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REALIZING THE POTENTIAL OF ANTIBODY-DRUG CONJUGATES

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ABSTRACT Antibody-drug conjugates (ADCs) have long been described as a promising component of the industry's oncology toolkit. The specificity of ADCs has allowed them to meet the growing demand for targeted, safer treatment options for cancer patients. However, their complex nature has led to some challenges when approaching the development and manufacturing of ADCs. This article discusses some of the main ways in which ADC safety and efficacy can be maximized, and highlights the importance of choosing the right CDMO partner during the development process.

KEYWORDS:
- Antibody-drug conjugates
- ADCs
- Oncology therapeutics
- Drug development
- Conjugation chemistry
- Payload
- Linker

Antibody-drug conjugates (ADCs) have long been described as a promising component of the pharmaceutical industry's oncology toolkit. Due to their exact nature, ADCs meet the growing demand for efficacious therapies that provide targeted and safer treatment options for cancer patients. However, even with a growing number of ADCs in the pipeline, the full promise of ADCs has yet to be fully realized.

EASY AS ADC?

ADCs comprise three major components: a small molecule payload, a linker, and an antibody (see Figure 1). While this seems straightforward as a concept, in practice, designing, developing, and manufacturing ADCs is a complex and multi-faceted undertaking.

Each of the components in an ADC adds a layer of complexity. To ensure developmental success, pharma teams must safely handle the payload's highly potent nature. Experts must apply their biopharmaceutical and analytical expertise to develop and purify monoclonal antibodies (mAbs), utilizing proper cell culture techniques and complex conjugation chemistry know-how.

The complexities don't stop there. The field of ADCs is rapidly evolving, constantly developing new strategies, applications, and innovations, and in recent years, novel linkers have been created using biological processes such as fermentation. Biosynthesis can be used to develop linkers with specific properties that are impossible to achieve using traditional chemical synthesis methods. This can be useful for improving the stability, efficacy, or safety of ADCs.

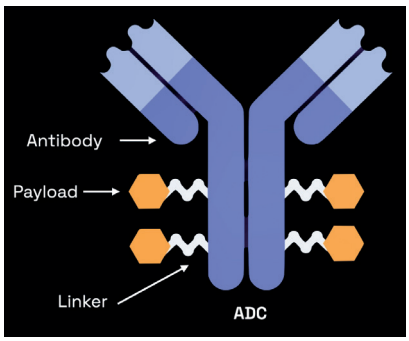


Figure 1. Labeled diagram of an antibody-drug conjugate (ADC).

Further, ADCs are used in increasing treatment areas, including breast, colorectal, gastric, and acute myeloid leukemia. For example, one emerging treatment area for ADCs is lung cancer. Due to their specificity, ADCs can target the epidermal growth factor receptor (EGFR), effectively treating patients with EGFR-positive lung cancer. Additionally, ADCs that target the programmed cell death receptor-1 (PD-1) are being investigated to treat lung cancer resistant to other therapies. An improved understanding of the interactions between ADCs and tumors are essential to realize this drug class's true potential for cancer treatment.

As more ADC programs – with more complexities – progress from the early to late stages of clinical development and begin to penetrate the market, there is a clear need to manufacture ADCs safely, efficiently, and economically, with an eye toward commercial production from the earliest stages of development.

ADC DEVELOPMENT AND MANUFACTURING: THE KEY CHALLENGES

As mentioned, the development of ADCs is multifaceted, requiring a vast spectrum of knowledge, technologies, and strategies. There are several key factors that developers need to consider in order to manage this process successfully.

1. Sorting out selection

Firstly, choosing an effective antibody and payload and an optimal linker molecule for the process is critical. This requires an in-depth understanding of the properties of antibodies, payloads, and their conjugation chemistries. Therefore, it is essential to establish a well-defined development plan, including clear goals, milestones, timelines, and a risk management strategy that can identify the risks associated with each step of the development and manufacturing process.

As an example, the design of the linker, which connects the antibody to the cytotoxic drug, plays a vital role in the ADC's stability and drug release. Developers must study different linkers' properties to ensure controlled drug release at the target site and minimal premature release in circulation.

Moreover, new conjugation chemistries can help to improve the potency, stability, and safety of ADCs. For example, new conjugation chemistries have been developed to attach linkers and payloads to antibodies with greater precision and control (1). This can help to ensure that the linker and payload are connected to the antibody in a way that does not compromise its efficacy or safety.

2. Deciding drug developability

Assessing the drug's developability early in the process is also important. Adopting a "gene to ADC product" approach can accelerate ADC production and lead selection, ensuring that promising candidates can be rapidly moved to advanced stages of development. This will help to shorten the time it takes to bring ADCs to patients who need them. Additionally, using real-world data helps to guide the process, recognize gaps in the market, and identify the most effective areas for development moving forward. Incorporating these strategies in the early R&D phase can help developers narrow down potential ADC candidates that are both efficacious and developable.

