An ADC's Path to Market

Analysis of Difficulties and Key Points in ADC Process Scale-up

Complex Processes Require Precise Control

An Antibody-Drug Conjugate (ADC) is a novel therapeutic agent which can deliver a highly-potent traditional small molecule drug to a specific site or cell within the body. It is formed when an active drug (the payload) is connected to an antibody using a linker. The complex is referred to as an ADC and it uses the cellular specificity of antibodies to direct the payload and deliver to the active disease site within the cell. This enables ADCs to selectively treat cancer cells, tumor microenvironments, or other target cells, while reducing systemic, off-target toxicity. This targeted delivery of ADC agents has shown great promise and explosive growth in recent years.

ADCs have high technical barriers as they progress through discovery, clinical development and commercial production. Many technical challenges exist, including the ADC conjugation production process. ADC production is an extremely complex process and requires rigorous control to ensure the conjugation's reproducibility, efficiency and homogeneity so that a known quantity of the small molecule toxins molecules are bound to the antibody. At the same time, it is also necessary to avoid impurities and by-products generated during the conjugation process of ADCs.

The final step in the ADC manufacturing process is purification which removes unconjugated antibodies, linkers, payloads, as well as impurities and by-products or side-products generated during the conjugation process. Due to the complex structure of ADCs, the unique requirements of purification involve a combination of various chromatographic and filtration techniques. To reduce the potential difficulties and risks in this process, Porton ADC Conjugation Process R&D and MFG team has summarized the following 8 key points from our past experience that deserve focused attention:

1. Full development and optimization of process steps

Before conducting process scale-up, it is necessary to fully develop and optimize the manufacturing process of ADC drugs, from the manufacturing of the starting antibody, linker and payload followed by the conjugation, purification, and formulation to finally obtain the drug product. Each corresponding manufacturing process has quality control strategies to ensure that each step of the process is well controlled and optimized.

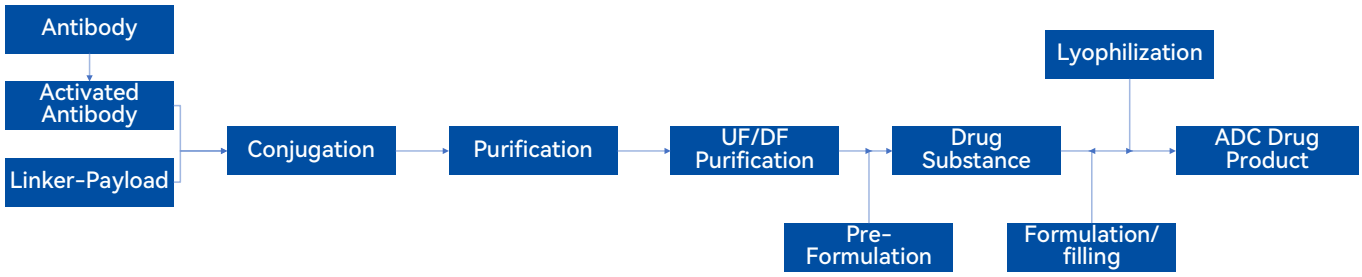

Fig1. ADC Drug Product Manufacturing Process

2. Stable uniformity of DAR

DAR (drug to antibody ratio) is one of the most important quality attributes of ADC drugs, which determines the amount of "payload" that can be delivered to the tumor, which directly affects the safety and efficacy of the drug. As the entire process undergoes scale-up, it is important to ensure that reproducible DAR will be obtained at all manufacturing scales.

