Yaohabio
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PROFESSIONAL MICROBIAL EXPRESSION SYSTEM

Recombinant Plasmid DNA

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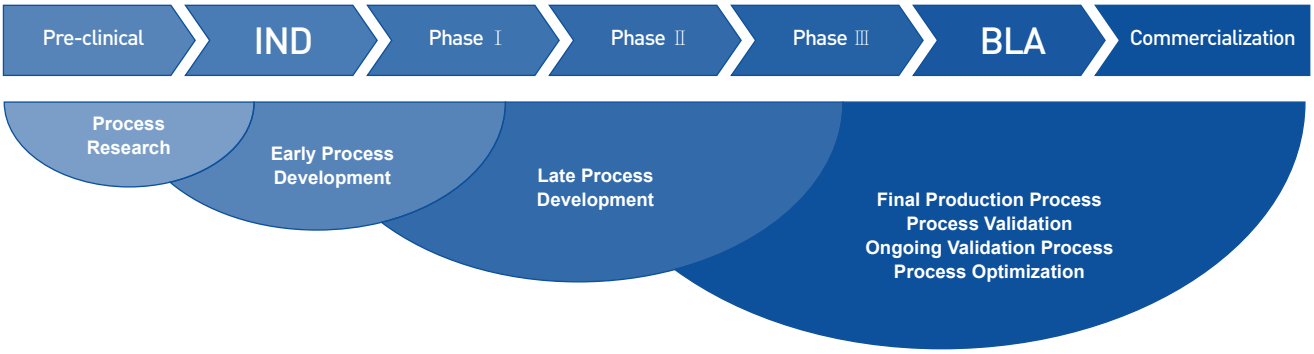
NUCLEIC ACID DRUGS

PLASMID CDMO SERVICES

Plasmid CDMO Services Overview

Yaohai Bio-Pharma is committed to delivering one-stop plasmid CDMO services. It has constructed a GMP-compliant circular plasmid production platform and a linearized plasmid production platform, as well as extensive process development and GMP production experience. The company provides clients with integrated CDMO services from plasmid construction, strain bank construction, process development, quality analytical methods development, stability study, non-clinical research plasmid production to clinical plasmid GMP production and registration application, meeting the needs of plasmid services at different stages including preclinical research, IND application, clinical trial and commercial production.



SERVICES

- PLASMID CONSTRUCTION
- STUDY ON STORAGE AND STORAGE STABILITY OF STRAIN
- DEVELOPMENT AND VALIDATION OF ANALYTICAL METHODS
- STRAIN CONSTRUCTION AND SCREENING
- DEVELOPMENT AND OPTIMIZATION OF FERMENTATION PROCESS
- HUNDRED-MILLIGRAM PLASMID PRODUCTION PREPARATION AND DETECTION [GMP-LIKE]
- ESTABLISHMENT OF STRAIN BANK [PCB/MCB/WCB]
- DEVELOPMENT AND OPTIMIZATION OF PURIFICATION PROCESS
- PRODUCTION AND RELEASE OF GMP PLASMID
- TEST AND PASSAGE STABILITY STUDY OF STRAIN BANK
- PROCESS VERIFICATION
- STUDY ON PLASMID STABILITY
- WRITING OF REGISTRATION MATERIALS

Different Levels of Plasmids

Yaohai Bio-Pharma can provide plasmids at different levels to meet the needs of different stages of pre-research, IIT, IND application, clinical research and commercial production

Plasmid production of non-registration clinical research level (IIT)

Development and production of plasmids for non-registration clinical research level

Overall solution for plasmid clinical application (IND)

Plasmid development and production of gene cell therapy and nucleic acid drug for clinical registration and application

GMP production of plasmids at clinical level

Clinical samples and commercial GMP production for gene cell therapy and nucleic acid drugs

Plasmid level	Scale	Applications	Preparation Conditions
Plasmids at research level	1-500mg	Preclinical research	Process development laboratory
GMP-like plasmids	100mg-5g	Non-registration clinical/preclinical research	GMP workshop
GMP plasmids	100mg-5g	IND application/phase I-III/commercial production	GMP workshop

Plasmid Process Development Platform

The Yaohai Bio plasmid process development platform, adopting the Quality by Design (QbD), possesses comprehensive capabilities in CMC process development and optimization, analytical method development, and quality control. It supports the preparation of research-grade plasmids under non-GMP and GMP-like conditions, providing plasmid vector services that meet various needs.

Fermentation purification systems at different scales to meet the needs of different scales from laboratory development to GMP production.

		Laboratory	Pilot Scale Up	GMP Production
Fermentation system	Equipment	Quadruple fermenter	Fermentation system*2	Tofflon fermentation system*5
	Scale	2L/7L*4 sets	20L/30L fermentation system*1 50L/69L fermentation system*1	50L-100L-200L-500L-1000L-2000L
Ultrafiltration system	Equipment	Fluxs tangential flow membrane filtration system	Hollow fiber/Membrane Cartridge	Fully automated ultrafiltration system
	Scale	50ml-5L	100ml-30L	5L-60L
Chromatography system	Equipment	AKTA(pure/Avant)	RJBIO LPLC 180G	Gradient chromatography system
	Scale	9L/H	3L/H-180L/H	60L/H、180L/H、600L/H

Plasmid Process Development Platform

With GMP plasmid production and process development workshops, Yaohai Bio-Pharma can provide plasmid production services at different stages of non-registration clinical research, IND application, clinical research and commercial production.

01

With five independent production lines of drug substances and two automatic aseptic production lines of drug products, enabling automatic aseptic production of injection (vial), lyophilized powder, and pre-filled cartridges.

02

Provide plasmid production at different scales from 30-2000L to meet the production needs of research, lab-scale and pilot-scale production

03

GMP production workshop, meeting the standards of FDA, EMA, and NMPA

04

International mainstream automated fermentation, ultrafiltration and purification system

05

Unidirectional design of human flow, material flow and sample flow to avoid cross-contamination

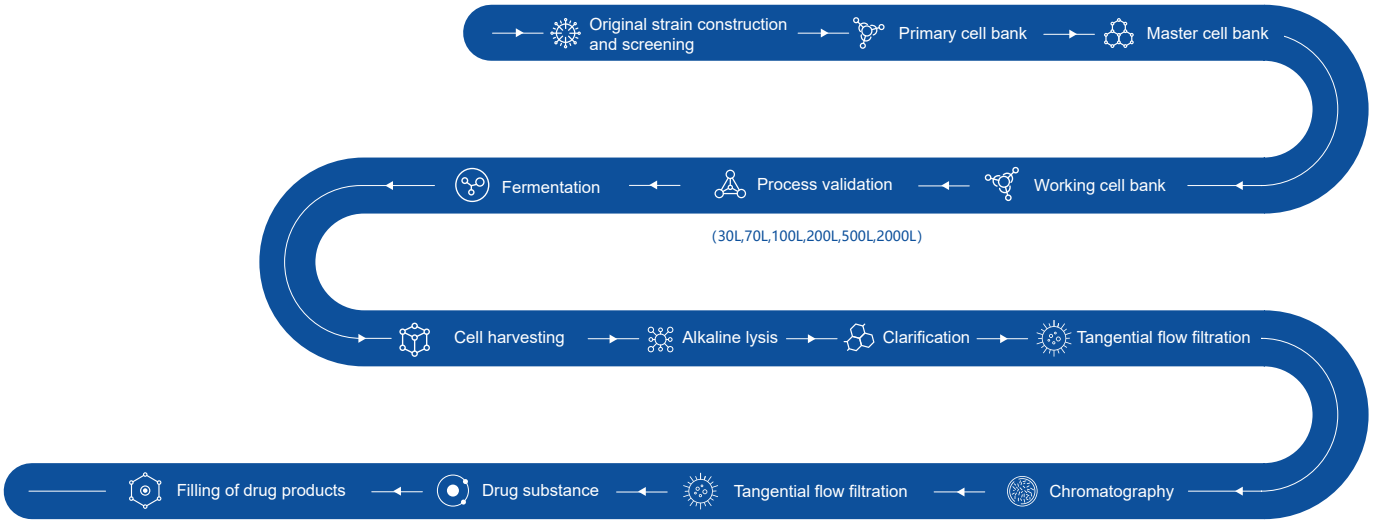
Plasmind GMP Production Process

Supercoiled Plasmid Process Development Flow

- Recombinant plasmids
- Genetically stable strain screening
- Microbial cell bank construction (PCB/MCB/WCB)
- Passage and storage study
- Fermentation process development/optimization
- Purification process development/optimization
- Process scale-up study and validation

Application Types	Naked plasmid products, DNA vaccines/DNA drugs, viral vector constructs (LV/AAV), viral vaccines, LcDNA
Preparation Conditions	Lab scale plasmid preparation under non-GMP/GMP-like conditions
Scale	GMP-like plasmid sample preparation at a scale of 100 mg

Supercoiled Plasmid Production Process



High-density fermentation

In-line lysis process

Two/three-step chromatography

IND Project Progress Overview

Development of Plasmid Project Cycle	Month	1				2				3				4			
Milestones	Week	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Recombinant strain construction	4	●	●	●	●												
Microbial cell bank construction and passage stability	5					●	●	●	●	●							
Lab-scale plasmid development and verification	4						●	●	●	●							
Analytical method validation	4								●	●	●	●					
GMP plasmid production, testing and release	4												●	●	●	●	
Long-term stability study (as per protocol)	N / A																→

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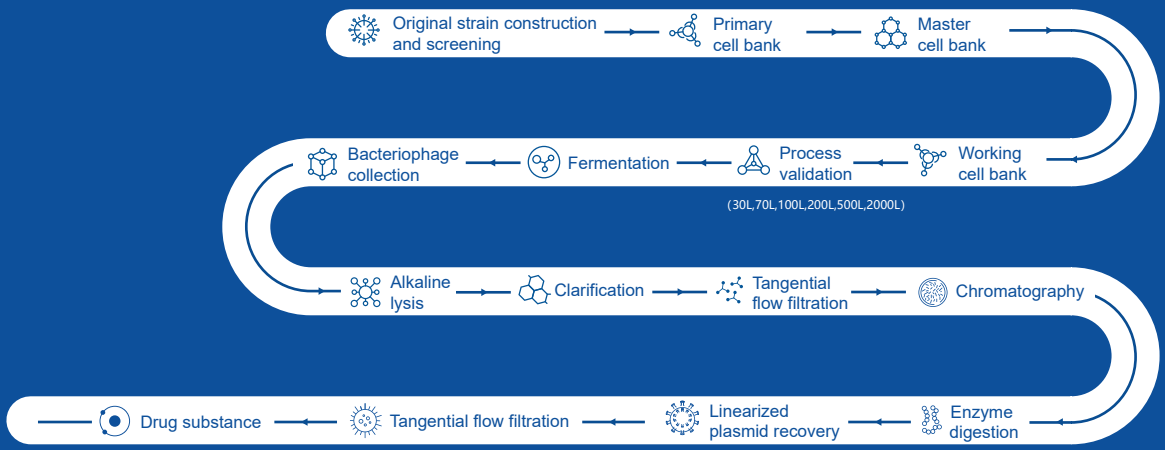
Linearized Plasmid Process Development Flow

- Recombinant plasmids
- Genetically stable strain screening
- Microbial cell bank construction(PCB/MCB/WCB)
- Passage stability study
- Fermentation process development/optimization
- Supercoiled plasmid purification process development/optimization
- Enzyme digestion and linearization plasmid purification process study
- Process scale-up study and validation

Provide GMP-like linearized plasmid sample preparation at a scale of 100 mg

Linearized Plasmid Generation Process Flow



High-density fermentation | In-line lysis process | Two/three-step chromatography

IND Project Progress Overview

Plasmid Project Cycle	Month	1				2				3				4			
Milestones	Week	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Recombinant strain construction	4	●	●	●	●												
Microbial cell bank construction and passage stability	5					●	●	●	●	●							
Lab-scale plasmid process development and validation	5						●	●	●	●	●						
Analytical method validation	4								●	●	●	●					
GMP plasmid production, testing and release	5												●	●	●	●	●
Long-term stability study (as per protocol)	N/A																→

