during conjugation. Those materials can degrade or extract components out of filters, bags, tubing, and other SU equipment. Similarly, some ADC payloads and intermediates can adsorb to equipment surfaces. Material compatibility is critical. All materials that will contact process solutions must undergo extensive testing for solvent compatibility to ensure against leaching and loss of integrity. Testing disposable, polymeric equipment is challenging and requires extensive validation. For example, it can involve confirming that organic solvents will not weaken a SU bag's film or extract plasticizers into products. Incompatibility can lead to SU equipment failure and even product contamination.

Organic-solvent use brings other difficulties, as well. For instance, some solvents (e.g., acetonitrile, ethanol, and isopropyl alcohol) are flammable. Large volumes of flammable solvents can trigger explosive-atmosphere (ATEX) facility measures and related precautions to enhance operator safety.

DAR Control: Conjugation reactions must be controlled carefully to achieve target average DARs — which is, for many ADCs, between 2 and 4 — and to limit proportions of unconjugated and overconjugated species. DAR affects potency and

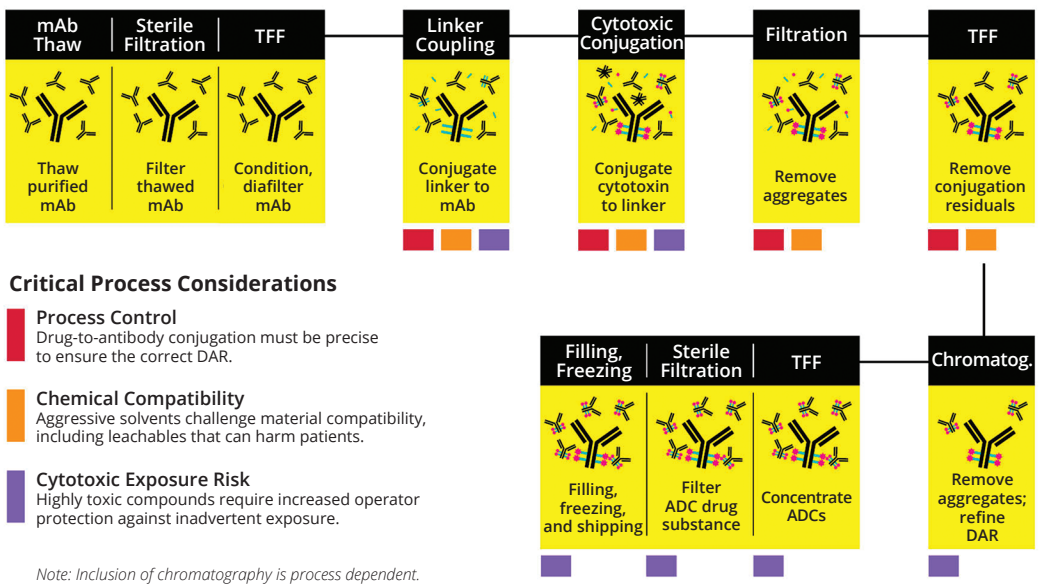
pharmacokinetics: If the DAR is too low, then efficacy suffers, but if the ratio is too high, then toxicity and/or aggregation increases. Even after purification, ADC products can contain a mix of species with different DARs. Manufacturers need robust analytical methods and process controls to monitor DAR and ensure product consistency. In-process analytics based on ultraviolet (UV) spectroscopy (for measuring drug absorbance) and reversed-phase high-performance liquid chromatography (RP-HPLC, for DAR profiling) can be used to adjust conjugation conditions as needed. The need for DAR control also has driven the field toward site-specific conjugation to reduce heterogeneity and costs.

Preventing Cross-Contamination: Given the potency of cytotoxic payloads, manufacturers must prevent carryover of ADC product and free drug to other production lines and products. Companies often use dedicated equipment and/or SU flow paths for manufacturing ADCs. Traditional multiuse stainless-steel systems raise concerns because associated cleaning validation for toxin clearance is time-consuming and costly. Thus, manufacturers often prefer SU technology to eliminate cross-batch contamination. Facilities also need to segregate ADC manufacturing areas properly from other drug-production areas to comply with good manufacturing practice (GMP) guidelines.

