XDC
The Bioconjugation Leader

One-Stop ADC Platform: Addressing Bioconjugates Production Challenges and Accelerating Drug Development

The development of a new antibody-drug conjugate (ADC), from initial laboratory exploration to patient application, represents a protracted and highly intricate journey involving multiple pivotal stages, from research and development to manufacturing and eventual commercialization. Among these, manufacturing introduces profound complexities and uncertainties that significantly influence the successful market launch of a new ADC drug. CMC considerations are especially critical as evidenced by FDA data: 11 out of 32 Complete Response Letters (CRLs) issued were attributed to CMC-related deficiencies, highlighting the paramount importance of addressing these challenges.

This article aims to explore the multifaceted challenges encountered during the process development and production of ADCs, with a focus on late-stage CMC strategies and regulatory consideration. Additionally, it examines how a one-stop ADC platform can leverage scientific methodologies and technical innovations to overcome these challenges, paving the way for efficient drug development and commercialization. Such platforms serve as indispensable enablers, ensuring readiness for the anticipated surge in ADC approvals and maximizing their therapeutic impact. (Table 1)

Table 1: New drugs rejected by the FDA in recent years due to CMC issues

Date	Product	Company	Reasons
2024.6	Patritumab Deruxtecan	Daiichi Sankyo	CMC deficiencies in third party contract manufacturing
2023.12	cosibelimab	Checkpoint Therapeutics	CMO issues
2023.10	lebrikizumab	Eli Lilly	CMO issues
2023.9	Ultomiris (ravulizumab)	AstraZeneca	Required by the FDA to revise ultomiris risk evaluation and mitigation strategy (REMS)
2023.8	ONS-5010	Outlook Therapeutics	CMC issues, open observation of pre-approval manufacturing inspections, and lack of substantive evidence
2023.7	Lymphir	Citius Pharmaceuticals	Required by the FDA to supplement information on product testing and elevate controls
2023.6	Eylea™ 8mg	Regeneron Pharmaceuticals	Third-party manufacturer issues
2023.5	Anktiva (N-803) combined with Bacillus Calmette-Guérin (BCG) vaccine	ImmunityBio	CMC deficiencies in third party contract manufacturing
2023.5	Alhemo (concizumab)	Novo Nordisk	Required by the FDA to supplement information related to patient monitoring and dosing, and additional information on the manufacturing process
2023.5	TransCon PTH	Ascendis Pharma	For reasons that the drug or device does not guarantee a uniform delivery dose
2023.4	mirikizumab	Eli Lilly	Concerns about the manufacturing process
2023.3	ABBV-951	Abbvie	Required by the FDA to supplement information

Source: Pharma DJ, added by the author

Challenges in ADC Development and Production

ADC drugs, comprising antibodies, payloads, and linkers, exhibit a unique molecular complexity that spans the domains of large molecules, small molecules, and the conjugation. This complexity necessitates strict adherence to current Good Manufacturing Practices (cGMP) and a comprehensive understanding of molecular-level attributes to ensure safety and efficacy. Key considerations include selecting optimal antibodies, ensuring linker stability, addressing the toxicity and pharmacological mechanisms of the payload, and maintaining precision in the drug-to-antibody (DAR). Effective management of these interdependent factors is essential for achieving consistent quality and reliable production outcomes.

The development of ADC processes involves several critical stages, including process development, clinical supply, process characterization & validation, and commercial supply. Each stage brings distinct challenges, particularly during scale-up, which requires seamless technology transfer, rigorous process optimization, and continuous monitoring to maintain production consistency and robustness. The complexities are especially pronounced in the preparation of ADC drug substance (DS) and drug product (DP), as these tasks differ significantly from the production of standalone large molecules or small molecules. (Table 2)

The preparation of ADC DS represents a pivotal step in production, requiring precise control over conjugation reaction conditions to ensure high efficiency and product purity. Following the bioconjugation reaction, unreacted antibodies, small molecules, linkers, and process impurities, such as organic solvents, must be meticulously removed through advanced purification techniques. Due to their complex molecular structures, ADC DS preparation process faces heightened stability challenges compared to antibody alone, with susceptibility to polymerization, degradation, or payload detachment. Ensuring stability and maintaining consistent quality throughout this phase tests the technical expertise and problem-solving capabilities of DS production team.

ADC drug products, often presented as freeze-dried formulations, demand exceptional attention to the design and optimization of the lyophilization process. Formulation development must balance multiple factors – including pH, ionic strength, and temperature – to ensure the final product's stability, efficacy, and safety. Without sufficient expertise, the management of these variables can be a significant risk to the achievement of a robust and scalable formulation process.

Ensuring quality throughout the manufacturing process is paramount. Continuous quality monitoring, supported by advanced analytical techniques such as high-performance liquid chromatography and mass spectrometry, is critical for identifying and eliminating impurities, monitoring batch-to-batch variability, and validating conjugation efficiency and bioactivity. Overcoming these challenges requires the concerted efforts of a highly skilled technical team equipped to maintain rigorous quality standards.

Furthermore, the inherent toxicity of ADC payloads necessitates the implementation of stringent safety protocols to prevent cross-contamination and safeguard operator health. This involves the high containment system and negative-pressure environments, the use of specially-designed equipment to eliminate residues during cleaning and product transitions, and the establishment of comprehensive risk management frameworks to address potential hazards proactively.

