Yaohabio
耀海生物

CRDMO Services

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Yaohai Bio-Pharma

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PROFESSIONAL MICROBIAL EXPRESSION SYSTEM

CRDMO SERVICES PROVIDER

- ☐ RECOMBINANT PROTEINS/PEPTIDES
- ☐ NANO-ANTIBODIES
- ☐ RNA DRUGS
- ☐ RECOMBINANT NOVEL VACCINES
- ☐ RECOMBINANT PLASMIDS

CONTENTS

ABOUT YAOHAI BIO-PHARMA

Yaohai Bio-Pharma was founded in August 2010, a state high-tech enterprise, based in China Medical City(CMC), Taizhou, Jiangsu Province, China, and received the Drug Production License in 2012. It is a CRDMO (Contract Research, Development and Manufacturing Organization)focusing on microbial expression system, with business focalizing the recombinant proteins/polypeptides, nano-antibodies, gene therapy and nucleic acid drugs, novel recombinant vaccines, and other areas. The company is committed to build an open and integrated production and research service platform for CRO/CDMO. The scope of business covers one-stop CMC services throughout the entire drug lifecycle, such as engineering bacteria construction, cell bank construction, lab scale process development and optimization, pilot process scale-up and production, clinical sample preparation, quality specification establishment, analytical method development and validation,compliantmproduction(GMP), quality management system establishment and registration application, etc.

Adhering to the service concept of “Serve with heart, create the future together”, we persevere in empowering the global new drugs development with the mission of “Establish global standards, boost new drug development process, and achieve healthy life”.

Yaohai Bio-Pharma ——

THE LEADING CRDMO, EMPOWERING AND ACCELERATING NEW DRUG DEVELOPMENT PROCESS

12 years +

Diligent Development

as a pionner in microbial expression systems CRDMO services，national high-tech enterprise

100+

Project Experience

100+ CRDMO projects successfully delivered

300+

Global Customers

and many world-renowned companies as strategic partners

100+

Successful Audits

successfully passed NMPA inspection

300+

Project Reserves

with 100+ clinical projects
200+ commercial project under negotiation

CRDMO SERVICES PLATFORM

C

- Contract customization services

R

- Nano-antibody recombinant expression and purification
- mRNA UTR/IRES sequence-based screening
- CircRNA trial sample preparation and activity evaluation
- Establishment of analytical method
- Recombinant protein trial sample preparation
- Host bacteria screening
- LNP preparation

D

- Strain construction
- Primary cell bank construction
- Fermentation process development
- Purification process development
- Formulation process development
- Pilot scale-up
- Pilot production
- Quality specification establishment
- Analytical method development
- Process sample testing
- IND application