Testing Standards

Supercoiled Plasmid

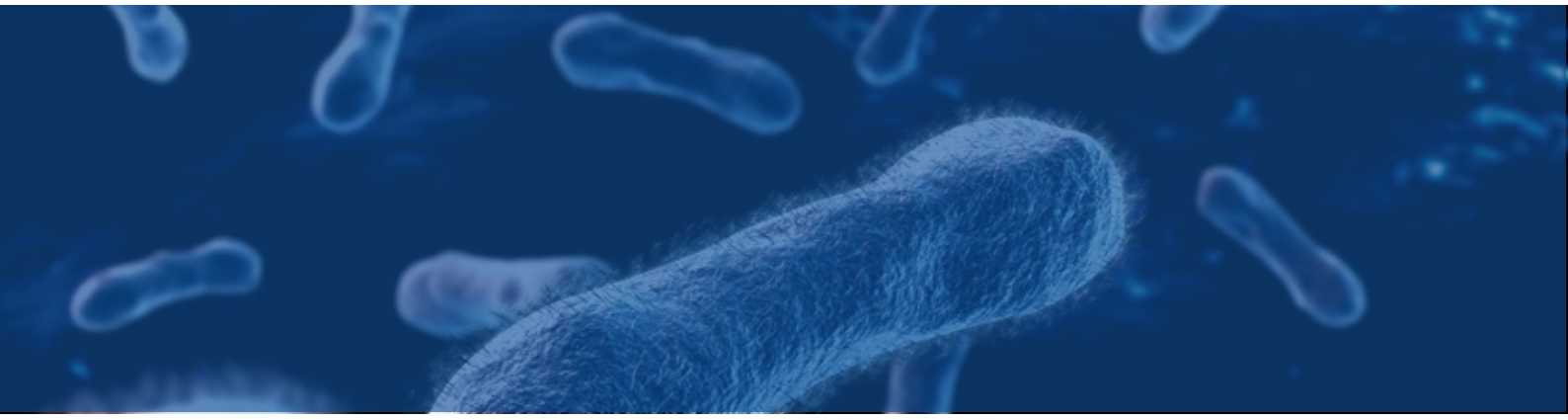
Test Items	Test Methods	Specification
pH	pH determination method	7.2±0.5
Appearance	Visual method	Colorless clear liquid
Plasmid concentration	UV method	N/A
Plasmid identification	Sanger sequencing	Consistent with theoretical sequence
Plasmid assay	Restriction nuclease method	Consistent with the theoretical chromatogram
Plasmid purity	UV260/UV280	1.8~2.0
Supercoil ratio	CE	＞80%

Test Items	Test Methods	Specification
Residual host genomic DNA	Q-PCR	＜0.2%
Host cell protein	Enzyme-linked immunosorbent assay (ELISA)	＜0.1%
Residual host genomic RNA	qRT-PCR	＜50μg/mg
Endotoxin	Gel method	＜10EU/mg
Antibiotic residues	Enzyme-linked immunosorbent assay (ELISA)	＜50ng/mg
Sterility	Direct inoculation/ film filtration	Meet the requirements

Linearized Plasmid

Test Items	Test Methods	Specification
pH	pH determination method	N/A
Appearance	Visual method	Colorless clear liquid
Plasmid concentration	UV method	N/A
Plasmid identification	Sanger sequencing	Consistent with theoretical sequence
Plasmid purity	UV260/UV280	1.8~2.0
Linearized plasmid ratio	CE	＞80%

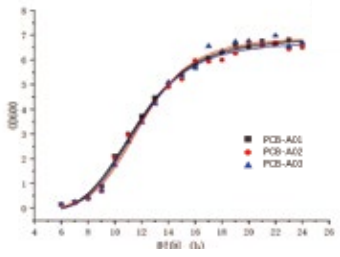
Test Items	Test Methods	Specification
Residual host genomic DNA	Q-PCR	＜0.2%
Host cell protein	Enzyme-linked immunosorbent assay (ELISA)	＜0.1%
Residual host genomic RNA	qRT-PCR	＜50μg/mg
Endotoxin	v	＜10EU/mg
Antibiotic residues	Enzyme-linked immunosorbent assay (ELISA)	＜50ng/mg
Microbial limits	Direct inoculation method/film filtration method	Conformity
Poly A length(Optional)	LC-MS	N/A



Plasmid Service Cases

Good Strain Stability

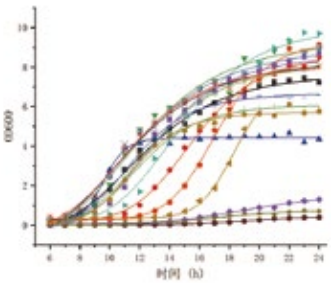
Primary cell bank (PCB) growth curve



PCB growth curve

Achievable DoE Design of Fermentation Process

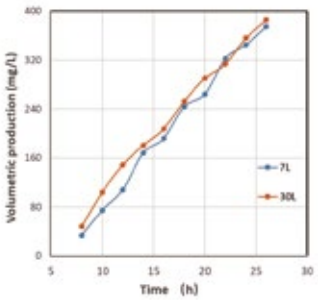
DoE design of medium screening



fermentation strain growth curve

Good Stability and Scalability

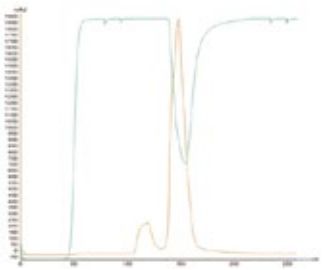
3 batches of plasmid yield at different fermentation scale of 7L and 30L



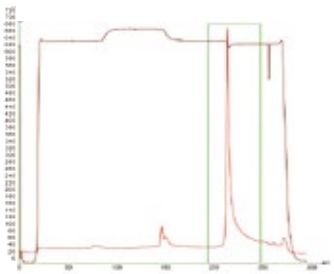
fermentation plasmid yield

Three-step / Two-step Purification Process

Purification chromatogram



plasmid purification:
Bastarsose 6FF chromatogram



plasmid purification:
Plasmid Cap HP chromatogram

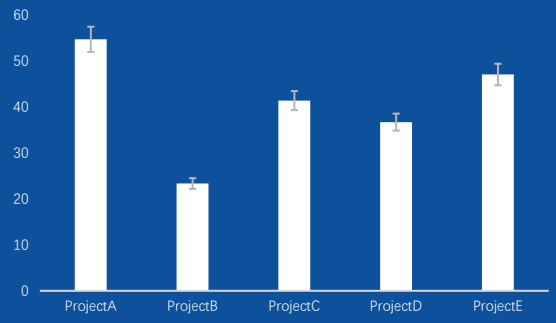
Plasmid Purification Platform

Recovery rate up to 54.67%

Supercoil ratio up to 97.20%

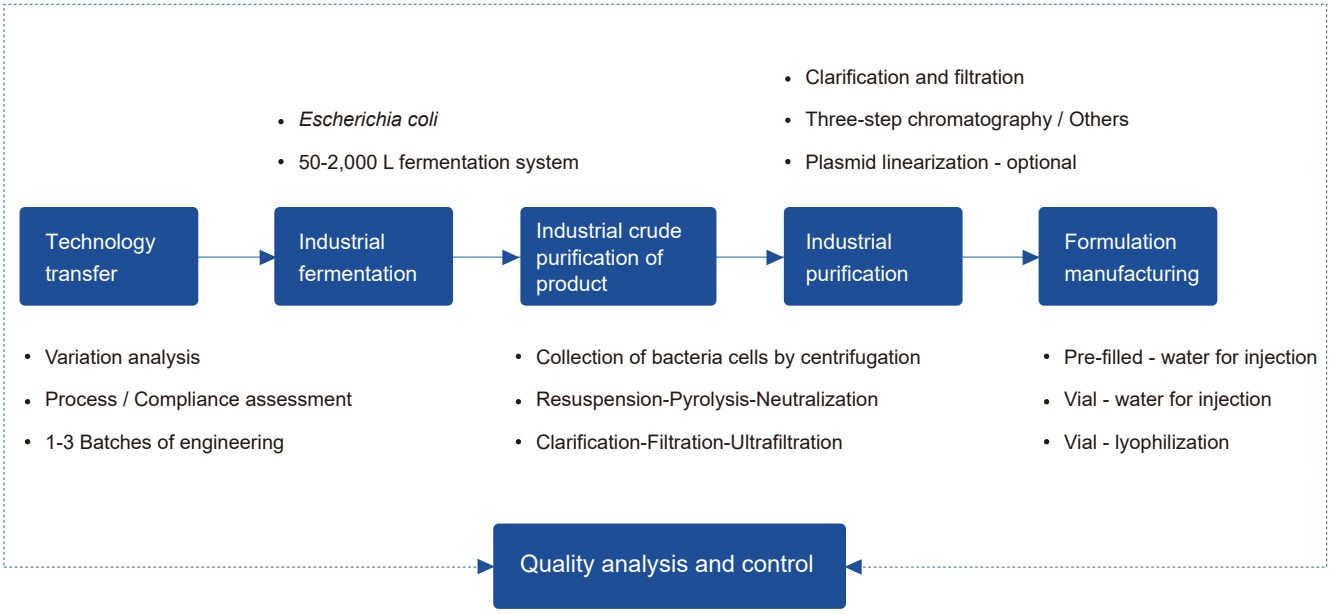
Critical residues:

HCP < 0.01%， HCD < 0.2%。



	Project A	Project B	Project C	Project D	Project E
IEC(%)	96.09	97.20	92.46	93.15	96.04
HCP(%)	< 0.1	< 0.1	< 0.01	< 0.1	< 0.1
HCD(%)	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2

Overview of Recombinant Plasmids CMO Services



Recombinant plasmids are an important vector in the field of cell and gene therapy (CGT) and gene editing, which can be used for:

Naked Plasmid Therapy Drugs

Naked plasmids are used as a gene expression vector and an alternative to protein therapy;

Raw Materials of Viral Vector

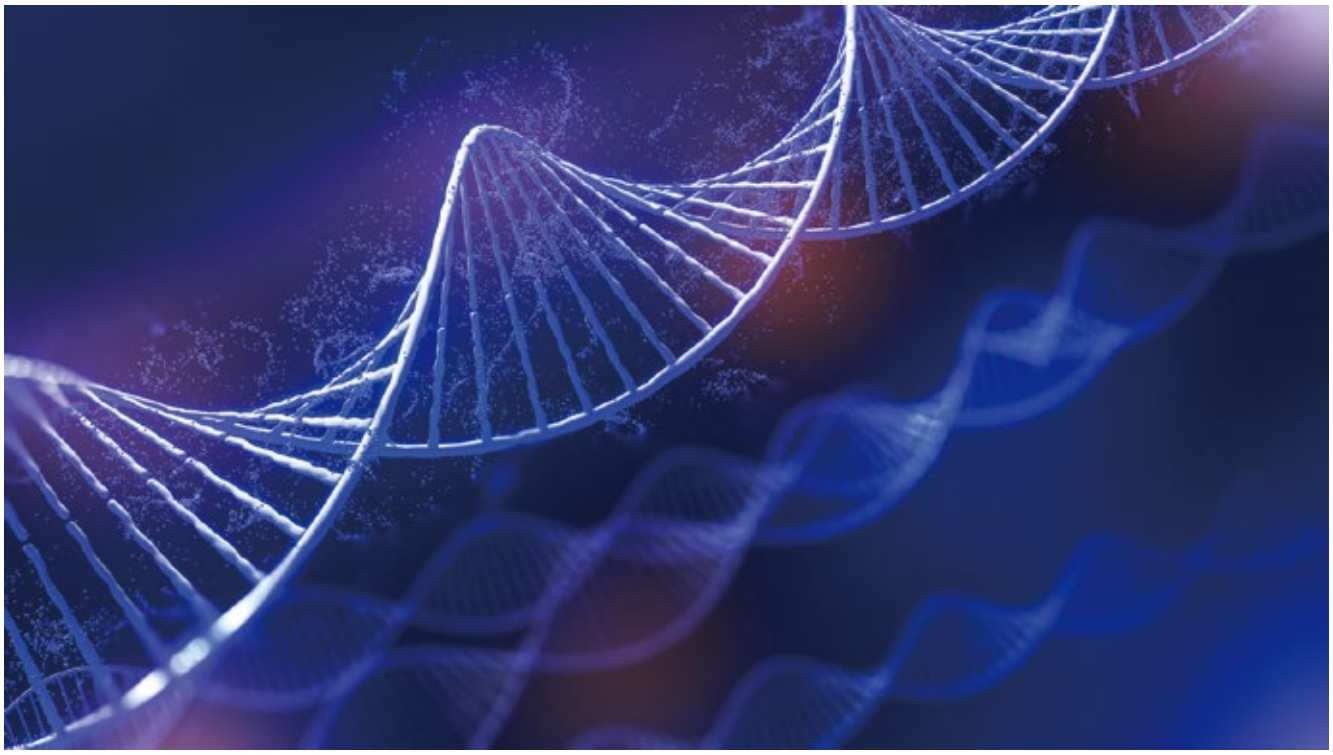
Recombinant plasmids may be used to assemble lentivirus (LV) and adeno-associated virus (AAV) for DNA vaccine, gene therapy or gene editing;

Raw Materials of mRNA/circRNA

Linearized plasmids, as mRNA transcription templates *in vitro*, are important upstream raw materials for mRNA/circRNA vaccines or drugs.

