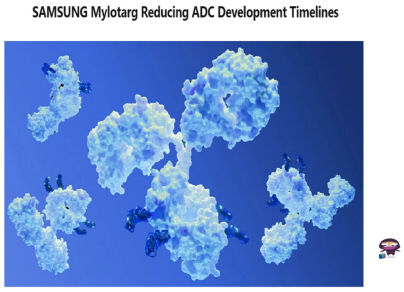

SAMSUNG Mylotarg Reducing ADC Development Timelines User Guide

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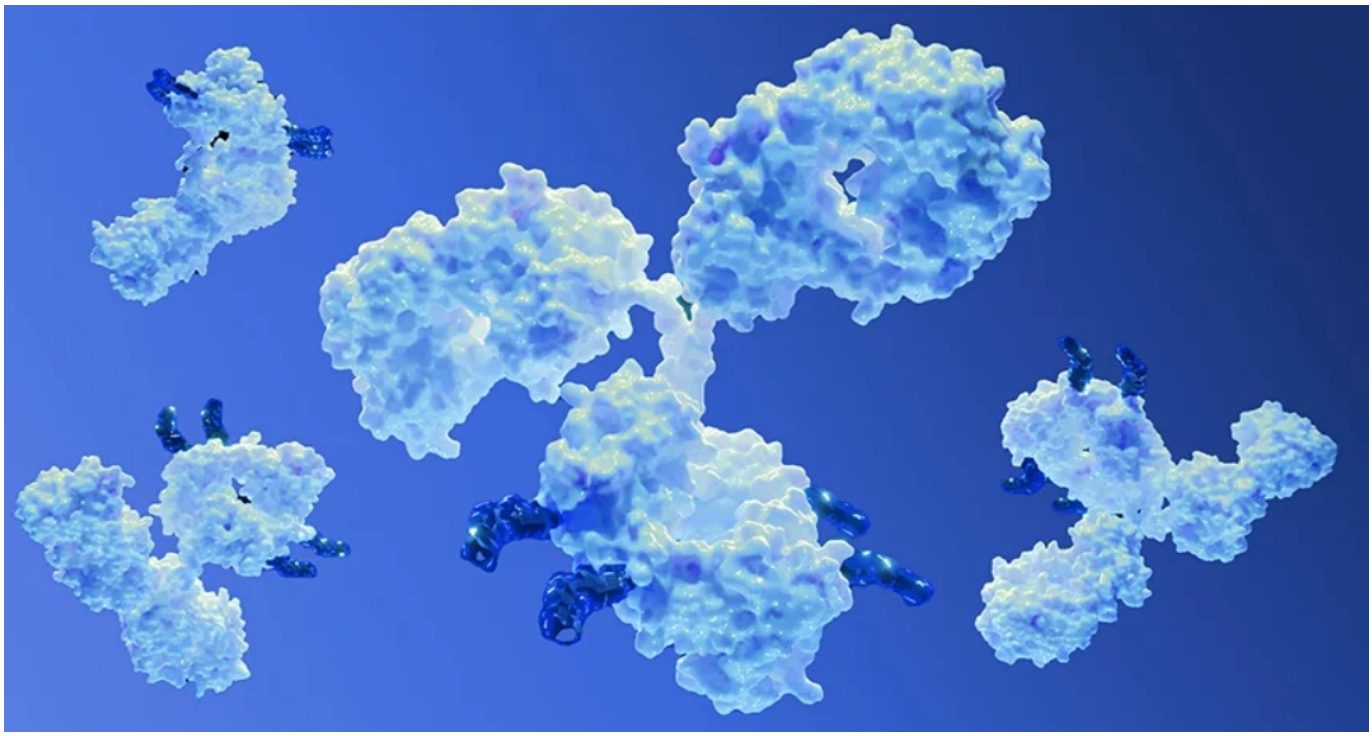

Specifications

- Product Name: Bioconjugates Development and Manufacturing Services
- Market Value: Approximately $9 billion in 2023
- Compound Annual Growth Rate: Around 11%
- Number of FDA-approved ADCs in June 2023: 11
- Main Applications: Anticancer therapies

Product Usage Instructions

1. **Understanding Bioconjugates**
   Bioconjugates consist of a biomolecule linked to a small molecule payload, often used in diagnostic and research applications to investigate disease mechanisms.
2. **Evolution of ADCs**
   First-generation ADCs faced stability issues, leading to improvements in second-generation ADCs with controlled linker locations and cleavable linkers for specific payload release.
3. **Third-Generation Advancements:**
   Third-generation ADCs feature dual-cleavage linkers for precise payload release, multiple payload binding for increased potency, and solutions for better solubility.
4. **Overcoming Supply Chain Challenges**
   Integrated development and manufacturing services help streamline ADC development by managing multiple suppliers and ensuring quality control.

