THOUSAND OAKS

TOBio ADC Technology Platform Introduction

An Integrated CMC Organization

One-stop Technical Service Platform for CMC of ADC Drugs

- Antibody Preparation
- ADC Drug Substance Preparation
- CMC Feasibility Evaluation
- ADC Conjugation Process Development

- ADC Purification Process Development
- ADC Formulation and Process Development
- Establishment of Analytical Methods for Antibodies and ADCs
- Small Molecule Analytical Method Development

- Analytical Method Transfer and Validation in Compliance with GMP
- Structural and Functional Characterization Studies of Biologics
- GMP Manufacturing of Antibodies
- GMP Conjugation and Purification Manufacturing
- GMP Fill-Finish and Freeze-Drying

- GMP Product Release and Stability Testing
- Technology Transfer and Gap Analysis
- Process Change Management and Comparability Assessments
- Domestic and International Regulatory Registrations

Conjugation Process Development

TOBio's conjugation process development team boasts extensive experience in process development. Our platform technology is built on the principles of speed, cost control, and reproducibility. Notably, our platform technology eliminates the need for chromatography steps, resulting in improved yield, reduced costs, and shorter cycles. This accelerates the research and development process for conjugation. Additionally, we offer a range of conjugation platforms, including chemical conjugation (lysine, cysteine) and enzymatic conjugation (transpeptidase, glycosidase).

Conjugation process development | Purification process development | Coupling process optimization | Characterization of the coupling process | Conjugation process validation | Milligram to gram sample preparation

Our state-of-the-art facilities include reactors of various sizes (1mL, 25mL, 250mL, 500mL, 2L), negative pressure isolators (OEB-5 level), AKTA Avant chromatography system, and ultrafiltration fixtures/systems.

ADC DS Manufacturing

- Equipped with 50L, 200L, and 500L disposable/glass/stainless steel conjugation reactor, capable of producing up to 150 batches of conjugation per year;
- Thousand Oaks provides transpeptidase and glycosidase enzymatic conjugation production and online DAR value detection;
- Equipped with disposable chromatography and ultrafiltration equipment (Cytiva, Merck);
- Equipped with OEB5 level stainless steel isolator and disposable soft isolator;
- Use disposable consumables to effectively prevent cross contamination;
- Isolator and workshop with yellow light control, capable of producing photosensitive drugs;
- Meet the drug use and commercial production needs in key clinical trials of ADC.

ADC DP Manufacturing

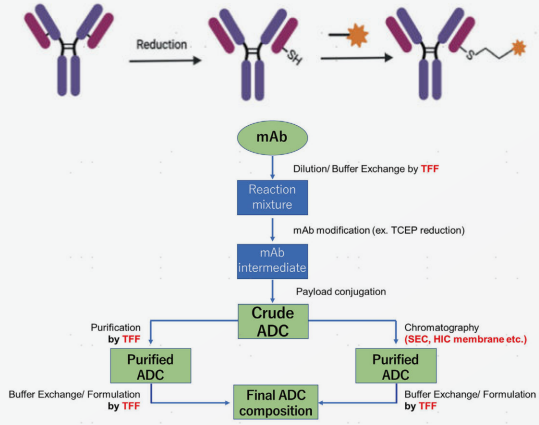
- Using Tofflon isolator liquid vial filling line, equipped with OEB5 level isolator;
- Rapid Transfer Ports (RTP) are implemented in the production line, equipped with VHP atmospheric clean sterilization, 100% online
- IPC weighing, refilling when the filling volume is insufficient, tunnel oven cooling section sterilization, and bottle outer wall cleaning functions;
- Equipped with the function of emptying the tail liquid of the filling machine, ensuring the filling yield;
- Use disposable filling system to effectively prevent cross contamination;
- The filling line is compatible with the production of 2R-50R specification injection and lyophilized formulations, with a maximum operating speed of 300 bottles per minute;
- Equipped with KYOWA 10m^2 and 25m^2 lyophilizers, both with independent fully automatic feeding and discharging system;
- With the function of filling nitrogen before and after bottle filling, filling nitrogen and pressing the stopper of lyophilization, capable of producing oxygen sensitive products;
- Isolator orange light control and workshop yellow light control can be used for photosensitive drugs production.