Yaohai Bio-Pharma is a preferred partner for clients in the field of microbial expression systems in China. We have extensive experience in recombinant plasmids and recombinant proteins manufacturing services. Relying on GMP-level production workshops and the comprehensive quality management system, we focus on *Escherichia coli* and yeast expression systems.The process flow will be strictly controlled, as well as the releasing specification of the raw materials and excipients, intermediates and final products of recombinant biologics, thus to ensure an inter-batch consistency. The BLA reporting strategy is adjusted according to the regulations of different countries to meet the requirements of our clients in both China and other regions. We have served more than 100 domestic and international clients, including four plasmid projects in Phase II/III clinical stage and several projects in IND application stage.

Yaohai Bio-Pharma can provide GMP-level recombinant plasmids manufacturing services for clients, including cyclic plasmids and linearized plasmids. Our platform covers multi-scale fermentations of 50 L-100 L-200 L-500 L-1,000 L-2,000 L. The platform is equipped with multiple sizes of low/medium/high-pressure chromatography systems, and also the automatic aseptic filling system such as water for injection vials, pre-filled syringe/cartridge. Guaranteed by diversified production line scales, Yaohai Bio-Pharma can provide the manufacturing services for IND application samples and phase I-III clinical samples, as well as the MAH commercialization manufacturing services. We can accelerate the drug development process for our clients in a comprehensive manner.



Service Details

Service Names	Service Items	Service Details	Minimum Delivery Cycle (working days)	Deliverables
Technology transfer	Document transfer	Manufacturing process/analysis methods/quality specification	TBD	Process transfer report
	Assessment of technical and regulatory compliance	Man, machine, material, method and environment variation analysis	1	
		Assessment of formulation and process	1	
		Assessment of analysis methods	3	
	Protocol transfer	Determination of overall transfer protocol	7	
	Process validation	Manufacturing of 1-3 batches of engineering	TBD Subject to client's process	
Recombinant plasmids industrial fermentation services	Confirmation before fermentation	Man, machine, material, method and environment	1	Intermediates
	Preparation of fermentation system	Preparation of culture medium and solution	2-3	
		Seed tank-fermentor sterilization		
	Fermentation manufacturing	Seed propagation-fermentation	2-3	
		Cooling down the tanks		
Recombinant plasmid industrial crude purification service	Confirmation before production	Man, machine, material, method and environment	1	
	Manufacturing preparation	Solution preparation	1-2	
	Crude purification of product	Bacterial cell collection	3	
		Bacteria resuspension - alkali lysis - acid neutralization		
		Flocculation-filtration and clarification -concentration		

Service Names	Service Items	Service Details	Minimum Manufacturing Cycle (working days)	Deliverables
Recombinant plasmids industrial purification services	Confirmation before purification	Man, machine, material, method and environment	1	Plasmid stock solution
	Preparation of chromatography system	Buffer solution preparation	2-3	
		Filler preconditioning		
	Industrial purification	Filtration and clarification	TBD Subject to client's process	
		Two-step / three-step chromatography		
		Plasmid linearization and purification - optional		
		Concentration		
Recombinant plasmids formulation manufacturing services	Confirmation before formulation production	Man, machine, material, method and environment	1	Vial-water for injection Vial-lyophilization Prefilled syringe-water for injection Cartridge-water for injection
	Preparation before formulation production	Apparatus cleaning and sterilization	1-2	
	Formulation manufacturing (Containing placebo)	Filling of sterilized preparation	TBD Subject to client's process	
		Lyophilization-optional		
		Capping and visual inspection	2	
		Labeling or blind coding	-	

Note:
TBD: to be determined (subject to the client's process); multiple testing items can be carried out at the same time.
For CMO project of recombinant plasmids stock solution + preparation, Yaohai Bio-Pharma's average delivery cycle is 1-3 months (including engineering batch, cycle for reference), and the actual delivery cycle is subject to the client's process.

Continued Table -
Quality Analysis and Control of Recombinant Plasmids

Service Items	Test Items	Test Methods	Minimum Delivery Cycle (working days)
Release testing for raw materials and excipients/ packaging material	Raw materials and excipients-critical items	Conducted in accordance to the specific test items	2
	Raw materials and excipients-full inspection		11
	Packaging materials		60
Recombinant plasmid quality analysis and control	Appearance, visible foreign material	Visual	1
	Insoluble particle	Light obscuration method	1
	Particle diameter	Zeta potential method	2
	pH	Potential method	1
	Electrical conductivity	Electrode method	1
	Osmotic pressure molar concentration	Cryoscopic method	1
	Moisture content	Titration method	1
	Loss on drying	Atmospheric pressure/ Vacuum drying method	2
	Residue on ignition	Ignition method	2
	Deviation of deliverable volume	Volumetric/gravimetric method	1
	Supercoiled plasmid purity or linearized plasmid purity	AGE, HPLC, CE	1-3
	Plasmid DNA concentration	UV	
	Restriction enzymes analysis spectrum	AGE	

Service Items	Test Items	Test Methods	Minimum Delivery Cycle (working days)
Recombinant plasmid quality analysis and control	Nucleotide sequence examination of target gene	Sequencing-alignment	20-30
	Whole plasmid DNA sequencing	Sequencing-alignment	20-30
	Whole genome sequencing	Whole genome sequencing	20-30
	Host protein residue-HCP	ELISA	2
	Host DNA residue-HCD	qPCR	1
	Host RNA residue	RT-qPCR	1
	Other customized test items	-	TBD
	Bacterial endotoxin residue	Gel method, chromogenic method	3
	Antibiotic residue	ELISA, culture method	5
	Microbial limit test	Plating method, membrane filtration method	10
	Sterility test	Direct culture method, membrane filtration method	18
	Investigation of sample stability	High-temperature test	40
		Photostability test	40
		Repeated freeze-thaw test	40
		Accelerated stability test	Sampling: 0, 1, 2, 3 and 6 months
		Long-term stability test	Sampling: 0, 3, 6, 9, 12, 18 and 24 months
GMP workshop environmental monitoring	Non-host strain monitoring	Plating method	5
	Settling microbe monitoring	Culture method	8
	Surface microbial monitoring	Culture method	8
	Planktonic bacteria monitoring	Culture method	8
	Compressed air monitoring	-	10

Note:
TBD: to be determined (subject to the client's process); Multiple testing items can be carried out at the same time.
For CMO project of recombinant plasmid stock solution + preparation, Yaohai BioPharma's average delivery cycle is 1--3 months (including engineering batch, cycle for reference), and the actual delivery cycle is subject to the client's process.

CMO Service Features

Multi-scale CMO Service Platform

50 L-100 L-200 L-500 L-1,000 L-2,000 L multi-scale fermentation platform match with centrifugal, hollow fiber and low-pressure/medium-pressure/high-pressure chromatography equipment of corresponding scale. The preparation workshop is accommodated with GMP-level automatic filling systems, covering 1-25 mL water for injection vials (60,000 vials/batch), lyophilization (37,800 vials/batch) and 1-3 mL prefilled syringes/cartridges (20,000 vials/batch).

Standard GMP-level Explosion-proof Workshop

The explosion-proof solution dispensing system meets the requirements of explosion-proof. The workshop is equipped with electrostatic discharge instruments and flammable gas alarm devices, which can meet the needs of explosion-proof solution dispensing for special process.

Compliance Ensuring Platform

Comprehensively assess the compliance of products and quality specification, such as host source, antibiotic type, toxicity or sensitization, meeting the requirements of registration application.

Quality Control and Analysis Services

Quality control services driven by the latest edition of Pharmacopoeia and the guiding principles of pharmaceutical manufacturing in China and at abroad, involving the release of raw materials and excipients/packaging materials, intermediates and final products.

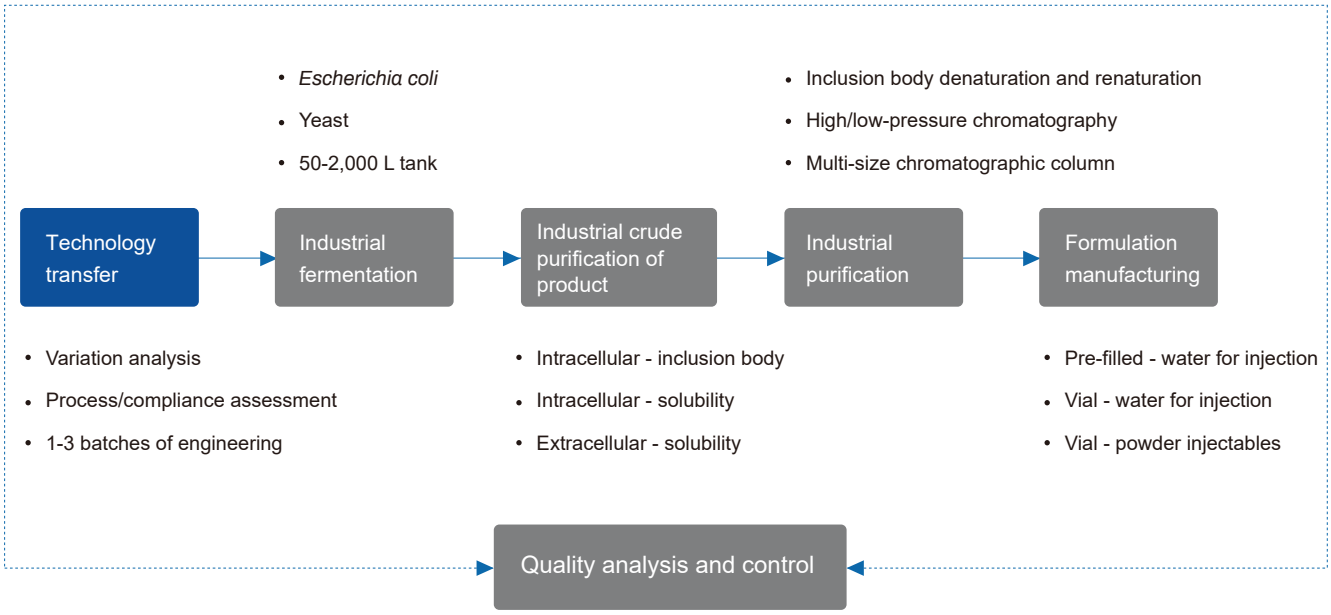
Extensive Experience in Technology Transfer/Process scale-up

The parameters for conversion and process scale-up can be adjusted for fermentation and chromatography systems with different scales. We have successfully finished 100+ recombinant proteins & peptides & plasmids CMC projects, four of which are in phase II-III clinical stage and several of which are in IND stage.

Open Online Audit Platform

Open online audit port, sharing VR videos of GMP workshop.