M

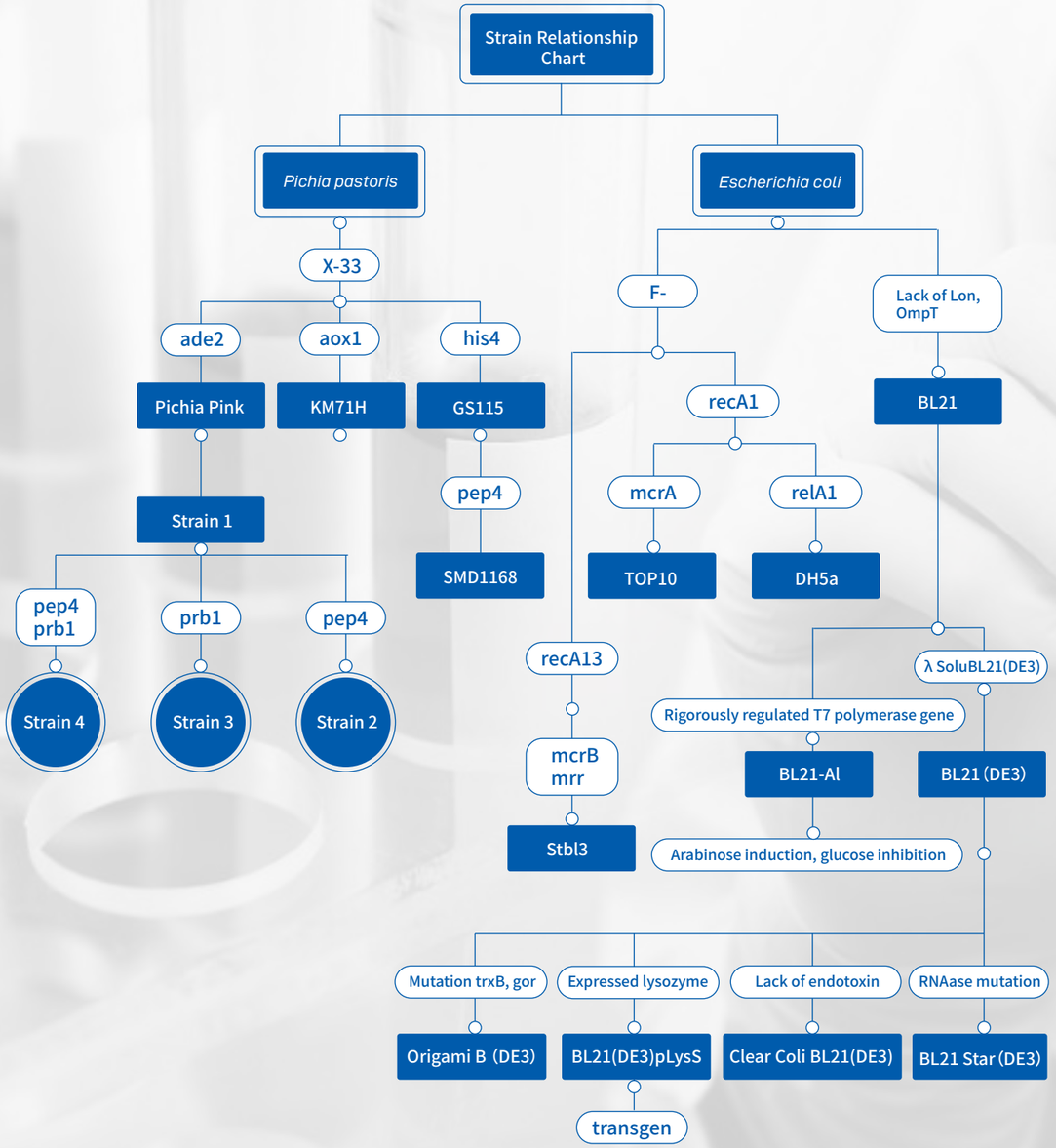
- MCB/WCB construction
- Strain stability study
- API and excipients testing
- Analytical method transfer, verification, validation
- GMP production of drug substance (Phase I, II, and III)
- GMP production of drug product (Phase I, II, and III)
- Release testing of intermediates, drug substance, semi-finished product and finished product
- Preparation of standard substance/reference substance and structure characterization
- Industrialized production
- Stability study
- BLA application support

O

- Omni-directional end-to-end services

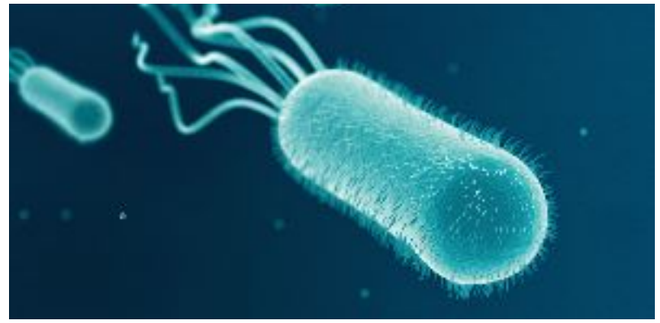
Scientific Sample Customization → **Customized R&D** → **Customized Production Services** → **Commercialized / Customized Production Lines**

STRAIN RELATIONSHIP



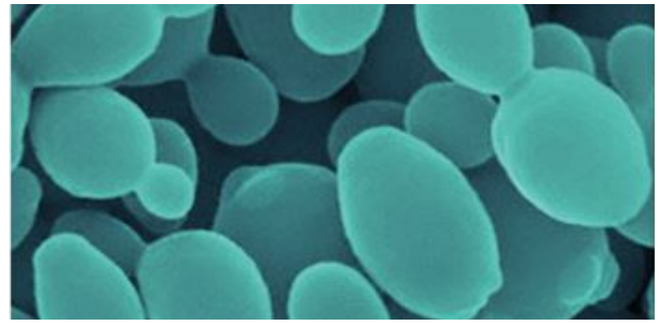
E. coli

K-12 strains & derivatives (DH1.DH5a. RV308,W3110,MG1655,JM109,BW25113...)
B strains(BL21,BL21(DE3)，BL21(DE3) pLysS,BL21(DE3) Rosetta...)