ADC Conjugation R&D and Production Technology Platform

Antibody to ADC Drug Substance (DS) to ADC Drug Product (DP) are all produced within the same premises, mitigating the potential risks associated with segmented manufacturing

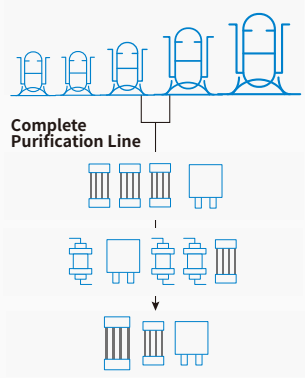
Fed-batch DS & iDS line: 200L / 500L / 2000L
ADC DS line: 50-200-500L conjugation reactor
ADC DP line: liquid vials (2ml-50ml, 144,000 vials / batch)
lyophilized product (25m^2 lyophilizers, 2ml-50ml, 100,000vials/batch)

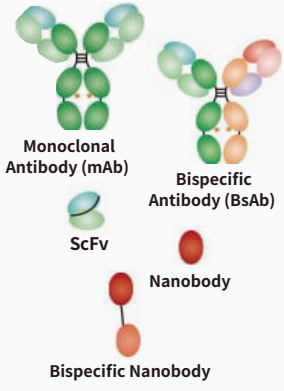
Support based on sulfhydryl, amino and other different ways of chemical Conjugation preparation and production



Support the preparation and production of various forms of naked antibodies

Bioreactor: 50 L/ 200 L/ 500 L/ 2000 L

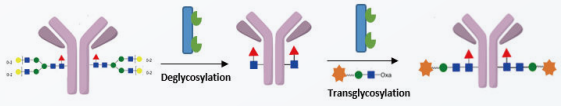


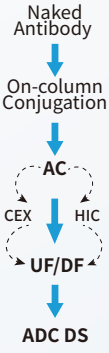


Support enzymatic Conjugation preparation and production based on different methods such as transpeptidases and glycoside transporters

iLDC (intelligent Ligase Dependent Conjugation)

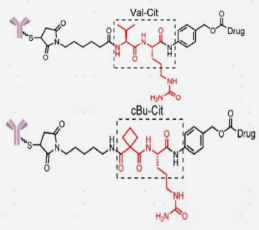
iGDC (intelligent Glycotransferase Dependent Conjugation)



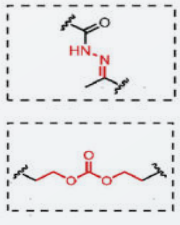


Support the Conjugation use of multiple different forms of linker toxins

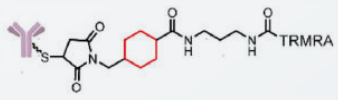
Cathepsin-cleavable



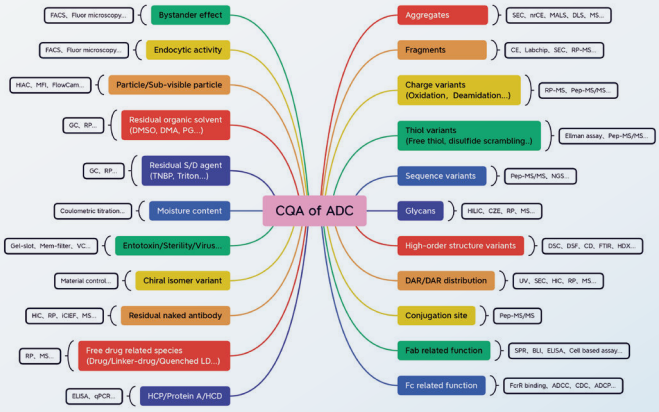
Acid-cleavable



Noncleavable



Support comprehensive analysis of ADC release, stability, structural and functional characterization, etc



Integrated Reg-CMC Solns for mAbs, Proteins and ADCs

At TOBio, we offer comprehensive R&D and production services for monoclonal antibodies, bispecific antibodies, fusion proteins, ADCs, and other drugs. For more detailed information, please refer to the following details.