Process Considerations: ADC manufacturing has many unit operations, each of which can diminish yield through increased aggregation, antibody fragmentation, and residual free drug. An ADC process must be optimized to maximize yield while meeting specifications for monomer purity, free drug, endotoxins, and more. ADC products also pose difficulties for scalability and consistency — e.g., for scaling a conjugation reaction from laboratory to commercial scale while maintaining a consistent DAR distribution or for efficiently removing a hydrophobic toxin at large scale using TFF. Each step — including filtration, chromatography, and TFF — must be tailored for an ADC's specific properties.

Analytics: As hybrid products, ADCs require extensive characterization. Manufacturers must demonstrate not only typical biologic attributes such as antibody purity and potency, but also chemical-drug aspects, including drug content, linker stability, and so on (**18**). Analysts need to perform mass spectrometry (MS), binding and potency assays, stability analysis, and impurity analysis for detecting free drug molecules. The analytics and validation workload is high, potentially complicating development timelines. Moreover, process changes such as new linkers or SU components will necessitate revalidation to ensure that they do not alter critical quality attributes (CQAs).

Figure 3: Overview of an example antibody–drug conjugate (ADC) manufacturing process from thawing and filtration of monoclonal antibodies (mAbs) to conjugation, purification, aggregate removal, and final filling and freezing; DAR = drug:antibody ratio, TFF = tangential-flow filtration



In summary, ADC manufacturing must balance bioprocessing precision with high-containment safety operations. Combining biological and chemical constraints makes the process uniquely difficult. The next section explores solutions that have been developed — particularly SU, closed-system approaches — to overcome those hurdles and improve the safety and efficiency of ADC production at scale.

Technologies for Enhancing ADC Manufacturing

To address the challenges described above, the biopharmaceutical industry has adopted an array of engineering controls, process innovations, and SU technologies. A comprehensive solution for ADC manufacturing typically involves integrating specialized equipment and protocols at each step to enhance safety, compatibility, and efficiency. Some key strategies and best practices follow.

Closed, Single-Use Processing Systems: One of the most effective measures for facilitating ADC operations is using fully closed, SU assemblies — from conjugation reaction vessels to TFF cassettes and filtration manifolds — for as many steps as possible to isolate products and protect personnel. Disposable bags, tubing, and connectors come presterilized and can be used in contained formats, greatly reducing the risk of operator exposure to potent drugs. For example, conjugation often takes place in a SU bag handled through an isolator. Postreaction mixtures can be transferred through SU TFF cassettes and filters in a closed format. Leveraging SU, gamma-irradiated, closed-loop solutions is safer than performing unconnected steps in stainless-steel equipment.

Disposable systems eliminate much need for cleaning because entire product-contact flow paths can be discarded after processing. An SU approach minimizes cross-contamination by obviating need for shared equipment. Moreover, containment is simplified because closed disposables act as barriers between toxic process fluids and operators and the environment. Suppliers now offer integrated, ADC-compatible SU kits and assemblies that provide seamlessly closed connections across conjugation, TFF, and filtration steps.

Material Compatibility and Solvent-Resistant Components: To ensure that SU technologies can accommodate ADC processes, suppliers have developed solvent-resistant plastics and membranes. Filters, bags, and tubing undergo extensive chemical-compatibility testing with common ADC solvents such as DMA, DMSO, and N-methylpyrrolidone (NMP). For instance, vendors conduct rigorous studies exposing SU equipment/consumables to those harsh solvents to confirm the absence of degradation and extractables and leachables (E&L). Thus, specialized components such as TFF cassettes, bag films, and gaskets are confirmed to withstand aggressive organic solvents and cytotoxic materials without performance loss.

As a best practice, ADC manufacturers should work closely with vendors to verify all contact materials. That might include performing E&L studies under worst-case solvent conditions. Using preflushed filters and assemblies can remove loose particles and soluble compounds before they contact an ADC product, helping to reduce toxic waste flows. Overall, Sartorius recommends investing in proven, solvent-compatible SU equipment and consumables to maximize product purity, operator safety, and equipment integrity during ADC processing.

