

ADCs and their Drug Development Process



One of the fastest-growing modalities in the pharmaceutical industry, antibody-drug conjugates (ADCs), combines a targeted antibody with a cytotoxic payload to offer numerous therapeutic benefits. Veranova's experts have a deep understanding of the challenges involved in ADC development and have explored how advanced techniques such as preparative chromatography can help streamline the process.

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Can you describe the current landscape of ADCs in terms of their therapeutic potential and market impact?

Antibody-drug conjugates (ADCs) have made great progress in recent years, targeting more than 260 recognized antigens today. The landscape is becoming more diverse, beyond conventional antibody-based conjugates to peptide-drug conjugates, radio conjugates, and other cutting-edge modalities. This scientific and commercial promise is reflected in the more than a dozen ADCs that have already received US approval. Leading the effort are Daichi Sankyo and AstraZeneca with Enhertu, sales of which hit \$1.6 billion in 2022, and,

based on current projections, are expected to reach an astounding \$9 billion by 2028. By utilizing these changing development methodologies, it is anticipated that the ADC industry, with its immense potential, will grow to around \$30 billion by 2028.

Q2 - What are the primary challenges faced during the development of ADCs, especially regarding efficacy, safety, and manufacturing scalability?

Developing ADCs is a complex endeavour where precision medicine intersects with advanced drug delivery systems. During development, one must select the most suitable target antigens for the specific ADC – those primarily expressed on the intended tumour cells – to prevent cross-reactivity with healthy cells. The precision of the ADC also comes from the expertly engineered linker, which allows the antibodies in the compound to be released at the site of the tumour and not before. The drug-to-antibody ratio (DAR) is crucial to ensure ADC performance.

Regarding safety, the specificity of the ADC is of the utmost importance to minimize toxicity to non-cancerous cells. One must constantly calibrate the therapeutic window and determine the proper dosing requirements through rigorous clinical studies. Additionally, there is always the potential for immunogenicity—the immune system can recognize and react against the ADC, which can limit its effectiveness and pose safety risks.

The manufacturing stage demands high precision to ensure each batch is consistent, especially when upscaling production. Quality control becomes more challenging as the scale increases, and all components of the ADC need to be tested and observed, from the DAR to the purity of the product. The components of ADCs often require specialized handling and storage, which can get more logistically complicated as volume increases. The process is like a symphony of finely tuned instruments - all must work harmoniously to afford the best patient benefits.

Q3 - How do you approach selecting antibody targets and cytotoxic payloads to optimize ADC effectiveness?

When developing ADCs, choosing the antibody target and the cytotoxic payload is pivotal for ensuring therapeutic effectiveness while minimizing risks. The ideal antibody target, an antigen, is predominantly expressed on tumour cells, minimizing exposure to healthy cells and enhancing the delivery precision of the cytotoxic payload. Such target antigens should be readily externalizable upon ADC binding, allowing the entry of the cytotoxic agent into the cancer cell. These targets must also be accessible and not obscured by the tumour microenvironment. They are essential to the survival or proliferation of cancer cells, making them the most effective point of attack.

The cytotoxic payload must be highly potent, allowing maximum efficacy at lower ▶

ADCs have become a beacon of hope in cancer treatment, with a market projected to reach \$30 billion by 2028.

doses and reducing potential side effects. The payload's mechanism should be chosen for its action on the targeted cancer. Integrating the payload with the antibody via the linker is also crucial; the linker must stabilize the bond in the bloodstream and allow for the timely release of the payload inside the target cell. Key factors such as the DAR require optimization to balance effective drug delivery with maintaining the antibody's functionality. Additionally, the linker's design must ensure that the ADC remains stable until reaching the target site. Finally, the scalability of the manufacturing process is essential to transition ADCs from the lab to commercial production, encompassing every stage from antibody production and payload-linking to purification, ensuring a steady supply for clinical use.

Q4 - What role does bioconjugation chemistry play in ADC development, and what are the critical considerations in designing stable and effective linkers?

Bioconjugation chemistry is essential in developing ADCs, as it enables the precise attachment of potent cytotoxic drugs to antibodies targeted at cancer cells. This integration transforms the antibody into a particular vehicle, delivering lethal doses to tumour cells. The process involves various strategies for covalently bonding the drug to the antibody, each tailored to preserve the antibody's targeting capabilities while ensuring effective drug linkage.