Discovery >>

Molecular Assessment:

- Druggability & developability assessment
- Drug candidate in silico analysis
- Transient transfection for sample preparation
- Affinity, in vitro binding activity and MOA-related cell-based functional activity
- Physiochemical analyses and biological analyses, mass spectrometric structural characterizations and post-translational modification (PTM) analysis
- Thermal stability (Tagg, Tm) and forced degradation studies

IND Enabling >>

IND Enabling CMC:

- Stable cell line construction, GMP cell banking (RCB, MCB, and WCB)
- Media screening and cell culture process development and qualification
- Purification process development and qualification
- ADC conjugation screening & process development
- Formulation development
- Analytical method development and qualification
- Toxicology material production
- GMP manufacturing of DS and DP (liquid / lyo / pre-filled syringe)
- Product characterization, impurity analysis, stability studies
- IND dossier preparation in Chinese and English

Phase Ⅰ/Ⅱ >> Phase III >> BLA >> Commercial

During Clinical Studies:

- Phases Ⅰ/Ⅱ clinical supplies: GMP manufacturing, release and stability studies
- Process optimization, quality change control and comparability studies, define product CQAs
- Filing strategies and CMC communications with regulatory agencies
- Process and quality profile lock for phase III or pivotal trial materials and stability studies
- Risk analysis and PC to define process parameters (CPP, KPP & GPP)
- Establishment of scale-down models and virus clearance validation
- Development of product-specific HCP kits and HCP coverage study
- INN applications to WHO & Chinese Pharmacopoeia
- Scale-up, manufacturing efficiency improvement, and cost reduction

BLA and Commercial Manufacturing:

- Process characterization and validation for BLA filing and commercial GMP manufacturing
- Optimization and validation of analytical methods for commercial release of DS and DP
- Compatibility studies and transportation stability studies
- Detailed process descriptions, DS and DP materials specifications, and method SOPs for BLA filing
- Preparation of Module 3 for BLA and Pre-BLA Prep
- Pre-approval inspections (PAI)
- Supplier management program for commercial production
- Commercial product manufacturing, packaging and coding
- Post-approval studies (PAS) and process change control strategies
- PAS comparability studies and regulatory filing

Customer product marketing registration and GMP compliance Dynamic verification (PAI)

We obtained the drug production license in January 2019 and have successfully passed the pre-market on-site inspections (PAIs) conducted by the national bureau and the provincial bureau, as well as GMP compliance assessments in March 2021, July 2022, and October 2023.

▲CDMO signature and seal after verification

Quality system

Thousand Oaks Biologics adheres to the stringent requirements set forth by regulatory bodies such as the Chinese NMPA, US FDA, European EMA, and PIC/S. Our quality management system, aligned with the ICHQ series guidelines, covers the entire drug lifecycle across six FDA modules: research, technology transfer, clinical sample preparation, commercial production, and post-approval process changes. In recognition of our commitment to quality, we obtained the Manufacture License of Pharmaceutical Products in January 2019. Furthermore, Thousand Oaks Biologics has successfully passed three national drug registration production site inspections and GMP pre-approval inspections (PAI). Our quality system has undergone multiple audits by the National Medical Products Administration, the European Union, and international partners. Leveraging our extensive experience in research and development, production, registration, on-site verification, clinical trials, and post-approval changes, Thousand Oaks Biologics is well-equipped to provide comprehensive and high-quality CMC services, spanning from research and development to commercial manufacturing.

Quality Assurance Management

- File and Data Management
- Personnel training and qualification confirmation
- Deviation, Change, CAPA Management
- On site supervision and regular inspections
- Material/Product Release
- Audit and self inspection
- Confirmation/validation management, etc

Quality Control Management

- Instrument management and reagent management
- Management of standard and reference materials
- Sample/retention management
- Stability assessment
- Material Quality Standards/Inspection SOP/Records
- Product Quality Standards/Inspection SOP/Records
- OOS, OOT, UAR management
- Environmental monitoring and water quality monitoring
- Analysis method transfer and confirmation/validation, etc

Six major QA system

Material Management

- material management (Acceptance, testing, release, inventory)
- Supplier Management (Evaluation, Audit, Approval)
- Warehouse management (Material and product storage)
- Logistics management, etc (Shipping of cells/materials/products)

R&D management

- Data management
- Experimental record management
- Technical report management
- Measurement management, etc

Production management

- Cell bank management
- Process procedure/SOP/batch record/material list
- Simulated filling of culture medium
- Site clearance management and signage management
- Environmental cleaning and disinfection
- Production workshop personnel access control, etc

Equipment and facility management

- Facility and equipment maintenance
- Daily inspection of factory buildings/public systems
- Measurement/calibration of instruments and meters
- Confirmation of factory buildings/public systems
- Equipment confirmation and pest control
- Computer system/access control system management, etc

Thousand Oaks Biologics Inc.

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