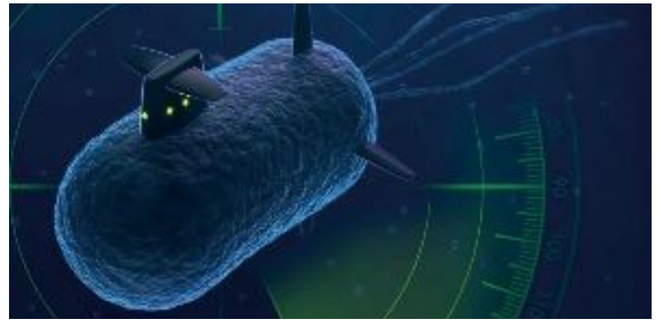
Yeast

*Pichia pastoris, Hansenula polymorpha, Saccharomyces cerevisiae,*etc.



Tailor constructed Strains

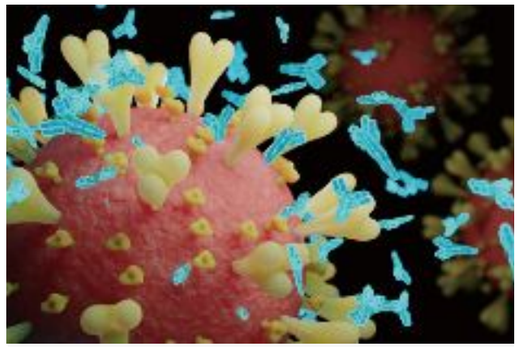
Other microbe/microbiota/microbiome provided by clients
Customized strains



SCOPE OF SERVICES

Recombinant Proteins/Polypeptides

- Provide services from strain bank construction, process and analytical method development, cGMP production to aseptic filling of drug product
- A production scale of 2-2000L
- Support recombinant polypeptides/proteins, recombinant antibodies (antibody fragments), and recombinant vaccines (VLP), etc.



Nano-antibodies

- *E.coli* prokaryotic expression system, eukaryotic expression system, and mammalian cell expression system
- Monovalent, bivalent and trivalent diversely nanobodies
- Expression level from μg to kg
- GMP production capacity of drug substance at a scale of 7-2000L