Recombinant Plasmids Technology Transfer Service



According to the ICH Q10 guidelines, the life cycle of a drug product (DP) is divided into four stages: drug R&D, technology transfer, commercial manufacturing, and product discontinuation. Technology transfer is an important part of the drug life cycle and is the key connecting link between drug R&D and commercial manufacturing. Technology transfer mainly includes manufacturing processes, intermediates control, quality specification of raw materials and excipients, testing methods and other technologies and methods related to product quality. The main goal of technology transfer is to achieve the transfer of products and related knowledge between R&D and manufacturing or between different manufacturing sites, including the transfer between MAH and CDMO, CMO, as well as CRO enterprises, so as to achieve the sustained and stable manufacturing of products.

Yaohai Bio-Pharma has established technology transfer management measures from small test process development, pilot-scale production, to GMP production (both for drug substances and finished formulations), and specified the technology transfer procedures in accordance with the Chinese Pharmacopoeia 2020 edition, ICH Q10, WHO, PDA TR65, ISPE and other technology transfer guidelines. Based on the concept of Quality by Design (QbD), a comprehensive risk assessment has been conducted on the transfer process in terms of regulations and quality management. Besides, the management of the drug's whole life cycle is strengthened, to ensure the success of technology transfer and fully guarantee the safety, efficacy, and quality control of drugs.

01 **Project launch**

- Team building
- Personnel training

02 **Document transfer**

- Manufacturing process
- Quality standards
- Analysis method

03 **Technical assessment Regulatory compliance assessment**

- Man,machine,material,method and environment
- Process/formulation assessment
- Test method assessment

04 **Protocol determination**

- Manufacturing conditions
- Sampling plan
- Release criteria

05 **Process verification**

- 1-3 batches
- Engineering batch verification

Service details

Service Names	Service Items	Service Details	Minimum Delivery Cycle (working days)	Deliverables
Recombinant plasmids manufacturing technology transfer	Document transfer	Manufacturing process	TBD (subject to client's needs)	Process transfer report
		Quality specification		
		Analysis method		
	Assessment of technical and regulatory compliance	Man, machine, material, method and environment variation analysis	1	
		Assessment of formulation and process	1	
		Assessment of analysis methods	3	
	Protocol determination	Transfer protocol determination	7	
	Process validation	Manufacturing of 1-3 batches of engineering	TBD (subject to client's needs)	

Note:
TBD: to be determined (subject to the client's process).
Referred Regulations: Chinese Pharmacopoeia 2020;
ICH Q10. Guidance for Industry Q10 Pharmaceutical Quality System;
WHO Guidelines on the Transfer of Technology in Pharmaceutical Manufacturing;
PDA Technical Report 65: Technology Transfer;
ISPE Good Practice Guide: Technology Transfer.

Service Features

Extensive Experience in Process Transfer

Fully assess the completeness and feasibility of process flow, and the test methods, providing clients with comprehensive process transfer solutions.

Compliance Ensuring Platform

Comprehensively assess the compliance of products and quality specification, such as host source, antibiotic type, toxicity or sensitization, meeting the requirements of registration application. Develop compliant release standards for raw materials, excipients, packaging materials, intermediate products, and final products, ensuring the entire process complies with the latest pharmacopeia and relevant GMP guidelines.

Professional Project Management Team

Professional PMs are specialized in fermentation, purification and preparation process transfer and manufacturing process, able to identify and control project risks and drive project operation in whole cycle.

Extensive Experience in Technology Transfer/Process scale-up

Key parameters can be fast identified and adjusted for fermentation and chromatography systems with different scales. We have successfully finished 100+ recombinant protein & Peptide & plasmid CMC projects, four of which are in phase II-III clinical stage and several are in IND stage.

Key Parameters for Technology Transfer

Critical Equipment	Reasons Affecting Process Parameters	Key Parameters	Yaohai Bio-Pharma equipment
Fermenter	Culture volume, diameter-to-height ratio, mixing blade, maximum rotational frequency	Aeration, rotational frequency, dissolved oxygen	Tofflon
Centrifuge	Sample size, type of equipment (benchtop type, floor type, drum type, disc stack type)	Rotational frequency, feeding, residue discharge time	GEA, Beckman, Junmiao
Chromatography system	UV detector, maximum flow rate	Retention time, sample collection time	Hanbaon, Rongjie
Chromatography columns	Processing batch, column volume	Column volume, loading/buffer solution volume	GE, Hanbon, Rongjie
Filtration/Ultrafiltration system	Processing batch, membrane area	Membrane area, flow rate	PALL, Sartorius

Note: The Yaohai Bio-Pharma equipment column lists some equipment brands we have. Please consult our staff for more information.

During the process of technology transfer, Yaohai Bio-Pharma will perform parameter conversions for process transfer or scale-up due to the inconsistent equipment models (e.g. fermenters, centrifuges and homogenizers). We will face differences in diameter-to-height ratio, stirring blade distribution and maximum speed of different brands of fermenters. Process validation and scale-up can be completed by controlling key parameters such as ventilation, rotational frequency and dissolved oxygen. Different centrifugation equipment are available (benchtop type, floor type, drum type or disc stack type), and homogenizers with different capabilities are applicable for different volumes of samples. Therefore, during the process scale-up, the processes of some projects require conversion of centrifugation and homogenization equipment. The data that needs to be converted includes centrifugation process parameters such as speed, feeding and residue discharging times (disc stack type), and the key homogenization parameters, including flow rate, pressure and times.

A conversion is required only for process scale-up parameter under the condition that the Yaohai Bio-Pharma's equipment models are basically the same. During chromatographic purification, with the column height and column efficiency being maintained within a controlled range, we maintain the retention time, loading capacity and elution conditions (linear flow rate) of the original process. Only the column volume and loading volume are required to be changed according to the actual scale. During filtration or ultrafiltration, we need to change the membrane area and control the flow rate according to the actual scale-ups.

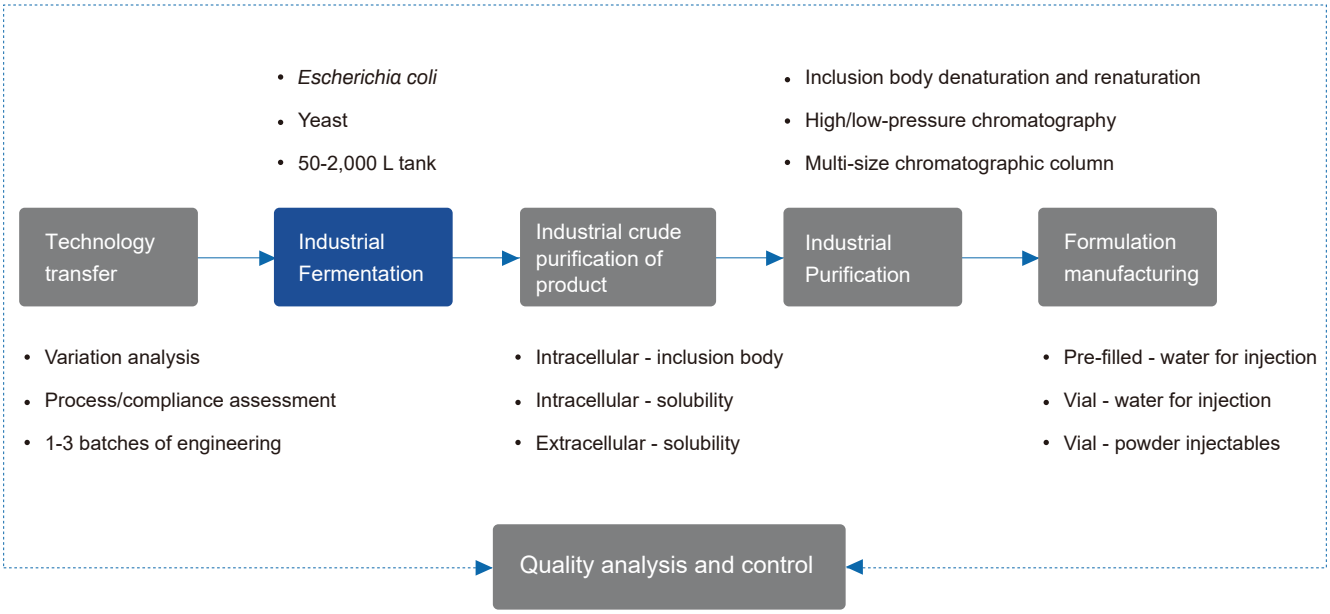
Based on the extensive CMO projects experience of recombinant proteins/peptides/plasmids, Yaohai Bio-Pharma has accumulated experience in equipment-related process transfer of various brands, performances and models. We can quickly identify and adjust key equipment parameters to facilitate our clients to achieve fast delivery while maintaining the original quality of their products.

Yaohai Bio-Pharma TIPs: Times of process scale-up is recommended to be within 10 times, and 1-3 batches of engineering are recommended to be used to control the risk of process scale-up.

Other Services

- Technology transfer
- Industrial fermentation service
- Industrial crude purification service
- Industrial purification service
- Formulation manufacturing service
- Quality analysis and control service

Fermentation Manufacturing Services



Yaohai Bio-Pharma, in the field of microbial expression system, has extensive experience in the manufacturing services of recombinant plasmids and proteins. Relying on five independently operating GMP-level customized production lines with fermentation scales of 50 L-140 L-200 L-500 L-1,000 L-2,000 L, we can meet different project needs of clients, and have served more than 100 clients in China and abroad, with extensive experience in industrial fermentation process.

During the fermentation process scale-up, process control parameters unrelated to scale are also kept consistent, including culture conditions such as basal medium, fed-batch medium, temperature, and pH, as well as the inoculation and feeding supplement. For scale-related parameters, including culture volume, aeration and agitation rate, are the key parameters needed to be controlled during process transfer.

Based on the extensive experience in CMO service, Yaohai Bio-Pharma can perform the appropriate process transfer and scale-up for different size/brand of fermenters, control key parameters, successfully achieve scale-up manufacturing of upstream processes and transfer to downstream processes with high-quality.

01 **Preparation of fermentation system**

- Sterilization of empty feeding tank
  Culture medium--sterilization of feeding tank
  Preparation and sterilization of other solutions

02 **Shake flask culture**

- Transfer the working seed to the shake flask for culturing (Primary or secondary)

03 **Seed tank culture**

- Seed tank inoculation
  Culture process control

04 **Fermentation culture**

- Feeding control
  Fermentation process control

05 **Cooling down the tank**

- Lowering tank in cooling
  Workshop line clearance

Service details

Service Items	Service Details	Detailed Procedures	Minimum Delivery Cycle (working days)	Deliverables
Recombinant plasmids fermentation manufacturing services	Confirmation before fermentation	Confirmation of man, machine, material, method and environment	1	Intermediates
	Preparation before industrial fermentation	Receipt of document and material		
		Reconfirmation of conditions before production in GMP workshop		
	Preparation of fermentation system	Sterilization of empty seed tank, culture medium preparation, Sterilization of seed tank	2-3	
		Sterilization of empty fermenter, culture medium preparation, Sterilization of fermenter		
		Sterilization of empty feeding tank, culture medium preparation, Sterilization of feeding tank		
		Preparation of acid and base and defoamer solution		
	Industrial fermentation	Seed culture in shake flask	2-3	
		Seed tank culture		
		Fermentation culture		
		Cooling down the tank		
Line clearance procedure	Line clearance procedure	Equipment cleaning, sterilization and environmental disinfection	-	-

Note: the table shows the shortest service period by taking *Escherichia coli* as an example, and the yeast is increased as appropriate rate according to the fermentation process.

Service Features

Mature GMP Management System

The workshop staffs and QA/QC personnel have been strictly trained and instructed under GMP, and comply with all specifications of the latest GMP requirements.

Multi-size Fermentation System

There are five manufacturing lines for stock solution, which are built in accordance with international GMP requirements, can provide fermentation scales of 50 L-140 L-200 L-500 L-1,000 L-2,000 L and support manufacturing needs at different development stages.

Diversified Fermentation Platform

According to the needs of clients' process, meeting the needs of the high-density fermentation process, customized feeding process of *Escherichia coli* with or without resistance.

Compliant Testing and Releasing Specification

The brand and batch number of materials (raw materials and excipients) are verified, and the key materials are tested for releasing to ensure consistency and effectiveness of the materials.

Single Project Operation System

Only one project is allowed to be operated in each workshop during each time period to effectively prevent contamination and mix-ups, and the subsequent project shall be carried out only after line clearance passes the requirements.