Table 2: Typical ADC process development flows

Process Development			Clinical Supply	Process Characterization	Commercial Supply
Orthogonal design of experiments method	Process verification	Process development for purification	Batches for clinical studies	Process design	Commercialized batches
Milligram		Gram	Hundred grams and above	Gram, milligram	Kilogram and above

Source: Publicly available information, compiled by the author

WuXi XDC's manufacturing facilities

Source: Screenshot from the video of the production line of WuXi XDC

Cost Control and Supply Chain Management for Late-stage and Commercial CMC Strategy

By the Biologics License Application (BLA) stage, process development—more precisely, process optimization—shifts its focus toward ensuring the consistency and robustness of production at a commercial scale. At this advanced stage, cost control becomes a critical factor. Unlike earlier stages, where the emphasis lies on exploratory optimization, late-stage process development requires balancing product quality with cost-effectiveness. Maintaining consistent product quality during scale-up to commercial manufacturing is a nuanced process that necessitates careful planning and execution to achieve both reliability and economic efficiency.

A comprehensive understanding of the supply chain's impact on the manufacturing process and product quality is indispensable when devising a robust CMC strategy. For ADC drugs, the inherent complexity of their multi-component nature requires prioritizing supplier stability and the reliability of quality systems at every stage of the supply chain. This approach ensures a seamless transfer from research and development to commercialization, minimizing risks and safeguarding product integrity throughout lifecycle.

Regulatory Considerations

In Nov, 2024, the Center for Drug Evaluation of China's State Drug Administration released the "Technical Requirements for Pilot Registration and Declaration of Segmented Production of ADCs". This regulatory document underscores the intricate challenges and inherent in ADC production and mandates the establishment of a comprehensive and robust quality control strategy. ADC manufacturing organizations, particularly CDMOs, are required to ensure that their production processes comply with regulatory standards, maintain detailed and traceable records for problem identification, and demonstrate both flexibility and compliance management capabilities to address varying regulatory frameworks effectively.

The document highlights that ADC production processes are inherently complex and influenced by numerous factors, necessitating the adoption of a comprehensive quality control strategy grounded in risk assessment. Research and validation must encompass the entire production chain and lifecycle of ADC production ensuring compliance at every stage of segmented manufacturing. Furthermore, the applicant or MAH bears primary responsibility for validating transportation processes between production sites, reinforcing the quality control of received intermediates, and maintaining effective lifecycle management to uphold product integrity and safety.

Collaboration between pharmaceutical companies and CDMOs becomes paramount within segmented production models. Both parties must establish synchronized and consistent risk management frameworks to ensure the stability and quality of ADC intermediates and raw materials across the production continuum. This partnership is essential to mitigating risks, optimizing resources utilization, and ultimately supporting the successful commercialization of ADC therapies.

One-Stop ADC Manufacturing: A Comprehensive Solution

The one-stop CMC development and production platform provides an optimal solution to the complexities of ADC production. By streamlining the production process, it minimizes risks and human errors, offering the pharmaceutical industry a path to efficient and safe manufacturing. WuXi XDC, as a leader in one-stop production solutions, operates a state-of-the-art facility at its Wuxi City site. This site

integrates and manages the entire production process using a unified quality system, effectively reducing batch-to-batch variability and enhancing product stability and consistency.

Unified Quality Systems within a Centralized Production Environment: WuXi XDC employs a robust and comprehensive quality control system that spans from raw materials to final product delivery. Each step in the process is meticulously monitored to ensure adherence to the highest quality standards. By producing all four components within the same facility and adhering to unified quality standards, WuXi XDC ensures seamless coordination of technology transfers, minimizing inter-system risks, and simplifies production processes, ultimately improving overall efficiency and product quality.

WuXi XDC's fully integrated "All-in-One" manufacturing model within one single site

Source: WuXi XDC's master deck

Dual-function Facility to Support Production: WuXi XDC's newly launched second dual-function production line (XBCM2 Line2) represents a significant advancement in the industry. This line supports integrated processes ranging from cell culture and antibody purification to bioconjugates production. The novel design not only addresses diverse and evolving production needs but also reduces waste caused by unnecessary transfers and delays, offering a streamlined and time-efficient solution. By expediting drug filing and commercialization timelines, the facility empowers ADC developers to bring their therapies to market more swiftly and reliably.

Summary

ADC production entails navigating a spectrum of challenges, encompassing the integration and manufacturing of its core components, rigorous process controls, stringent quality assurance, compliance with complex regulator frameworks, and the coordination of global supply chains. The one-stop production platform provides comprehensive solutions through seamlessly integrating end-to-end processes, implementing advanced quality systems. The platform's robust capabilities not only empower ADC developers to overcome these hurdles but also enhance production efficiency and ensure product quality at every stage. Through superior supply chain optimization and unwavering compliance with global standards, one-stop platform facilities the reliable delivery of ADC products to market.

WuXi XDC's innovative integration of these capabilities highlights its leadership in ADC manufacturing. This approach accelerates patient access to ADC therapies while fostering continuous innovation in the ADC space. The combination of operational flexibility, robust quality assurance, and industry-leading expertise underscores the pivotal role of one-stop platforms in shaping the future of ADC production.

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