FAQ

- **Q: What are the main targets of ADCs?**
  A: Most ADCs target oncoproteins like HER2 and TROP2, along with other biomolecular pathways such as BCMA, CD19, CD22, and more.

- **Q: How has the evolution of ADCs improved therapy?**
  A: Advancements in ADC technology have led to increased stability, better pharmacokinetic properties, and enhanced potency in targeting cancer cells.

WHITEPAPER
Reducing ADC Development Timelines with Integrated Development and Manufacturing Services

Abstract
Antibody–drug conjugates (ADCs) are highly effective in therapeutic applications, particularly as anticancer agents. Technologies for linking small molecule payloads to biomolecules have steadily evolved since the field's inception, resulting in continuous improvement in safety and performance. Manufacturing these multi-component therapies is challenging, however, given the three different elements—antibody, linker, and payload—require specialized capabilities. Integrating development and production activities within a single outsourcing partner can dramatically simplify ADC projects and accelerate timelines.

Growing Applications for Bioconjugates

- Bioconjugates comprise a biomolecule, such as an antibody, protein, or peptide, linked to a payload, which is typically a small molecule active pharmaceutical ingredient (API) with a specific therapeutic
- activity. Proteins conjugated to small molecules find use in diagnostic applications, and various types of bioconjugates are used by researchers to investigate disease mechanisms and other biomolecular pathways.1
- Antibody–drug conjugates (ADCs) are the most well-known bioconjugates and have been shown to be highly effective targeted therapies, particularly in the oncology space. The U.S. Food and Drug
- Administration (FDA) approved eight ADCs between 2019 and 2022. Furthermore, the number of ADCs entering phase I clinical trials in 2022 was 90% higher than in 2021, while the total number of clinical studies investigating ADCs that were initiated in 2022 was 35% higher than in the previous year.2
- The global market for ADCs is valued at approximately $9 billion in 2023 and is estimated to be expanding at a compound annual growth rate around 11%.3,4 In June 2023, 11 FDA-approved ADCs were on the market.1 This strong growth is attributable to the increased effectiveness of later-generation ADCs, which have significantly improved stability and pharmacokinetic properties.
- Most approved and candidate ADCs are anticancer therapies, with approximately one-fifth targeting the oncoproteins HER2 and TROP2. Other targets being explored include BCMA, CD19, CD22, CD30, CD33, Fra, and TF, among many others.2 Over 30 different linker chemistries and more than 60 different payloads have been employed in clinical candidates, although approximately half of clinical ADCs have leveraged tubulin inhibitors, which disrupt the cytoskeleton in targeted cells, leading to cell death.
- Advances continue to be made in linker chemistry, payload design, and antibody engineering. Examples include immune-stimulating antibody conjugates (ISACs) that activate immune responses and radioactive and cytotoxic payloads. Payloads, such as kinase inhibitors, are being investigated to determine if targeted administration will improve the therapeutic index. In addition, researchers and biopharmaceutical companies are showing growing interest in the use of other biomolecules, most notably peptides, that can penetrate solid tumors more efficiently than antibodies. Single-chain antibodies, antibody fragments, bispecifics, and other alternatives are also being explored. ADCs are being evaluated in the clinic as combination therapies with other chemotherapeutic agents.