Figure 4: Innovative single-use (SU) solutions for enhanced safety and efficiency in antibody–drug conjugate (ADC) manufacturing; AQ = AseptiQuik (Colder Products Company), EtO = engineered to order

Pain Point	Chemical Compatibility	Contaminated-Waste Handling	Cleaning Validation	Risk for Cross-Contamination	Closed or Open Processing	Scalability	EtO Solutions
SU Solutions	Sartorius has comprehensive data to ensure that materials are compatible with applied solvents.	SU solutions enable proper management of contaminated waste.	SU equipment is properly cleaned and free from contaminants.	SU equipment reduces the risk of contamination between different batches.	Several standard products with AQ connectors are available.	Scalable solutions for development-, pilot-, and commercial-scale manufacturing are available.	Sartorius can tailor hardware and wetware solutions to customer requirements.
Benefits	Compatibility ensures that materials withstand process conditions.	SU reduces compliance costs and impacts to environment; minimizes operational disruptions, lowering overall production costs.	SU solutions ensure product quality and compliance with regulatory standards.	Risks for cross-contamination are minimized.	SU ensures a closed process environment, enhancing safety and reducing risk of contamination.	SU provides flexibility and scalability for different stages of ADC manufacturing.	Customized solutions help users to meet specific requirements.

High-Containment Facility Design: Even with closed systems, manufacturers still need a holistic containment strategies. Modern ADC facilities often use segregated suites with airlocks and specialized heating, ventilation, and air conditioning (HVAC) systems to ensure containment of accidental release. Key operations involving dry powders and/or open handling of toxins, such as weighing payload materials or connecting feed bottles, must be performed inside ventilated glove boxes or isolators. By maintaining pressure differentials, manufacturers can keep rooms containing ADC materials at negative pressure relative to corridors, thus preventing escape of toxic aerosols.

Automated handling technologies such as robotic vial-filling lines can reduce operator exposure further. Many companies also implement personnel classification systems, according to which only trained individuals wearing PPE can enter ADC areas. A comprehensive solution includes validated decontamination procedures for equipment and waste: Lines can be flushed with quenching solutions to inactivate residual drug, and resulting waste can be collected for high-temperature incineration. By combining engineered controls such as isolators and closed systems with administrative controls such as procedures and training, leading ADC facilities reduce worker exposure levels well below the strict occupational exposure limits that regulators set for such toxins.

Optimized TFF and Chromatography: Manufacturers often use TFF in ADC manufacturing for buffer exchange, concentration, and removal of free drug. Suppliers have adapted their TFF cassette membranes to be compatible with solvents. For example, regenerated-cellulose membranes can tolerate a certain percentage of organic solvent. Additionally, TFF systems can be skid-mounted in contained enclosures with drip trays.

On the chromatography side, manufacturers sometimes use multicolumn chromatography methods to separate ADC species by DAR. New resins and methods (e.g., for HIC) that are tuned for ADCs can improve removal of free drug and yield desired DAR distributions. In practice, companies develop robust purification trains to ensure that each step is effective and mitigates risk of unconjugated-toxin carryover into the final product.

Real-Time Monitoring and Control: Given tight quality requirements for ADC products, advanced analytics should be introduced in line where possible. For instance, in-line UV monitors can be implemented during TFF to detect when free drug has been washed away because many payloads absorb at UV–visible-light wavelengths that are distinct from the absorbance values of proteins; rapid HPLC analysis can be performed on process intermediates to inform conjugation time adjustments. Some manufacturers also monitor conductivity and pH continuously because conjugation can generate by-products that alter those parameters. If deviations are detected, then manufacturers can adjust processes in response. Automation software and sensors can modulate and maintain processes within setpoint ranges, improving consistency.

Through a combination of innovative equipment and meticulous process design, the industry has built a toolkit to address ADC manufacturing challenges (**5**). Closed SU systems address containment and cross-contamination issues. Solvent-compatible materials and thorough testing ensure chemical compatibility. Purpose-built facilities and safety protocols protect workers from highly potent compounds. Such solutions make it feasible to manufacture ADCs at large scale with enhanced safety, reproducibility, and efficiency. Given the significant risks and complexities involved, the Sartorius team strongly advises companies developing ADCs to adopt innovative technologies rather than retrofitting systems designed for standard mAb processes (**1**).

Future Perspectives and Recommendations

The ADC field is evolving as ongoing improvements in antibodies, linkers, and toxins change how those components are produced. The Sartorius team identifies several trends and future implications for stakeholders.

Companies are likely to increase their use of **site-specific conjugation** and other advanced bioconjugation techniques to yield uniform products with well-defined drug loads. That shift could simplify manufacturing — e.g., if conjugation chemistry targets a unique tag on an antibody, a manufacturer could minimize excess drug and reduce burden on purification steps. Companies might invest in new conjugation chemistries to adjust their processes because some site-specific methods could require nonstandard buffers or enzymes. Emerging conjugate modalities, including radioisotope conjugates, might call for hybrid manufacturing setups with steps for radiolabel handling. Building flexibility into facilities and training could help to future-proof such operations.