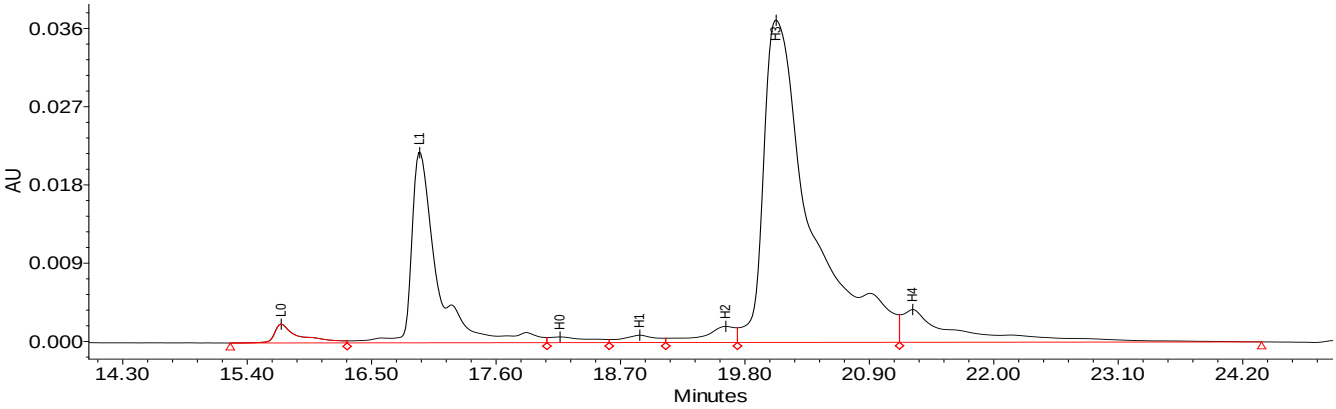

Fig 2. DAR of Laboratory Scale Samples

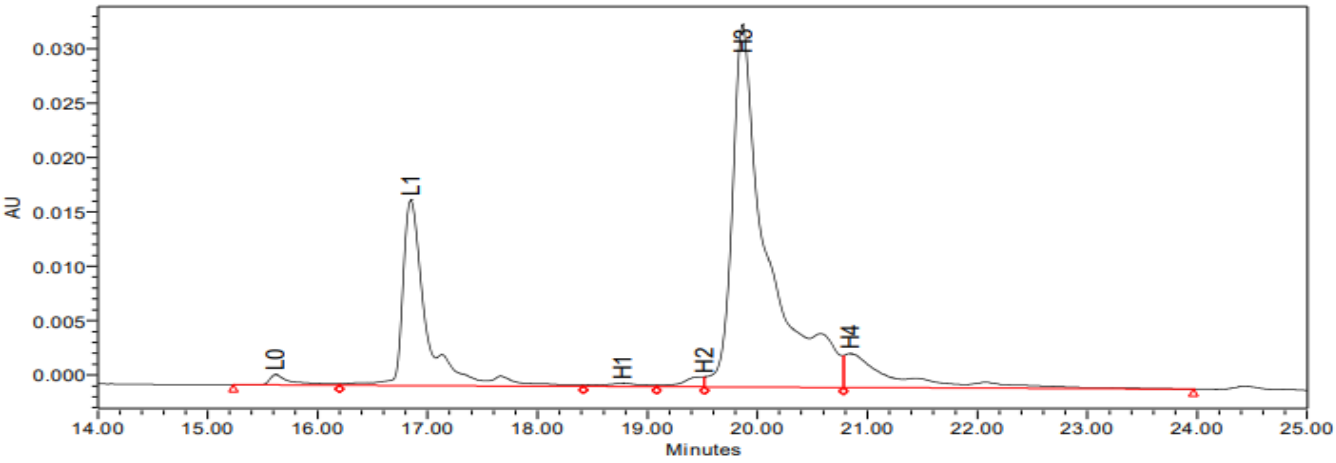

Fig3. DAR of Scale-up Scale Samples

3. Precise control of process parameter

During the conjugation step, physical parameters such as temperature, pH, mixing speed, antibody concentration, material mass and addition rate may all have an impact on product quality. During process scale-up, it is necessary to understand and precisely control each of these process parameters so that manufacturing at different scales will maintain consistent quality and produce the ADC with its expected attributes.