Evolving Bioconjugation Solutions
The first ADC was approved in 2000. Mylotarg (Pfizer's gemtuzumab ozogamicin) leveraged N-acylhydrazone

linker technology, which unfortunately proved to be unstable and resulted in severe liver toxicity, leading to a withdrawal of the drug in 2010. However, it received approval again in 2017 at a lower dosage administered over a longer timeframe, which reduced toxicity.
Challenges with early linker technology drove significant efforts to identify improved alternatives, and new approaches were introduced in 2004–2005. In general, the linker technologies used in first-generation ADCs provided no control over the number of payloads conjugated to the antibody, leading to unsuitable heterogeneity of drug-to-antibody ratios (DARs).5 Release and reattachment of payloads at different locations and conjugation to many areas of the antibody, including the binding region, led to reduced efficacy and in some cases release of the payload in non-target tissues.
Second-generation ADCs benefited from site-specific conjugation (controlled linker location and homogeneous DAR values) and linkers that only release their payload when exposed to certain conditions in the target cell (e.g., a certain pH, high concentration of certain enzyme).5 Such cleavable linkers were an improvement over early non-cleavable linkers that required degradation of the targeting agent for the payload to be released.
Based on prior experience with first- and second-generation ADCs, third-generation ADCs are built on advances with dual-cleavage linkers for more specific payload release and linkers that can bind to multiple payloads for greater potency, in combination with solutions that better accommodate hydrophobic payloads for improved solubility and bioavailability.5 An example is the use of liposomes and branch chain linkers that can be loaded with multiple payload molecules.

Overcoming Supply Chain Challenges with Integration

- ADC developers relying on a fragmented supply chain face a range of challenges associated with the intricacies of vendor management. With multiple suppliers to oversee, each specializing in a unique ADC component (antibody, linker, and payload), companies frequently wrestle with harmonizing quality controls, synchronizing timelines, and ensuring efficient communication among all entities. The absence of an integrated service also exposes developers to potential inconsistencies in product quality. As each vendor enforces its distinct set of quality parameters, discrepancies can emerge, affecting the final ADC product’s potency and safety. Moreover, aligning timelines among varied suppliers can evolve into a logistical conundrum, which may culminate in unforeseen production delays. The transportation and storage of ADC components pose another layer of complexity. Developers must navigate the logistical hurdles of receiving materials from different geographical locations, each presenting unique bottlenecks. The diverse storage prerequisites for distinct components, ranging from specific temperature controls to unique handling protocols, can further complicate the process, requiring heightened vigilance and resource allocation.
- Given these complexities, sourcing raw materials for ADC production can be more challenging than procuring material for conventional antibodies. ADCs — constituted of biological, small molecule components — and a linker, necessitate that each of these three elements be manufactured in compliance with cGMP standards. All three components must then be concurrently delivered to the site designated for bioconjugation. Recognizing these challenges, manufacturers have made concerted efforts to consolidate as many relevant activities as feasible, either in-house or through alliances with contract development and manufacturing organizations (CDMOs) that offer comprehensive support for ADC production.
- Integration of drug intermediate (antibody, linker, and payload) manufacturing within a single provider, coupled with drug substance and drug product manufacturing, streamlines project management, rendering the establishment of ADC production timelines more straightforward. Moreover, these timelines are typically shorter, and there is a heightened probability of adhering to them. Crucially, every element is fabricated under a unified quality management system, promoting efficient communication between development and production teams.
- Samsung Biologics aims to offer fully integrated capabilities for ADC development and manufacturing. Currently, the company has expertise in antibody engineering, process development, and large-scale

manufacturing of antibodies. The process development group is ramping up its capabilities in bioconjugation and adding experienced personnel to its expanding team.

- Samsung Biologics will add the capability to expand its drug product manufacturing to include cytotoxins. This move is not only aimed at achieving full integration, but also at circumventing the challenges associated with accessing fill/finish services for cytotoxics and shipping these materials globally. The company is currently evaluating whether small molecule manufacturing will be established internally, via an acquisition, or through a licensing arrangement with another company.
- Customers can expect that, regardless of the chosen route, Samsung Biologics will establish integrated capabilities and the necessary expertise for ADC manufacturing in the near future. Indeed, the company is a relatively recent upstart but is already one of the largest manufacturers of monoclonal antibodies in the world. The approach to integrated ADC manufacturing will be similar—and significant. The company is very adept at constructing facilities and reducing timelines. Samsung Biologics expects to be a major player in the ADC market moving forward.

Enabling Bioconjugation through Appropriate Facility Design

In addition to aseptic manufacturing, which is required for all biologics, the cytotoxic nature of most ADCs requires the establishment of an environment suitable for handling highly potent and cytotoxic molecules. Not only must personnel be isolated from the process, but the process must also be isolated from the personnel. Effective containment for highly potent compounds involves rigorous control of the flow of personnel, materials, and room air.