Up to 80% of ADC manufacturing is performed by **contract manufacturers**, and even companies that innovate ADCs often leverage CDMOs for production. Given the significant infrastructure investment and safety requirements, this outsourcing model is set to continue. ADC developers should choose partners with proven track records in that modality, with offerings for solvent-compatible SU equipment and consumables as well as regulatory experience in handling highly potent active pharmaceutical ingredients (APIs). Close collaboration will help to ensure smooth technology transfers and fulfillment of all containment needs. For organizations with multiple ADC programs, investing in an internal high-containment ADC pilot facility might be warranted to accelerate development, even if commercial production is outsourced.

Regulatory agencies will expect robust demonstrations of **containment, cleaning, and product characterization**. Recently established guidelines from the FDA and European Medicines Agency (EMA) that are specific to ADCs underscore that trend. Companies should engage regulators early in ADC product and process development to agree on approaches for leachables testing, cleaning validation (if using stainless-steel equipment), and worker-safety monitoring. Manufacturers also should adopt a quality-by-design (QbD) mindset: Identify CQAs such as DAR distribution, and include them in initial control strategies.

Effective ADC manufacturing relies not solely on technological innovation, but also on the competence and diligence of **involved personnel**. Given the extreme toxicity of some compounds handled, operational precision is imperative to reduce margins of error. Sartorius recommends that organizations implement robust and comprehensive training programs for all individuals engaged in ADC-related activities. Such programs should encompass correct operation of isolators; appropriate responses to accidental spills; and safe, compliant disposal of hazardous materials. It is equally important that companies cultivate safety-oriented cultures in which all operators maintain awareness of containment protocols and personal accountability. Teams should refresh training at regular intervals and conduct routine emergency decontamination drills to ensure preparedness and reinforce procedural discipline.

Supply Chains: Integrating SU systems at scale is becoming increasingly standard within the field, prompting suppliers to develop large-format solutions, such as 1000-L SU reactors, that can accommodate substantial batch sizes. As process volumes expand, it is essential for manufacturers to plan facility capacity with the scalability of disposable equipment in mind.

Organizations should ensure that their SU-system vendors are equipped to supply appropriately scaled components that will support future growth. Given inherent supply-chain risks specific to ADC manufacturing, which depends on highly specialized bags and filters produced by a limited number of suppliers, companies would do well to establish dual-sourcing strategies and maintain contingency options for critical disposable components.

Environmental and waste-management considerations are increasingly important for ADC manufacturing, which generates hazardous waste streams. Solvent-based liquid waste and soiled SU assemblies are contaminated with cytotoxic compounds. As sustainability gains prominence in pharmaceutical operations, it is becoming essential to address environmental challenges through structured and compliant waste handling.

A comprehensive waste-management plan should incorporate on-site neutralization methods for liquid waste, where feasible, and manufacturers should engage certified incineration services for solid-waste disposal. In parallel, organizations must remain vigilant regarding evolving environmental regulations governing the treatment and disposal of toxic materials. Future advancements in green conjugation chemistries — particularly those that minimize reliance on harmful solvents — will offer opportunities to reduce the environmental footprints of ADC production. Organizations must stay ahead of such innovations to align operational practices with evolving sustainability standards.

Integrated Approaches for ADC Success

Despite their high potential as therapeutic products, ADCs present distinct manufacturing difficulties that require equally specialized solutions. Combining scalable SU systems, advanced analytical platforms, and high-containment practices has enabled commercial-scale production of these complex therapeutics. To navigate the intricacies of ADC manufacturing successfully, developers must adopt integrated approaches that encompass solvent-compatible SU equipment, comprehensive safety protocols, and robust operational controls.

The recommendations outlined herein emphasize that success in the ADC domain is inherently multidisciplinary, requiring scientific innovation,

engineering precision, operational excellence, and an uncompromising commitment to safety and quality. Companies that demonstrate strength across these dimensions will be best positioned to lead in the evolving ADC landscape and to deliver these life-saving therapies to patients worldwide.

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Dr. ***Marc Jenke*** *is principal scientist in application and testing for tangential-flow filtration (TFF) and separation technologies at Sartorius; marc.jenke@sartorius.com; https://sartorius.com.*