Temperature Control	Temperature typically affects the conjugation rate and as well as the product ADC stability. Thermal tolerance testing must be conducted during the development stage to determine the effect of temperature variation throughout the entire process. Temperature changes can be modified and monitored to optimize process output.During the conjugation stage of ADC production, precise control of the reaction temperature is required to ensure that the reaction proceeds within the set temperature range. For example, a fully automatic temperature monitoring system can provide precise temperature control to ensure batch-to-batch consistency.
pH Control	The pH can have a significant impact on conjugation reactions, as it affects the charge state of antibodies, the reactivity of linkers, and the stability of small molecule toxins. Acceptable pH control ranges need to be defined based on experimental data to determine the operating window which will produce suitable results.During large-scale ADC conjugation, pH needs to be continually monitored and an online pH sensor can be used to achieve real-time monitoring of pH during the reaction process, ensuring that the reaction proceeds within an optimal pH range.
Mixing Process	The mixing speed affects the homogeneity and reaction rate of the reactants. The appropriate mixing speed should be selected based on the characteristics of the reaction system, and its effectiveness should be verified through experiments at each stage of the ADC preparation process. At the same time, the influence of different mixing types (such as magnetic mixing and mechanical mixing) and mixing impeller types on the process should be investigated during process development, and matched to the mixing equipment to be used in the largest scale of manufacturing to provide data that will support process scale-up.
Antibody Concentration	The concentration of the antibody directly affects the efficiency of the conjugation reaction and the purity of the product. It is necessary to precisely measure and then determine the appropriate range of antibody concentrations that will ensure the successful preparation and reproducibility of the product.
Material Mass and Addition Rate	The material mass and addition rate must be accurately measured and controlled to avoid potential impact of excessive or insufficient reaction. It is recommended to use an automated or mechanical addition pump in manufacturing. This can provide real-time online process control and reduce errors from manual operation and any potential toxicity risks caused by undercharging or overcharging any of the components.

Integrated Control Strategy

The conditions of temperature, pH, mixing speed, antibody concentration, material mass, and addition rate require coordinated control to ensure the reproducibility and efficiency of the reaction as well as the stability of the product. Extensive experiments are conducted to investigate the influence of these interrelated parameters on the reaction, and a reasonable control range and optimization strategy will be created.A comprehensive quality monitoring system needs to be established prior to manufacturing and followed to monitor and record key parameters in real-time during the reaction process, ensuring the stability and consistency of product quality.

4. Importance of Automation

Automated equipment can provide precise temperature and pH control, avoiding errors and potential deviations caused by manual operation. Porton utilizes a fully automated online monitoring system for ADC manufacturing, with online visual monitoring the temperature control strategy inside the reaction vessel and TCU, thus effectively improving the process stability and batch-to-batch consistency during process scale-up and manufacturing .

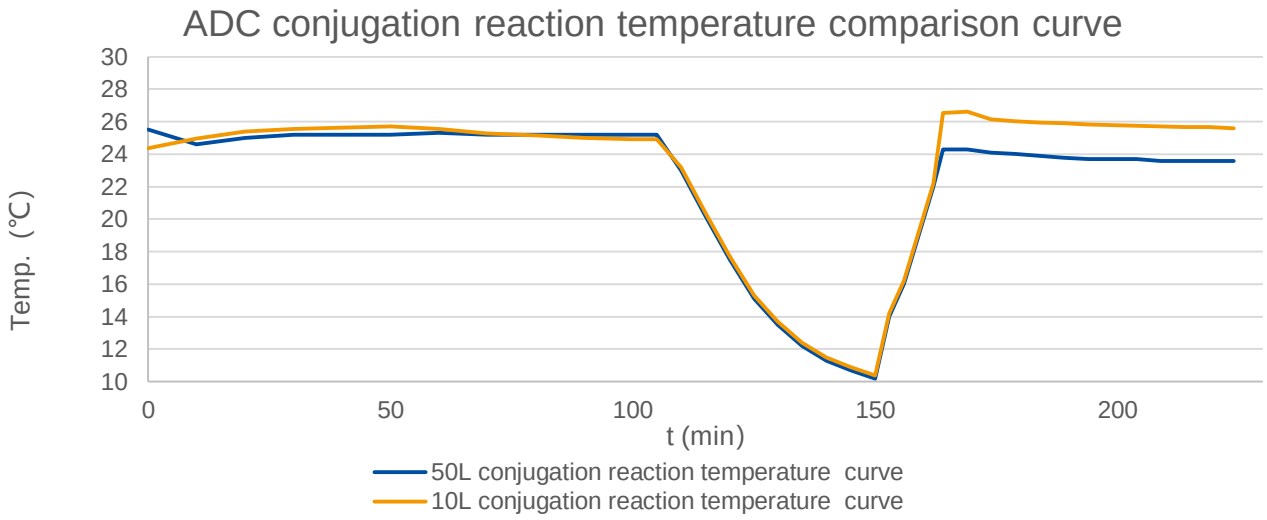

Fig 4. ADC conjugation reaction temperature comparison curve

5. Online Process Monitoring

As the process is scaled-up, the implementation of online process monitoring technology (e.g., online pH sensors, temperature control systems, etc.) ensures that process parameters are within tolerance in real. The temperature control accuracy can reach ± 0.1 ℃, to maintain consistency between production batches. This helps detect variations in a timely manner which may improve manufacturing efficiency and product quality to potentially allow a real-time correction to occur.