Experience Sharing of Fermentation Process Transfer

The key parameters of the fermentation process include dissolved oxygen (DO), temperature and pH. Dissolved oxygen is an valid feedback parameter of growth state of strains. Temperature and pH directly affects the growth, proliferation and product expression of strains.

Based on the extensive experience in CMO manufacturing services, Yaohai Bio-Pharma has summarized the questions frequently occurred during fermentation process transfer or scale-up and the corresponding solutions:

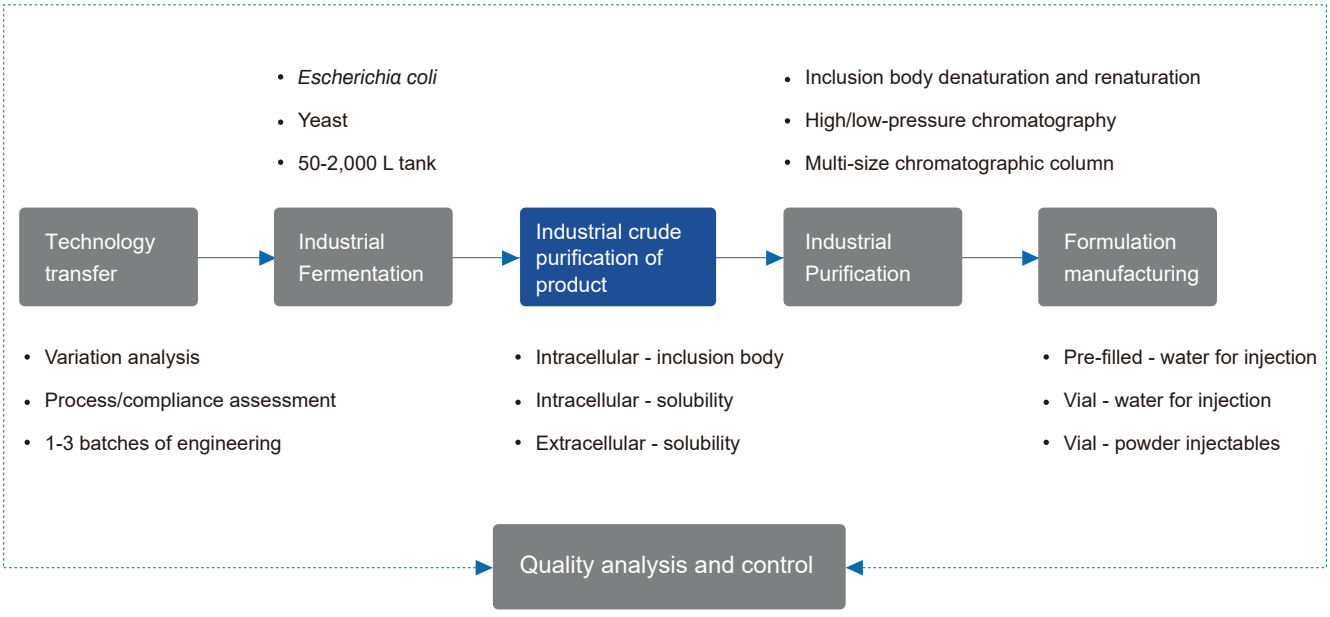
Parameter Types	Related Parameters	Frequently Asked Questions	Prevention or Solutions
Questions related to culture conditions	Temperature and pH	(Volume-independent parameters, consistent)	The temperature, pH sensor, pump and other equipment are calibrated and tested under GMP quality standards.
	Feeding strategy		
	Rotational frequency	How to conduct process transfer and scale-up if the maximum Rotational frequency of the fermenter is lower than the original process?	The function of agitation is to mix materials and improve the oxygen transfer coefficient, which is generally adjusted according to dissolved oxygen. A certain range of rotational frequency is recommended during the process development, which may facilitate process transfer and scale-up.
	Ventilation	How to determine the aeration volume of the fermentation process during process transfer or scale-up?	The purpose of aeration is to provide oxygen for bacterial cell, improve oxygen transfer coefficient, and discharge exhaust gas at the same time, and the amount can be set to a fixed value or adjusted according to **dissolved oxygen**. It is recommended that a certain range of aeration amount should be verified during process development to facilitate process transfer and scale-up.
	Dissolved oxygen	The influencing factors of dissolved oxygen include fermentation liquor volume, viscosity, rotational frequency, aeration volume, etc.	The process in which dissolved oxygen can be automatically controlled after the parameter range of dissolved oxygen is set, and by adjusting agitation and aeration volume.
Bacterial cell volume related questions	$OD_{600\ nm}$	There is a significant variation between $OD_{600\ nm}$ value and the value of original process	The variation of instruments should be considered. As the principle and sensitivity of different spectrophotometers are different, so it is not recommended to limit OD value excessively.
	Solid content of bacterial solution	-	It is recommended to use wet/dry weight of bacteria cells (weighing method) as the valid parameter of bacteria cell amount in reference to the solid content of bacterial solution (visual method).
	Bacterial cell weight	-	

Yaohai BioPharma TIPs: It is not recommended to establish quality standards for intermediate products when there are only few running batches. A collection of relevant data is recommended, and then the quality standards and error ranges can be set by using statistical methods when there are enough data.

Other Services

- Technology transfer
- Industrial fermentation service
- Industrial crude purification service
- Industrial purification service
- Formulation manufacturing service
- Quality analysis and control service

Industrial Crude Purification



In the field of microbial expression system, Yaohai Bio-Pharma has extensive experience in the manufacturing service of recombinant plasmids and recombinant proteins. Five independently operating GMP-level production lines are available, which are equipped with centrifugation equipment with different processing batches and different types. It can match the industrial crude purification for fermentation batches of 50 L-140 L-200 L-500 L-1,000 L-2,000 L fermentation tank. Yaohai Bio-Pharma can meet the needs of different projects of our clients. Currently, and has served more than 100 clients in China and abroad and has extensive experience in the industrial crude purification.

The function of crude purification is to separate substances with large differences, such as solid-liquid separation, intracellular or extracellular substance separation. The crude purification process of plasmids includes centrifugation, alkali lysis and membrane filtration. Collection of bacterial cells is performed by solid-liquid separation, and the plasmid DNA is released using alkaline lysis, then the suspended substances are finally removed through filtration. Due to the different scales of small-scale tests and manufacturing, the adapted centrifugation equipment also varies. The conversion of centrifugation parameters is particularly important during the manufacturing process, which can greatly affect the quality and yield of the product.

01 Solution dispensing

- Resuspension preparation
  Lysate preparation
  Neutralization solution preparation

02 Bacterial cell collection

- Centrifugal collection of bacteria cells
  Rotational frequency/feeding/residue discharge time

03 Bacterial lysis

- Suspension - lysis - neutralization
  Duration of lysis / neutralization

04 Clarification-filtration

- Solution clarification
  Solids removed by filtration

05 Concentration

- Hollow fiber
  Concentration/solution replacement

Service Details

Service Items	Service Details	Detailed procedures	Minimum Delivery Cycle (working days)	Deliverables
Recombinant protein industrial crude purification services	Confirmation before production	Confirmation of man, machine, material, method and environment	1	Intermediates
	Preparation before production	Buffer solution preparation	1-2	
	industrial crude purification	Collection of bacteria cells by centrifugation	1	
		Cell resuspension	1	
		Alkali lysis		
		Acid neutralization		
		Filtration and clarification	2	
		Concentration by ultrafiltration		
Line clearance	Workshop line clearance	equipment cleaning, sterilization and environmental disinfection	-	-

Service Features

Mature GMP Management System

The workshop staffs and QA/QC personnel have been strictly trained and instructed under GMP, and comply with all specifications of the latest GMP requirements.

Multi-scale Crude Purification Equipment

Five GMP-level production lines for stock solution are available, which are equipped with benchtop type/floor type/drum type/disc stack type centrifuges and membrane cassettes with different pore sizes, areas and flow rates to meet the crude purification needs of fermentation liquor product with different sizes.

Compliant Testing and Release Criteria

Key materials (raw materials and excipients) are tested for releasing to ensure effectiveness of the materials.

Single Project Operation System

Only one project is allowed to be operated in each workshop during each time period to effectively prevent contamination and mix-ups, and the subsequent project shall be carried out only after the line clearance passes the requirements.

Experience Sharing of Crude Purification Process Transfer

The purpose of centrifugation and filtration is to achieve solid-liquid separation, and the application scenarios include collection of bacterial cells and the removal of solid-shaped substances, etc. The key parameters of centrifugation equipment include rotational frequency, feeding speed and residue discharging time. The key parameters of filtration include aperture size of filter membrane, flow rate and filter pressure. Centrifugation or filtration that does not meet the criteria may result in poor solid-liquid separation, which may lead to the decrease in product yield, increase of the burden of downstream purification and pose impacts on product quality.

Based on the extensive experience in production, Yaohai Bio-Pharma has summarized the questions frequently occurred in the transfer process of centrifugation and clarification and filtration and their corresponding solutions:

Crude Purification Process	Frequently Asked Questions	Question Analysis	Solutions
Centrifugation	Turbid supernatant	Poor solid-liquid separation Reduced yield (intracellular products) Have negative effect on product quality	• Excessive feeding: reduce the feeding rate • Uneven feeding: fully stirring before feeding • Low rotational frequency: increase the rotate speed • Improper residue discharging time: adjust the residue discharging time
Filtration	How to ensure the effectiveness of filtration after clarification?	If obvious suspended matter exists after clarification, direct use of small aperture filter may lead to clogging.	• It is recommended to adopt at least two-step filtration, filter membrane aperture shall be from large to small. • Real-time monitoring shall be conducted for filter pressure to control the pressure below 0.2 Mpa.

Other Services

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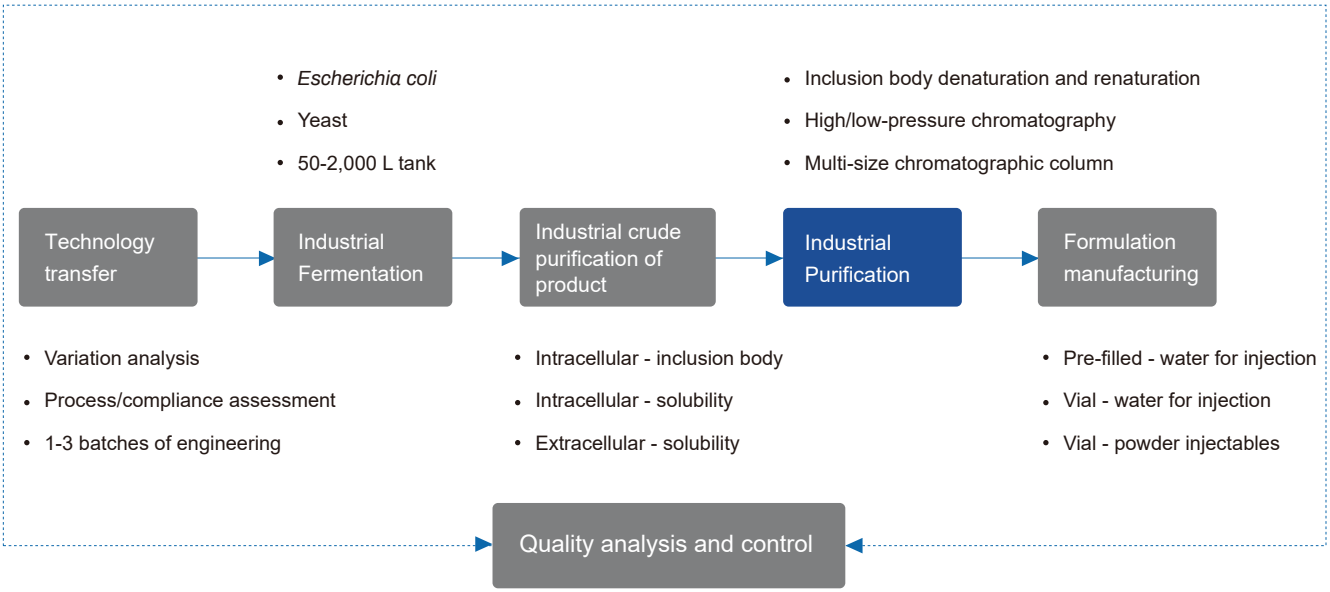
Industrial Purification Services



In the field of microbial expression systems, Yaohai Bio-Pharma has extensive experience in the manufacturing services of recombinant plasmids and recombinant proteins. The purification workshop is equipped with different sizes of automatic or manual membrane filtration systems and low/medium/high-pressure chromatography systems. It can meet the requirements of classical three-step chromatography (molecular sieve/gel filtration chromatography (SEC), sulfurophilic affinity chromatography (AC), anion exchange chromatography (IEX)) and GMP manufacturing requirements for other customized chromatography processes.