Preparing ADCs with improved homogeneity is also important for ensuring predictable efficacy and tolerability. Homogeneous ADCs have a consistent antibody composition, linker, and payload composition. Producing ADCs with a higher degree of homogeneity allows for a better understanding of their behavior in the body, which can help to identify any potential risks or side effects.

Implementing phase-specific procedures, particularly for early-phase clinical supplies, is paramount to capitalizing on the FDA's strategies for ADC market entry. When initiated at small scales and subsequently developed and validated at larger scales, these processes pave the way for smoother progression into Phase 2 clinical trials. Given the increasing significance of Phase 2 trials for ADCs, ensuring that the manufacturing process is commercially ready by this phase is vital. Such readiness can be achieved by integrating early process characterization, which, although demanding in terms of manufacturing expertise, can expedite timelines and solidify the drug's lifecycle.

3. Safety & Regulatory Considerations

Moreover, with potent compounds, safety is key. Various factors, including the properties of the substance, handling methods, and quantity used, influence exposure risk in manufacturing. Specific tasks, like weighing tiny yet potent quantities in ADC manufacturing, can increase this risk. As such, thoroughly assessing the production process is crucial to identifying and mitigating the highest exposure risks. It is essential to carefully evaluate the safety profile of the ADC in preclinical and clinical studies. Implementing rigorous handling procedures, robust quality assurance programs, and collaborating closely with regulatory agencies is vital to ensure that the ADC products meet all safety and efficacy standards.

For ADC projects, it's vital to set occupational exposure limits (OELs) through hazard assessments based on the ADC's properties. If specific data is lacking, comparisons are made with similar ADCs. After identifying hazards, teams assess exposure risks and determine containment measures. ADC manufacturing emphasizes safety for both the product and the workforce. Monitoring methods vary; payloads use LC-MS/MS, while ADCs employ enzyme-linked immunosorbent assay (ELISA) method. ADCs are stored frozen in sealed cryo-vessels for stability. Payload weighing and mixing occur inside isolators, adaptable for upscaling. Comparing ADCs with immune-mobilizing monoclonal T cell receptors (TCRs) reveals distinct action mechanisms and safety considerations. Understanding ADCs is crucial in advancing cancer treatment. New quality assurance standards have recently been developed to ensure that ADC linkers and payloads meet all safety and efficacy standards (2).

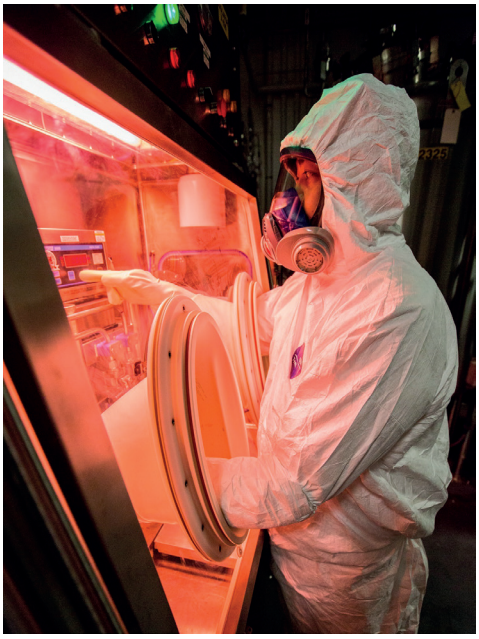
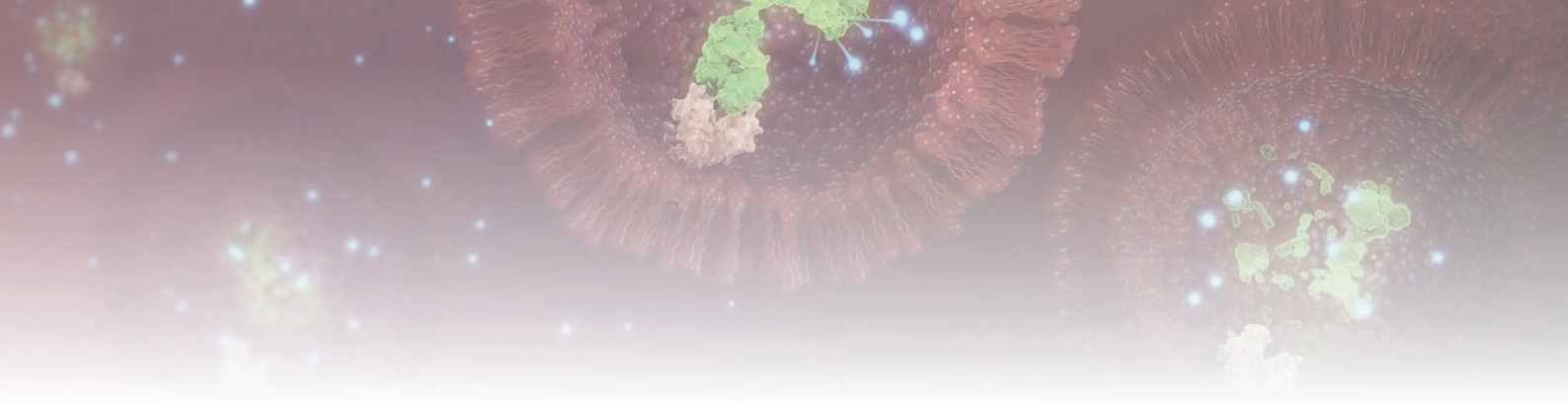