Multiple mechanical seals are employed when the conjugation vessel is operational to prevent any release of material to the surrounding environment. “Air curtains” are used as shields for certain steps. The air turnover rate in a room for processing highly potent compounds must be extremely high (somewhere between 25 and 50 air changes per hour). For certain molecules and operations, personnel may be required to wear special respirators or air masks. Gloveboxes are typically used when preparing solutions of the cytotoxic compound to prevent release of even very small quantities of cytotoxic powder into the environment. The facility must be equipped with HEPA and carbon filters to remove even trace amounts of cytotoxins in the air and prevent their exhaustion to the environment.

Unlike traditional biologic processes, waste generated during the processing of highly potent compounds must be incinerated. That includes liquids from chromatography columns and tangential-flow filtration (TFF) systems (up to thousands of liters) and solids.

Changeover from one bioconjugation process to another when cytotoxic payloads are involved is more challenging as well. In addition to monitoring for microbial contamination, it is necessary to determine whether any residual cytotoxic materials are present. That requires analysis using liquid chromatography-mass spectrometry (LC-MS) to detect minute levels of toxins.

A truly integrated ADC service provider should have equipment that will be dedicated to certain cytotoxic payloads widely used in ADCs (e.g., tubulin inhibitors). It is also expected that, where it is possible to limit the quantity of organic cosolvent required to solubilize the cytotoxic payload before conjugation, such as for less hydrophobic compounds, single-use systems will be employed. To meet the required co-solvent level, ADC candidates must be produced in stainless steel or borosilicate glass-lined reaction vessels simply because of the level of co-solvent required.

Importance of the Right Analytical Support

Given that ADCs involve a biologic large molecule, a small molecule, and linker components that may be enzymes, peptides, or polymers, a wide range of analytical capabilities are needed to support process development, process monitoring, and product release.

For product release, typical methods are required to analyze the naked antibody, but others are also needed to evaluate the conjugated antibody (e.g., DAR, sites of conjugation). It is also necessary to confirm that no free payload molecules are present. Separate methods are needed to confirm the identity and purity of the payload and the linker before their attachment and to confirm proper attachment to one another. Finally, at least one biological, cell-based assay is needed as well. All told, approximately 15 different analytical methods are required to release an ADC drug substance.

Overcoming Market Hurdles
The ADC field continues to advance at a rapid pace, with scientific knowledge expanding exponentially as more candidates progress through the development cycle. More information is being gained on how ADCs harness and activate the immune system and kill cancer cells. With this knowledge, the design of targeting agents is improving, and new payloads and linkers will enable treatment of a wider range of oncology indications. New companion diagnostics designed around the physiology of the therapeutic indication will increase the patient response rate. ADCs are designable therapeutics where our prior experience will increase the probability of success for the next generation of ADCs. The future is very exciting, and Samsung Biologics, given its unparalleled track record of success in biologics development and manufacturing services, is well poised to play a major role in bringing these novel treatments to patients safely and as cost-effectively as possible.

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ABOUT SAMSUNG BIOLOGICS

Samsung Biologics is a fully integrated, end-to-end CDMO service provider, offering seamless development and manufacturing solutions from cell line development to final aseptic fill/finish, as well as laboratory testing support for the biopharmaceutical products we manufacture. Our state-of-the-art facilities are cGMP compliant with bioreactors ranging from small to large scales to serve varying client needs.

To maximize our operational efficiency and expand our capabilities in response to growing biomanufacturing demands, Samsung Biologics fully completed Plant 4, which will further advance the company's standing as the world's largest manufacturing facility at a single site—holding a 604KL total capacity—and announced plans to construct Plant 5, which will be operational in April 2025. Additionally, Samsung Biologics America enables the company to work in closer proximity to clients based in the U.S. and Europe.
We continue to upgrade our capabilities to accommodate our clients by investing in technologies such as an anti-body drug conjugate (ADC) facility, a dedicated mRNA manufacturing facility, and additional aseptic filling capacity. As a sustainable CDMO partner of choice, we are committed to on-time, in-full delivery of the products we manufacture with our flexible manufacturing solutions, operational excellence, and proven expertise.

Driven. For Life.

Documents / Resources

	**SAMSUNG Mylotarg Reducing ADC Development Timelines** [pdf] User Guide Mylotarg Reducing ADC Development Timelines, Reducing ADC Development Timelines, ADC Development Timelines, Development Timelines, Timelines

References

- **User Manual**