01 Purification system preparation

- Buffer solution preparation
  Filler preconditoning

02 Filtration and clarification

- Filtration and clarification of samples
  Solids removing

03 Chromatography purification

- Classic three-step process
  Two-step process
  Other chromatographic process

04 Linear purification -purification

- Linearity plasmid
  -Optional steps

05 Concentration

- Hollow fiber
  Concentration/solution replacement

Service Details

Service Items	Service Details	Detailed Procedures	Minimum Lead Time (working days)	Deliverables
Recombinant plasmids industrial purification services	Confirmation before purification	Confirmation of man, machine, material, method and environment	1	Plasmid stock solution
	Preparation before purification	Receipt of documents and materials		
		Reconfirmation of conditions before production in GMP workshop		
	Purification system preparation	Buffer solution preparation	2	
		Filler preconditioning		
	Industrial Purification	Filtration and clarification	TBD subject to client's process	
		Classic three-step process Gel filtration chromatography → Sulfurophilic affinity chromatography → Ion Exchange chromatography		
		Other purification process-optional		
		Plasmid linearization and purification - optional		
		Concentration		
		Filtration sterilization		
Line clearance	Workshop line clearance	Equipment cleaning, sterilization and environmental disinfection	-	-

Note:
TBD: to be determined (subject to the client's process).
It can meet the requirements of classical three-step processes (molecular sieve/gel filtration chromatography (SEC), sulfurophilic affinity chromatography (AC), anion exchange chromatography (IEX)) and other customized processes requirements, including composite chromatography.

Service Features

Mature GMP Management System

The workshop staffs and QA/QC personnel have been strictly trained and instructed under GMP, and comply with all specifications of the latest GMP requirements.

Multi-scale Purification System

There are five independent purification production lines, which are equipped with low-pressure chromatography systems with flow rates of 6-600 L/h, multi-size solution dispensing tanks and chromatography columns, high-pressure chromatography for industrial preparation, and 5-60 L ultrafiltration system.

Standard GMP-level Explosion-proof Workshop

The explosion-proof solution dispensing system meets the requirements of explosion-proof, and the workshop is equipped with electrostatic discharge instruments and flammable gas alarm devices, which satisfies the needs of solution dispensing in special process, such as reversed-phase chromatography.

Compliant Testing and Releasing Specification

The brand and batch number of materials (raw materials and excipients) are verified, and the key materials are tested for releasing to ensure consistency and effectiveness of the materials.

Single Project Operation System

Only one project is allowed to be operated in each workshop during each time period to effectively prevent contamination and mix-ups, and the subsequent project shall be carried out only after the line clearance passes the requirements.

★★★ To meet the needs of solution dispensing of organic solvent in special processes such as reversed-phase chromatography, purification workshops are equipped with explosion-proof solution dispensing systems complying with the requirements of explosion-proof, and are installed with electrostatic discharge instruments and equipped with combustible gas alarm devices.

Experience Sharing of Purification Process Transfer

In the process of purification, filtration and clarification of the first step are essential. Clarification is designed to further remove particulate substances to avoid negative effects on downstream purification, which is usually completed by using hollow fiber or membrane packs. Key parameters during process transfer or scale-up include processed batch size, membrane area and flow rate.

Chromatographic purification is the procedure of removing impurities of different sizes, charges, polarities and specificities by using different chromatographic fillers to obtain a high purity target product. The classical three-step plasmid purification chromatography is: 1. RNA removal by molecular sieve/gel filtration chromatography (SEC); 2. superhelical plasmids capture by affinity chromatography (AC); and 3. dotoxin removal by anion exchange chromatography (ICX). Key parameters in chromatographic process transfer include processed batch size, column volume, loading volume and flow rate.

Based on the extensive experience in plasmid manufacturing services, Yaohai Bio-Pharma has summarized the questions frequently occurred during purification process transfer and process scale-up strategies:

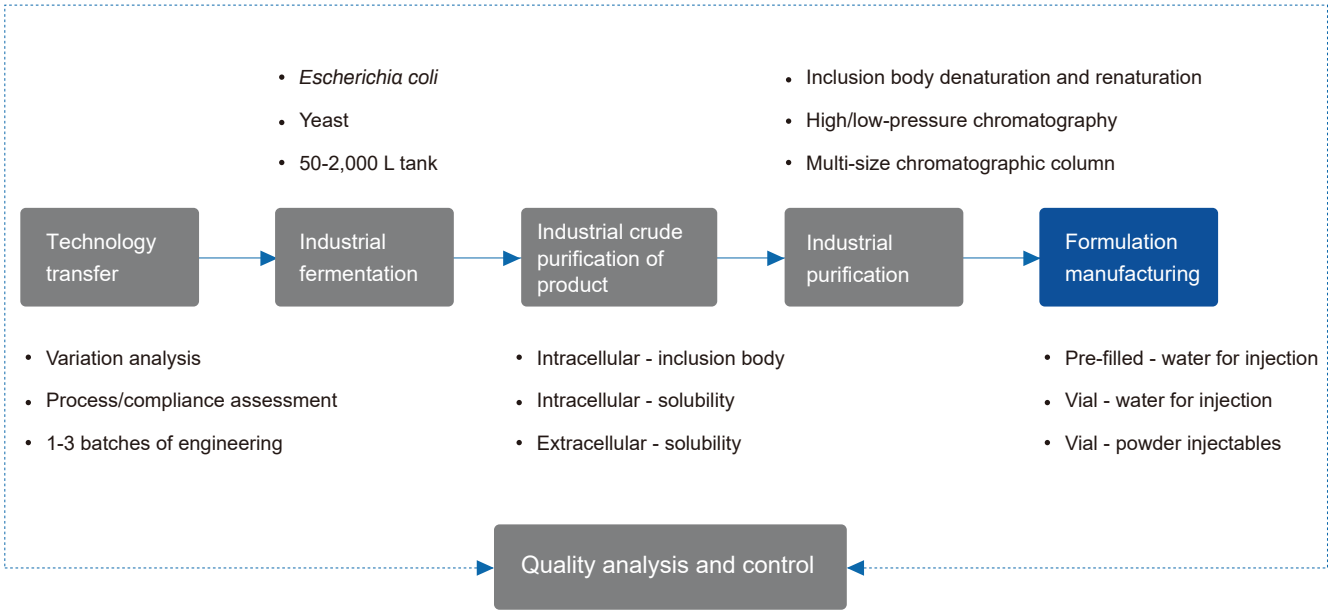
Purification Process	Frequently Asked Questions	Process Scale-up Strategies
Filtration and clarification	No clarification process This process step is omitted in the small tests or medium tests	*Suggestion*: clarify the samples during the process scale-up to remove the solid-shaped substances, so as not to increase the burden in the downstream purification.
Chromatographic process	How to calculate column volume and loading amount when scaling up the chromatography process?	*Consistent parameters*: sample concentration and composition, buffer solution composition, column height, linear flow rate, ratio of loading volume/ column volume; *Scale-up* parameters: sample volume, column diameter, buffer solution volume, volume flow rate.
Membrane filtration	How to calculate membrane area and flow rate when membrane filtration process is scaled up?	*Consistent parameters*: sample concentration and composition, membrane aperture, linear flow rate; *Scale-up parameters*: sample volume, membrane area, volume flow rate.

Note: the above table lists the simple and general purification process scale-up strategies. If there are special process needs, you can also communicate with the technical team from Yaohai Bio-Pharma to solve them.

Other Services

- Technology transfer
- Industrial fermentation service
- Industrial crude purification service
- Industrial purification service
- Formulation manufacturing service
- Quality analysis and control service

Formulation Manufacturing Services



Relying on the GMP-level high-tech automatic manufacturing lines with multiple processes (including vial washing, drying, sterilizing, aseptic filling, lyophilization, capping, etc.) integrated together, Yaohai Bio-Pharma provides the manufacturing services of sterile biopharmaceutical formulations. The types of formulations include vial water injectables 10 million vials/year, vial powder injectables 5 million vials/year, and pre-filled water injectables (prefilled syringes/cartridges 8 million vials/year.)

Yaohai Bio-Pharma's sterile formulations manufacturing lines conform to the manufacturing specifications for sterile preparations of FDA, EU EMA, China NMPA and Australia TGA, and can be used for the formulation and aseptic filling of drugs and placebos, meeting the needs for IND application, Phase I-III clinical research, and MAH commercialization.

Yields / Dosage Form	Water for Injection Vials 1 mL-25 mL	Lyophilized Vials 1 mL-25 mL	Pre-filled Syringe/Cartridge Water for Injection 1 mL-3 mL
Batch manufacturing	60,000 vials/batch (1-10 mL)	37,800 vials/batch (2 mL/4 mL) 20,043 vials/batch (7 mL/10 mL)	20,000 vials/batch
Annual yields	10 million vials/year	5 million vials/year	10 million vials/year

01 Preparation for formulation manufacturing

- Preparation and sterilization of formullation
  Sterilization of rubber stopper-aluminum cap

02 Vial sorting and vial washing

- Vial sorting - vial washing
  Drying sterilization

03 Filling and stoppering

- Normal/nitrogen filling/ vacuum
  Partial stoppering/full stoppering

04 Lyophilization

- Lyophilization - full stoppering
  Unique process of powder injectables

05 Capping and visual inspection

- Capping - light inspection - warehousing

Service Details

Service Items	Service Details	Detailed Procedures	Minimum Delivery Cycle (working days)	Deliverables
Recombinant plasmids formulation manufacturing services	Confirmation before preparation production	Confirmation of man, machine, material, method and environment	1	Vial-water for injection Vial-powder injectables Prefilled syringe-water for injection Cartridge-water for injection
	Preparation before production	Receipt of documents and materials		
		Reconfirmation of conditions before production in GMP workshop		
	Apparatus preparation	Apparatus cleaning and sterilization	1	
	Formulation manufacturing	Vial sorting and vial washing	1	
		Formulation preparation-optional	1	
		Sterilizing filtration of samples		
		Filling and stoppering (normal/nitrogen filling/vacuum)	1	
		Lyophilization-optional (normal/nitrogen filling/vacuum)	TBD subject to client' s process	
		Capping	1-2	
		Visual inspection		
		Labeling and blind coding	-	
Line clearance	Workshop line clearance	Equipment cleaning, sterilization and environmental disinfection	-	-

Note: TBD: to be determined (subject to client's process and batch size);
The current preparation workshop can provide the productions of water for injection vials/lyophilization, pre-filled water for Injection (pre-filled syringe and cartridge), and communication on other dosage forms are also welcomed.

Service Features

Mature GMP Training System

The workshop staff and QA/QC personnel have been strictly trained and instructed under GMP, and comply with all specifications of the latest GMP requirements.