The role of bioconjugation chemistry extends to designing and synthesizing linkers that connect the cytotoxic payload to the antibody. These linkers are engineered to be robust enough to withstand the bloodstream's environment and prevent the premature release of the drug, which could lead to side effects. However, they must also be sensitive to the specific conditions within tumour cells, such as acidic pH or enzymatic activities, to release the drug precisely where needed. The design of these linkers considers several factors, including stability to prevent breakdown before reaching the target site, cleavability for drug release inside the tumour cell, and biocompatibility to ensure the linker does not detract from the antibody's function.

Considerations for linker design also include the physical properties of the linker,

Q5 - Can you discuss the importance of pharmacokinetics and pharmacodynamics (PK/PD) studies in evaluating ADCs' performance in preclinical and clinical settings?

Pharmacokinetics (PK) and pharmacodynamics (PD) studies are vital in developing ADCs and are crucial in the preclinical and clinical phases. PK studies track how the body processes the ADC, while PD studies examine the biological effects and interactions with target cells. The insights we get from these studies refine the ADC design for efficacy and safety.

In clinical trials, PK/PD studies act as a patient safety mechanism by monitoring drug behaviour and identifying potential side effects. The drug exposure is correlated to the tumour response, which enables customized dosing based on individual patient factors such as metabolism and disease severity. This can enhance treatment outcomes and reduce adverse effects.

Recent FDA guidelines emphasize the importance of PK/PD studies, recommending best practices for dosing selection, linker stability assessment, and immunogenicity evaluation. Adherence to these guidelines ensures that the studies are robust, yielding reliable data that can be used to optimize ADC development and improve patient safety and efficacy.

PK/PD studies are essential throughout ADC development. Providing crucial data for dosage decisions, assessing drug delivery and action, and ensuring safety, efficacy, and a systematic approach is vital for successful ADC development into cancer treatments.

such as its length and flexibility, which can affect how the drug interacts with its target inside the cell. Additionally, the conjugation site on the antibody molecule is significant; the chosen site can influence the overall stability, efficacy, and distribution of the ADC within the body. By addressing these complex factors, bioconjugation chemistry helps optimize ADCs, making them potent and selective treatments for cancer.

Q6 - How do you navigate regulatory challenges specific to ADCs, such as characterization, stability, and safety assessments?

Navigating regulatory challenges specific to ADCs demands meticulous compliance with stringent standards focused on characterization, stability, and safety assessments. These challenges arise from ADCs' complex nature, combining small molecule and biologic drug properties. ►

Characterization requires understanding an ADC's antibody, drug, and linker using sophisticated analytical techniques like mass spectrometry and HPLC. Regulatory bodies require data on an ADC's molecular profile, including DAR, attachment sites, the distribution of conjugate species, unconjugated impurities, unreacted drug, site-specific conjugation, and heterogeneity within the product.

Stability testing is crucial for maintaining efficacy and safety over the ADC's shelf life. These tests involve physical, chemical, and biological assessments. Safety evaluations for ADCs are more complex than for traditional therapeutics due to their dual mechanism of action and the potential for off-target effects. They are essential to how well the ADC deals under stress and involve toxicological studies in relevant animal models, considering acute and chronic toxicity, immunogenicity, and PK/PD.

Companies should engage with regulators early in development and clarify expectations using pre-IND (Investigational New Drug) meetings. These conversations can guide the ADC and help clarify regulatory expectations for a successful IND application. Comprehensive risk management strategies, including robust quality controls and detailed documentation of all development processes, are essential to address regulators' concerns regarding ADCs.

Addressing the regulatory challenges of ADCs requires a thorough understanding of their complex nature and a strategic approach to development that incorporates advanced analytical techniques, rigorous stability

and safety studies, and proactive regulatory engagement to ensure safe and effective ADCs are brought to market.

Q7 - What strategies do you employ to enhance ADC manufacturing processes, including scale-up and production efficiency?

Optimizing ADC production for scale-up entails strategic adoption of key technologies and methodologies. These include but are not limited to:

Implementing modern conjugation techniques. Newer methods like click chemistry or enzymatic approaches enhance DAR's reaction speed, yield, and precision, which are crucial for uniformity and efficacy.

Enhancing manufacturing through automation. Automated systems streamline operations, reduce errors, and boost capacity. Continuous manufacturing (CM) minimizes downtime and increases output efficiency.

Utilize cutting-edge monitoring. Process analytical technology (PAT) ensures continuous quality monitoring, enabling immediate adjustments. High-throughput screening accelerates development and optimizes manufacturing parameters.