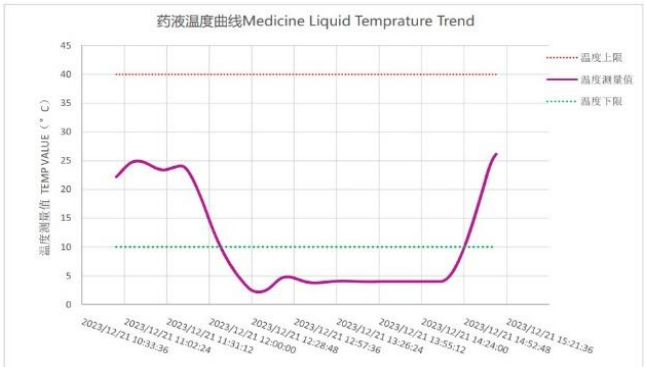

Fig5. Temperature of Conjugation Compound

Fig6. TCU Temperature Trend

6. A Gradual Rate of Scale-up

Process scale-up is done gradually so that each step can be fully validated and optimized on each subsequent scale. During this scale-up process, it is necessary to pay attention to the transferability and reproducibility of process parameters to ensure consistent product quality at each of the increasingly larger scales.

7. Compliance with GMP Requirements

The manufacture of ADC products must comply with cGMP (current Good Manufacturing Practice) requirements to ensure the safety and efficacy of the product. In the process of process scale-up, it is necessary to ensure that all end-stage steps comply with GMP requirements, using tested, qualified and validated equipment, raw materials, manufacturing environment, while following all appropriate SOPs.

8. Process Validation and Risk Assessment

After a process scale-up is completed, sufficient process validation and risk assessment are required to ensure the stability and reliability of the process. This includes evaluating and validating product quality, production efficiency, safety, and other aspects under each different manufacturing scale.

Summary

The scale-up of an ADC conjugation manufacturing process requires attention to multiple aspects, including the full development and optimization of process steps, stability and homogeneity of DARs, precise control of process parameters through the use of automation, on-line process monitoring, gradual scale-up of the manufacturing process, compliance with GMP requirements & regulations, and process validation and risk assessment. These key aspects combine to form a successful ADC conjugation manufacturing process scale-up.

Faced with the high promise and potential of ADCs, many of China's new ADC drug companies have also embarked on a global path. Through cooperation with integrated CDMOs, they have carried out reasonable division and distribution of key steps, significantly reduced the cost of ADC new drug research and development, improved production efficiency, accelerated project schedule, and successfully occupied a place on the international stage.

Porton Pharma Solution Ltd. has been deeply involved in the CDMO business for nearly 20 years having over 1000 customers worldwide with more than 3000 delivered projects. Its biologics conjugation CDMO division has completed the construction and startup of four R&D and manufacturing sites in Minhang, Fengxian, Waigaoqiao, and New Jersey (USA).

Porton can meet the one-stop CDMO service needs of global biopharmaceutical companies and R&D institutions for biologics conjugates from preclinical research to commercial production, including payload, linker, antibody, tides, oligonucleotide and ADC/PDC/AOC development research. Additionally, cell line construction, upstream and downstream process development, ADC conjugation process development, formulation development, clinical sample manufacturing along with analytical method development and qualification/validation has also been provided to our clients. Porton is committed to becoming the most open, innovative and reliable pharmaceutical service platform in the world and enabling the public's early access to good medicines.

Mr. Zhenkun Song

Associate Director of Production at the Large Molecule Platform

With 10 years of experience in biomacromolecule drug process scale-up, clinical and commercial production. He has rich experience in the construction of new sites, process scale-up, clinical and commercial manufacturing in the field of antibodies and ADCs.

✉ zhenkun.song@portonpharma.com

LinkedIn