Diversified Preparation Service

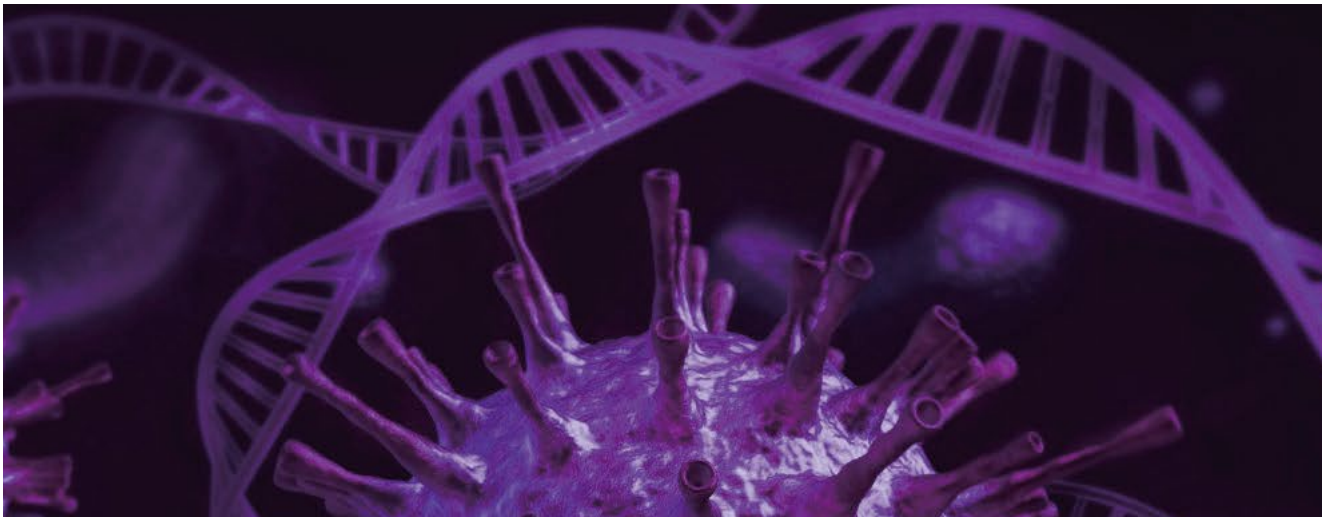
GMP-compliant automated sterile formulation production lines can serve the following products: 1-25 mL water for injection vials/lyophilization, 1-3 mL pre-filled syringe/cartridge water injectables.

Aseptic Formulation Production Line

Conforming to aseptic formulation manufacturing requirements of US FDA, EU EMA, China NMPA and Australia TGA, O-rabs system (Open Restricted Access Barrier System) are used to protect the exposure areas of products (and the packaging materials), providing grade A environmental protection under grade B background.

Extensive Project Experience

The professional PMs have 100+ CMO project experience and are proficient in aseptic filling, and can provide professional advice for a variety of plasmid drugs based on the products of client.



Experience Sharing of Aseptic Filling

The DNA purity of superhelical plasmids is an important index of plasmid products, which directly affects the release of products. However, some plasmids are sensitive to shear force and are easily affected by technological factors, resulting in fractures to affect the drug quality.

Therefore, in the process of plasmid production, we should control the process in all aspects to reduce the loss of supercoiled plasmids and ensure the high quality delivery of products. We strictly control the adverse effects of our manufacturing equipment and processes on plasmid DNA. For shear-sensitive plasmid products, we select equipment with high adaptability to minimize shear effects.

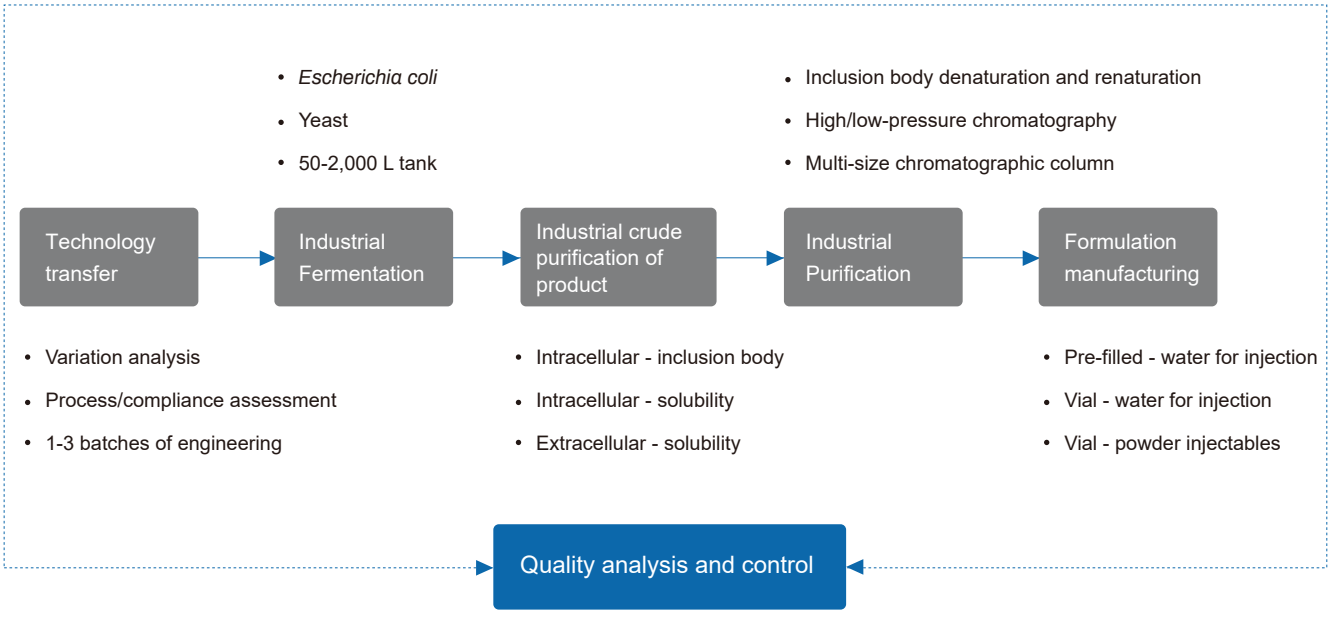
Preparation Process	Critical Equipment Type	Equipment Features
Aseptic filling	Ceramic plunger pump	• High filling precision, stable control of filling volume • Robust and corrosion resistant • Higher cost • Pump body is in direct contact with liquid medicine, resulting in a certain cleaning difficulty
	Peristaltic Pump	• Lower filling precision • The liquid in the pump only contacts the silicone tube • Low cost, only need to replace the silicone tube, facilitating exclusive use • Weak shear force, suitable for shear sensitive biomacromolecule drugs

Yaohai Blo-Pharma TIPs: some plasmid DNA is sensitive to shear force, so it is recommended to use peristaltic pump for filling control to avoid the impact of shear force on the quality of plasmid products. In addition, considering the cost of the equipment use, the liquid in the peristaltic pump only contacts the pipeline, not other pump body. Replacing the silicone tube will realize the exclusive use of a single variety, saving the cost.

Other Services

- Technology transfer
- Industrial fermentation service
- Industrial crude purification service
- Industrial purification service
- Formulation manufacturing service
- Quality analysis and control service

Quality Analysis and Control Services



Human gene therapy products include plasmid vector, viral vector or bacterial vector. According to the pharmacopoeia, the quality control system of gene therapy products mainly includes raw materials, excipients, package materials, manufacturing process, process control and tests of products. Quality control involves assessment of known/potential products and process-related substances by using standard substances, validated methods, and analysis of test items of product appearance identification, activity, purity and impurities.

Yaohai Bio-Pharma has a comprehensive quality analysis and control system. Our team members are proficient in pharmacopoeias and other regulatory specifications. We have extensive experience in quality testing and analysis. We can quickly complete the transfer and validation of analytical method and quality specification, and effectively guarantee the release specification of raw materials and excipients, intermediates, stock solution of recombinant plasmids and preparations.

Service Details

Service Items	Test Items	Test Methods	Minimum Delivery Cycle (working days)
Release testing of raw materials and excipients/ packaging materials	Raw materials and excipients-critical items	Conducted in accordance to the specific test items	2
	Raw materials and excipients-full inspection		11
	Packaging materials		60
Recombinant plasmid quality analysis and control	Appearance, visible foreign material	Visual	1
	Insoluble particle	Light obscuration method	1
	Particle diameter	Zeta potential method	2
	pH	Potential method	1
	Electrical conductivity	Electrode method	1
	Osmotic pressure molar concentration	Cryoscopic method	1
	Moisture content	Titration method	1
	Loss on drying	Atmospheric pressure/ vacuum drying method	2
	Residue on ignition	Ignition method	2
	Deviation of deliverable volume	Volumetric/gravimetric method	1
	Supercoiled plasmid purity or linearized plasmid purity	AGE, HPLC, CE	1-3
	Plasmid DNA concentration	UV	
	Restriction enzymes analysis spectrum	AGE	
	Nucleotide sequence examination of target gene	Sequencing-alignment	20-30
	Whole plasmid DNA sequencing	Sequencing-alignment	20-30
	Whole genome sequencing	Whole genome sequencing	20-30
	Host protein residue-HCP	Enzyme-linked immunosorbent assay (ELISA)	2
	Host DNA residue-HCD	qPCR	1
	Host RNA residue	RT-qPCR	1
	Other customized test items	-	TBD

Service Items	Test Items	Test Methods	Minimum Delivery Cycle (working days)
Recombinant plasmid quality analysis and control	Bacterial endotoxin residue	Gel electrophoresis, chromogenic method	3
	Antibiotic residue	Enzyme-linked immunosorbent assay (ELISA), culture method	5
	Microbial limit test	Plating method, membrane filtration method	10
	Sterility test	Direct culture method, membrane filtration method	18
	Investigation of sample stability	High-temperature test	40
		Photostability test	40
		Repeated freeze-thaw test	40
		Accelerated stability test	Sampling: 0, 1, 2, 3 and 6 months
		Long-term stability test	Sampling: 0, 3, 6, 9, 12, 18 and 24 months
GMP workshop environmental monitoring	Non-host strain monitoring	Plating method	5
	Settling microbe monitoring	Culture method	8
	Surface microbial monitoring	Culture method	8
	Planktonic bacteria monitoring	Culture method	8
	Compressed air monitoring	-	10

Note: Multiple test items can be carried out at the same time.

CMO Service Features

Mature GMP Training System

The QA/QC personnel have been strictly trained and instructed under GMP comply with all specifications of the latest GMP requirements.

Compliant QC Testing process

Being able to reasonably assess the compliance of analytical methods and quality release specifications, and can quickly complete the transfer and validation of the analytical methods.

Whole-process Quality Control

The raw materials and excipients, intermediates, stock solution of plasmid DNA and preparations are tested for releasing, with the releasing quality specification of materials and samples strictly controlled.

Complete Quality Analysis Platform

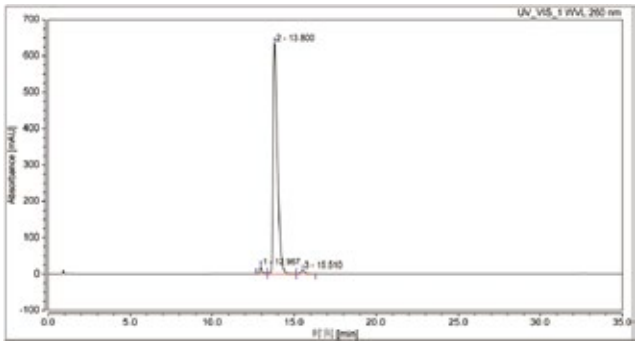
Based on our extensive experience in CMO services, the quality control team of Yaohai Bio-Pharma has established a highly applicable, robust and reliable analysis platform that can meet the requirements of physiological, biochemical and microbiological testing with stringent specification.

Quality Analysis Case Sharing

In a project of testing the long-term stability of AAV raw plasmid samples, the QC team of Yaohai Bio-Pharma tested long-term stored GMP-level plasmid products after successfully transferring the analytical method, including supercoiled plasmid purity, residual endotoxins, residual host proteins (HCP), residual host DNA (HCD), residual host RNA, and residual antibiotics, etc. All of the results met the quality acceptance specification, and a complete test report was delivered to the client.

Purity of Supercoiled Plasmid:

According to HPLC analysis, the proportion of superhelix plasmids could reach more than 97% (Figure-Peak 2).



Critical Residual Items	
Endotoxin residue	＜40 EU/mg
Kanamycin residue	＜0.1 ng/mg
Host protein residue(HCP)	＜0.003 μg/mg
Host DNA residue(HCD)	0.93 μg/mg
Host RNA residue	＜0.0004 μg/mg

Note: All the above test results are with good repeatability.