Efficient supply chain and inventory management. Early supplier collaboration ensures high-quality materials. Just-in-time inventory systems minimize storage costs and align supply with production needs. Apply global project management to standardize processes and anticipate geopolitical impacts.

Linker stability and manufacturing scalability are pivotal for ADC success, ensuring targeted efficacy and consistent supply.

Scalability and flexibility in process design. Single-use systems enable quicker setups and minimize contamination risks. Design of Experiment (DoE) optimizes process parameters for robust and scalable manufacturing. Standardize quality control across facilities, update regulatory strategies, and robustly manage intellectual property, integrating continuous training and expert consultations to maintain high standards and secure operations.

Regular cost and efficiency evaluations. Ongoing economic analysis ensures practical, cost-efficient enhancements, supporting sustainable scale-up and commercialization. This approach refines ADC manufacturing, effectively meeting regulatory standards and commercial demands.

Q8 - In your experience, what are the critical factors influencing the success or failure of ADC clinical trials?

In my understanding, the success or failure of clinical trials for ADCs hinges on critical factors across their development, from preclinical stages to regulatory compliance.

Linker stability is one of the most crucial factors for maintaining ADC integrity and ensuring targeted drug release within tumour cells. It helps avoid premature release and potential side effects. Optimization of the DAR balances efficacy and safety without compromising targeting or increasing toxicity.

Additionally, manufacturing scalability ensures sufficient ADC production for clinical trials and potential commercial distribution, maintaining consistency and quality. These factors collectively influence the trajectory of ADC clinical trials. Thoroughly addressing each aspect—from meticulous ADC design and rigorous preclinical testing to strategic clinical trial planning and robust patient monitoring—enhances the potential for successful outcomes, ultimately aiming to bring practical and safe cancer therapies to patients.

Q9 - How do you leverage advanced analytical techniques, such as mass spectrometry and chromatography, to characterize ADCs and ensure quality control?

Advanced analytical techniques such as mass spectrometry (MS) and various forms of chromatography play a pivotal role in the development, characterization, and quality control of ADCs. These techniques provide essential data that ensure the structural integrity, efficacy, and safety of ADCs throughout their lifecycle from development to manufacturing.

Intact mass analysis uses mass spectrometry to determine the ADC molecular weight. ►

This method captures the composite structure of the antibody, linker, and conjugated drug molecules and is crucial for finding the DAR ratio calculation, ensuring consistent drug attachment. Conversely, subunit analysis entails MS analysis of ADC subunits acquired post enzymatic digestion. This approach allows for detailed mapping of conjugation sites and evaluation of the distribution of DAR across different ADC molecules, facilitating the assessment of uniformity and expected activity of the ADC. High-resolution MS utilizes high-resolution accurate mass spectrometry to achieve precise mass measurements of the ADC and its components. This capability is invaluable for detecting and identifying potential impurities or modifications within the molecule and ensuring quality control.

We offer state-of-the-art chromatography and advanced manufacturing techniques used for purification and separation, which are challenging in ADCs due to their complex nature. These advanced techniques include Reversed-Phase Liquid Chromatography (RP-LC), where ADC components are separated based on their hydrophobicity, proving particularly useful in synthesizing linkers and cytotoxic payloads and their chemical conjugation process.

Q10 - Could you elaborate on the potential synergies between ADCs and other therapeutic modalities, such as immunotherapy or targeted therapies?

ADCs offer promising synergies with other therapeutic modalities, such as immunotherapy and targeted therapies. These combinations can enhance treatment efficacy, overcome drug resistance, and potentially improve patient outcomes by targeting cancer from multiple angles. Integrating ADCs with other cancer therapies is a promising, potentially revolutionizing treatment option. By addressing tumours on various fronts, these combinations aim to improve patients' survival rates and quality of life, significantly impacting the future of cancer treatment.

Tumours often create an immunosuppressive environment that inhibits the immune system's ability to fight cancer effectively. ADCs can counteract this by killing tumour cells and releasing tumour antigens, activating the immune system. This enhancement is particularly synergistic with checkpoint inhibitors, which bolster T-cell responses against cancer cells. As cancer cells can develop resistance to targeted therapies, combining ADCs with these treatments can enhance therapeutic effectiveness. ADCs target different molecular pathways or tumour markers, potentially outmanoeuvring cancer's adaptive resistances.