Image 1. Safety and effective PPE are paramount when handling ADCs and other highly potent molecules.

Globally, ADCs are generally regulated as biologics, but requirements vary by country. In the U.S., the FDA oversees ADCs as combination products requiring approval of both the drug and the antibody. The EU's EMA, Canada's Health Canada, and other agencies like Japan's PMDA, Brazil's ANVISA, China's NMPA, and Korea's MFDS have issued or are developing guidance on the chemical, manufacturing, and control (CMC) aspects and other clinical and non-clinical evaluations of ADCs. For generic ADCs in the U.S., similarity to the reference product is essential, with the possibility of a competitive advantage for generics using established components. Regulatory frameworks are designed to ensure ADCs' safety, purity, and potency while allowing for market competition (2, 3, 4).

4. Choosing the right CDMO partner

Working with the right CDMO secures the development of cost-effective, scalable manufacturing processes. Further, extensive expertise in technology transfer is invaluable to pharmaceutical companies operating in the ADC space. Leveraging shared technological breakthroughs and insights paves the way for cost-effective ADC advancements. Moreover, being aware of regional regulatory stipulations ensures compliance and facilitates seamless



ADC commercialization. By partnering with pharmaceutical companies, experienced CDMOs can build strategic collaborative partnerships, streamline workflows, and establish a unified approach to problem-solving.

Adaptability is key for a CDMO partner to respond to the market's changing demands. CDMOs must prioritize flexibility and demonstrate excellent customer service to meet their partner's product goals. Partnering with companies that can quickly problem-solve and prioritize their aims will give companies an advantage in the ADC market.

When it comes to achieving success in ADC development, CDMO partners need to be able to effectively assist their partner companies rapidly by utilizing a flexible, phase-appropriate strategy. By combining a wide array of instrumentation and expertise into an integrated process, CDMOs drive ADC therapeutics to market and ultimately address unmet patient needs. When selecting the right outsourcing partner, pharmaceutical companies must consider the CDMO's track record and their technology and customer service offerings to ensure they can access the critical elements that will set them apart in ADC development.

At Veranova, our decades-long legacy signifies expertise and dedication in the ADC domain. We relentlessly channel our vast knowledge into pioneering research, always aiming to elevate industry standards. Our collaborative ethos ensures our partners' success, and by staying updated on industry trends and maintaining exceptional customer service, we offer our clients the latest in ADC development and manufacturing.

THE FUTURE OF ADC THERAPIES

These advances will be made possible by innovations in new, cutting-edge technologies. As previously mentioned, developing new conjugation chemistries and linker technologies will ensure that ADCs continue to become more effective, while not compromising on safety, helping to improve the potency, stability, and safety of ADCs. Additionally, utilizing increasingly advanced analytical technologies will help ensure ADC linkers' and payloads' quality and safety throughout the development and manufacturing process. This can help to identify any potential impurities or degradation products that may be present in the linker or payload.

Improvements in ADC design, including linker technology, will continue to lead to the development of ADCs that are more effective against a broader range of cancers. Moreover, there is also the potential to expand the targets and applications of ADCs in medicine. More recently, ADCs have targeted a broader range of tumor antigens. ADCs have also been combined with other therapies to maximize drug processability and efficacy. These advancements are expanding the potential applications of ADCs and making them a more versatile cancer treatment option. In the future, ADCs will likely find application in many more areas, providing patients worldwide with access to effective and safe medicinal treatment.

The future of ADC development and manufacturing is bright. As innovation continues in the biotech and pharmaceutical industries, ADC development will only become a more vital source of safe and efficacious treatment for those in need. Moreover, by focusing on building strategic and collaborative partnerships, outsourcing partners can provide pharmaceutical companies with the flexibility and cost-effectiveness to drive ADC innovation and development and bring these therapeutics to market more quickly and efficiently.

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Dr. Hotha has extensive expertise in developing drug substances and products, particularly in small molecules, HPAPI, drug linkers, ADCs, and complex drug dosage forms. He has authored over 50 scientific research publications and serves on several editorial boards. Dr. Hotha received his Ph.D. from JNT University, India, and has held leadership positions at Lupin and Dr. Reddy's in Research & Development.