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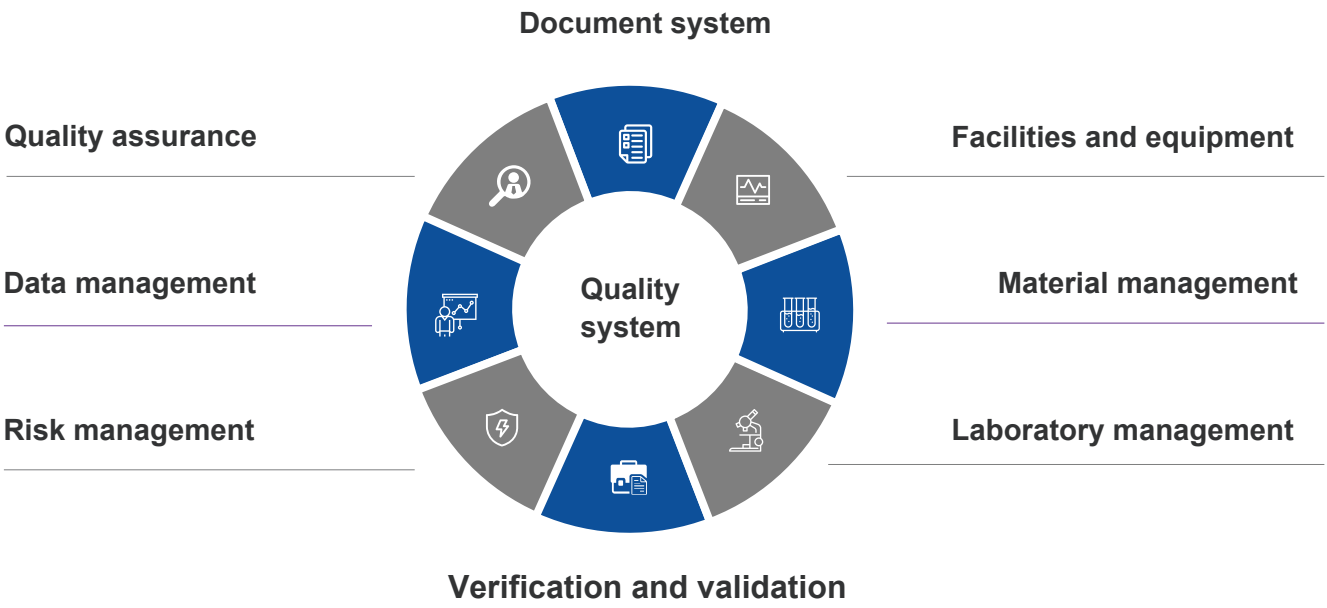
- Industrial purification service
- Industrial formulation service
- Quality analysis and control service

GMP Quality Assurance System

Good Manufacturing Practice (GMP) is the basic guideline for drug manufacturing and quality management, which applies to the whole process of drug formulation manufacturing and the key processes affecting the quality of finished products in API manufacturing. The vigorous implementation of GMP is to avoid contamination and cross-contamination in the drug manufacturing process to the maximum extent and to reduce the occurrence of various errors, which is an important measure to improve the quality of drug products.

The bio-quality system management personnel in Yaohai Bio-Pharma have GMP certification experience, and the executive team has extensive GMP work experience. Our team members are proficient in studying, interpreting and translating global regulations. We have developed a compliant quality management system by combining different life cycle stages of drugs. We also manage and control the whole process of man-machine-material-method-environment in the production stage.



Document System

- Policies of management (POL), standard operation procedures (SOPs)
- Process procedures/quality specification/standard test procedures (STP)
- Form records: adhere to SOP and STP, with independent approval

Quality Assurance

• System management: document/record, training, change/deviation/CAPA/complaints, self-test, material/supplier management

• Site management: manufacturing site, QC site, material control, utility system, record review, product release

Data Management

- Computerized system management
- Laboratory raw data management
- Data audit, data reliability management

Risk Management

- Line confluence risk control: stage manufacturing/dedicated apparatus
- Sterile contamination risk control: facility/equipment/material control
- Compliance risk control: self-test/audit/regulation translating
- Quality system risk control: change/deviation/CAPA

Verification and Validation

- Verification of plant and facilities
- Equipment verification
- Computerized system validation
- Process validation
- Metrology management
- Cleaning verification
- Aseptic process simulation
- Validity period validation, etc.

Laboratory Management

• Management of samples/references, reagents and consumables
• Verification and validation of analytical methods, management of entrusted testing
• Data, record and report management, quality information management

Material Management

• 1,400 m^2 storage area, conforming to GMP and FDA specifications
• For storage of raw materials and excipients, packaging materials, intermediates, finished products, and etc.
• Storage conditions include freezing, refrigerating or ambient/room temperature

Facilities and Equipment

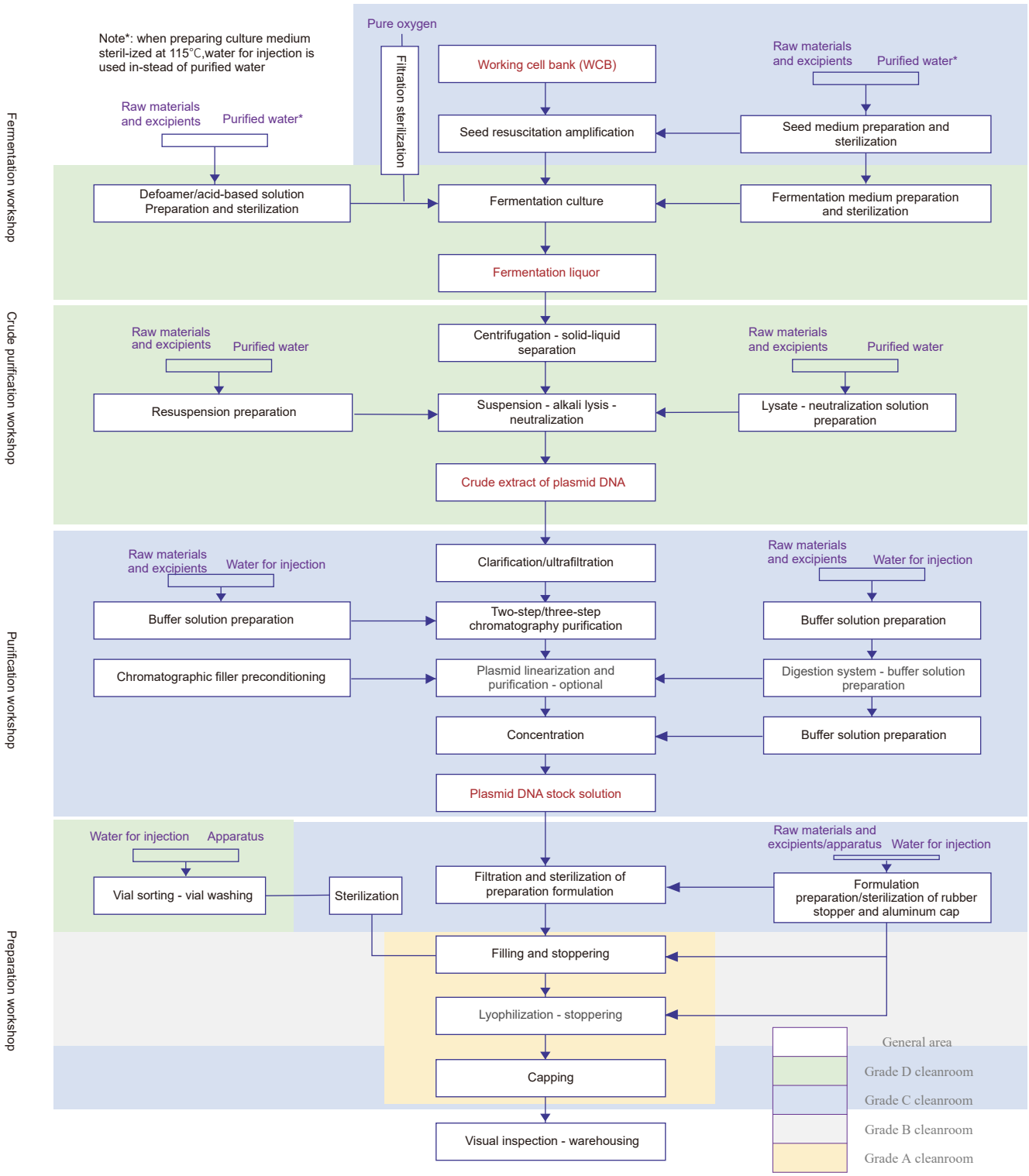
• Management of functional areas of different cleanliness classes: air conditioners are independently formulated to control differential pressure, temperature and humidity and suspended particles
• Safeguard of medium: water for injection, purified water, pure steam, and etc.
• Equipment: authority setting, on-line monitoring, verification and measurement

Management and Control of Clean Room in GMP Workshop

Maximum allowable number of suspended particles/m^3

Cleanliness Level	Static		Dynamic	
	≥0.5 μm	≥5.0 μm	≥0.5 μm	≥5.0 μm
Grade A	3,520	20	3,520	20
Grade B	3,520	29	352,000	2,900
Grade C	352,000	2,900	3,520,000	29,000
Grade D	3,520,000	29,000	No provision	No provision

Functional Areas of GMP Workshop



Presentation of GMP Workshop and Equipment

Solution dispensing system

Fermentation system

Disc stack type centrifuge

Cartridge centrifuge

Homogenizer

Hollow fiber system

Low-pressure chromatography system

High-pressure chromatography system

Aseptic filling system

Capillary electrophoresis instrument

Gas chromatograph

Liquid chromatograph

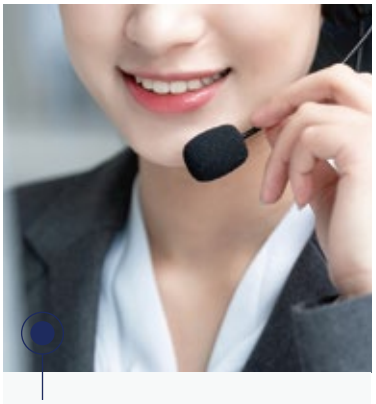
Service Process

PROJECT CONTACT

Project Communication
Confidentiality Agreement /
Needs Analysis

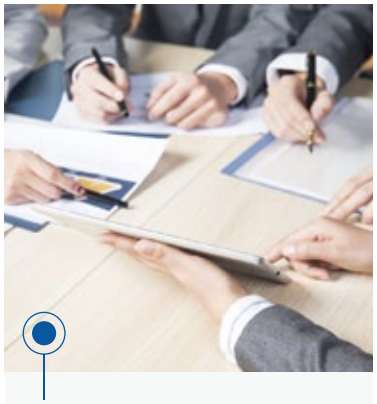
READY START UP

Contracting
Gap Analysis /
Quality Agreements



POST-SALE SERVICE

Follow Up Services
Assistance in Official Verification /
Technical Consultation



ACCEPTANCE DELIVERY

Project Delivery
Deliverables Management /
Cost Settlement

EXECUTIVE CONTROL

Project Implementation
GWBS Promotion /
Process Control

Yaohabio 耀海生物

SERVE **WITH HEART** & CREATE **THE FUTURE TOGETHER**

CHOOSE YAOHAI BIO-PHARMA

Project Experience

More than 100 projects have been successfully served, covering the preclinical research, and clinical phase I, II and III, including several registration projects filed for China, US FDA and Australia.

Professional Team

With experienced CRDMO services execution team supported by gradient professionals, the contracting services can be efficiently and collaboratively boosted.

Comprehensive Production Line Protection

High quality and diversified fermentation purification services can be provided with the fully automated fermentation systems at a scale of 2-7500 L.

Compliance Service

With professional, standardized and regulated service guarantee system, the whole life cycle complies with the requirements of the new edition of pharmacopoeia, GMP and other related guidelines.

Flexible Cooperation Mode

Offer customized services that cater to the specific requirements of diverse project types, ensuring quality and efficiency in delivering exceptional client satisfaction.

One-stop Service

Provide one-stop service from process development to commercial production.

CORPORATE CULTURE

Vision

To be a sustainable leader in the CDMO industry for microbial expression systems

Mission

To create global standards, facilitate the process of new drugs, and achieve a healthy life

CRDMO SERVICES

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