Prioritizing patient-centric processes and combining ADCs with other therapies aligns with this ethos. Meticulous research is crucial for optimal combination strategies, determining effective sequences and dosing for maximum benefit and patient safety. However, combining therapies can sometimes increase side effects,

requiring careful patient monitoring and expertise. Leveraging the genetic profile of a patient's tumour can inform tailored treatment strategies, employing specific combinations of ADCs and other therapies that target the unique characteristics of the cancer, thereby enhancing personalized medicine in oncology.

Q11 - What advancements do you foresee in the next decade in ADC technology and drug development strategies?

The next decade promises promising advancements in ADC technology and drug development strategies, which will transform oncology treatments by enhancing efficacy, safety, and specificity.

Researchers are expanding beyond traditional cytotoxins to explore novel payloads with diverse mechanisms of action. These include agents that target specific signalling pathways within cancer cells, radioisotopes for localized radiation therapy, and alternative mechanisms that induce tumour cell death. Additionally, ADCs are being developed with two antigen-binding domains to simultaneously target different molecules on the cancer cell. This approach enhances targeting specificity and may help overcome resistance mechanisms. Another pioneering method is to combine two different cytotoxic drugs, each with distinct mechanisms of action, in a single molecule. This strategy aims to broaden the therapeutic window and reduce the potential for resistance.

We have also seen some exciting advances in linker chemistry, such as biodegradable and triggered-release linkers. Biodegradable linkers degrade under specific tumour microenvironment conditions, improving the precise drug release and minimizing side effects from premature payload release. Triggered-release linkers are responsive to external stimuli such as light or ultrasound, enabling controlled drug release at the tumour site upon activation.

Manufacturing and analytical advancements are also anticipated in ADCs and will play a pivotal role in producing more complex ADCs with enhanced consistency and quality.

By integrating these advancements, the next decade in ADC development promises to deliver more sophisticated, effective, and patient-specific therapies. The focus on improving every aspect of ADC technology—from targeting and payload delivery to safety and manufacturing—underscores a shift towards more precise and effective cancer treatments.

Q12 - Considering the competitive landscape, what strategies do you recommend for companies looking to enter or expand their presence in the ADC market?

I strongly feel that the competitive ADC market needs a multifaceted strategy centered around scientific innovation, operational efficiency, and strategic collaborations.

Scientific innovation and differentiation are crucial. Companies should target novel ►

antigens and mechanisms, focusing on discovering and targeting unique cancer antigens and integrating novel cytotoxic payloads for distinct mechanisms of action. This may involve developing bispecific ADCs or exploring synergistic combinations with immunotherapies to enhance targeting specificity and treatment efficacy. Additionally, linker chemistry innovation can improve drug release stability and control. As such, developing linkers that respond to specific tumour microenvironment triggers or external stimuli is essential.

Operational excellence and development strategies also play a pivotal role. Prioritizing thorough preclinical studies and advancing rapidly into early-phase clinical trials establish the safety and efficacy of ADC candidates, attracting investors and partners. Moreover, investing in scalable, cost-effective manufacturing processes ensures consistent and reliable ADC supply for clinical development and commercialization.

Strategic collaboration and market preparation are also crucial. Partnerships between pharmaceutical companies and academic institutions could accelerate development timelines and enhance innovation. Antibody engineering can be used to develop particular antibodies, and investing in advanced analytical technologies for precise ADC characterization and quality control is also vital.

Regulatory navigation and commercial strategy are essential. Maintaining proactive engagement with regulatory bodies to navigate

the evolving landscape and articulate a clear value proposition that differentiates your ADC from existing therapies is more critical than ever as this modality picks up speed. Robust commercialization strategies that address pricing, market access, and healthcare stakeholder partnerships will also be essential.

By strategically addressing these elements, I believe companies can effectively compete in the ADC market, leveraging scientific advancements to deliver innovative cancer treatments and ensure readiness for future opportunities and challenges in the evolving oncology landscape. ■

AUTHOR BIO



Dr. Kishore Hotha has shaped the scientific business strategies of several companies. Over two decades in the pharmaceutical and CDMO landscape, with extensive expertise in developing drug substances and products - particularly in small molecules, HPAPI, drug linkers, ADCs, and complex drug dosage forms - Dr. Hotha has authored over 50 scientific research publications and serves on several editorial boards. He received his Ph.D. from Jawaharlal Nehru Technological (JNT) University and MBA from Southern New Hampshire University and has held leadership positions at Lupin and Dr. Reddy's in Research & Development.