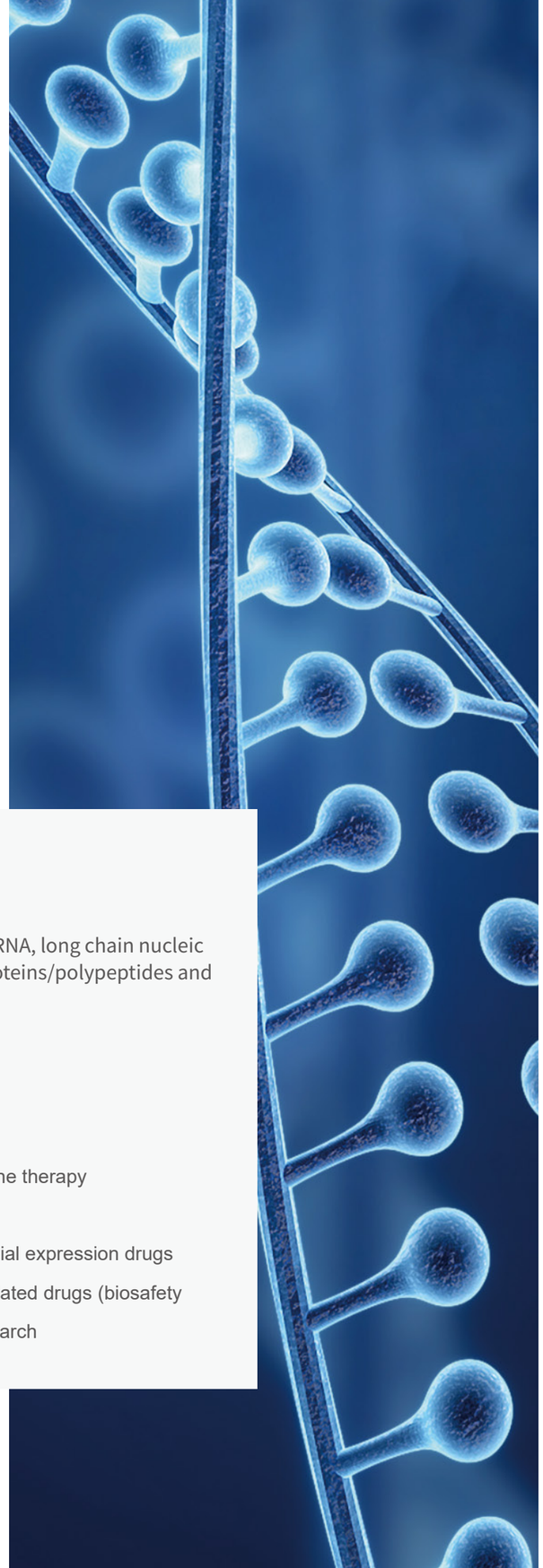
Nucleic Acid Drugs

- Process development from sequence design and optimization, gene synthesis, IVT, purification and mRNA quality control
- Provide pre-made/customized RNA products
- Support mRNA, CircRNA, etc.

Cell and Gene Therapy

- Provide different levels of plasmids such as nonGMP, GMP-like and GMP according to customer's requirements, to meet the needs of different phases of pre-research, IIT, IND registration and application, clinical research and commercial production.

CRO SERVICES



R&D Direction

Raw material enzymes, plasmids, mRNA, CircRNA, long chain nucleic acid drugs, nano-antibodies, recombinant proteins/polypeptides and many other categories

Service Contents

- Biological raw material development
- Lead screening and optimization
- Basic technology research in the field of gene therapy
- Quality research of biological products
- Preparation process development of microbial expression drugs
- Preparation process development of cell-related drugs (biosafety at BSL2 laboratory) and related quality research

mRNA CRO Services Platform

Yaohai Bio-Pharma sample preparation service platform of mRNA at a research level ("RNASci" mRNA) consists of four major technology modules: RNADes (mRNA structural design and optimization platform), RNASyn (mRNA synthesis and modification platform), RNAPur (mRNA purification platform), and RNAQua (mRNA quality analysis and control platform), which covers the whole life cycle of mRNA design to sample formation.

mRNA
service platform

PLATFORM TECHNICAL CONTENT	• 5' UTR and 3' UTR optimization design • CDS zone optimization design • PolyA tail optimization design	• mRNA template plasmid design and construction • Conventional mRNA (capping structure, PolyA tail structure) • Nucleotide modification (e.g. Φ, N1ψ, 5mC) mRNA synthesis	• LiCl precipitation and purification • Magnetic bead purification • Self-developed chromatography column process purification	• Purity detection system [AGE (agarose gel electrophoresis), CE] • (WB,ELISA)Translation expression detection system (WB,ELISA) • Capping rate detection system (TPI) • PolyA distribution detection system (TPI)
mRNA SERVICE PLATFORM	Platform for mRNA structural esign and optimization	Platform for mRNA synthesis and modification	mRNA purification platform	mRNA quality analysis and control platform
RNASci	RNADes	RNASyn	RNAPur	RNAQua

PLATFORM FEATURES

Highly Expressed Natural & Modified UTR

- Establishment of natural UTR library, and diversified UTR source selection to match the appropriate UTR sequence for different products;
- 5' UTR optimization for more efficient transcription of templates;
- Internationalized PolyA tail structural design strategy;
- Well-developed codon optimization methods and special optimization needs performed by the professional AI algorithm team.

Superior capping process for efficient transcription and improvement of application activity

- Highly productive and stable capping process with a capping efficiency of >95%;
- PolyA tail integrated transcription formation, with more uniform distribution;
- Diversified mRNA modified nucleotides to effectively reduce the adverse immune response of mRNA in human;
- Flexible plasmid template design scheme to meet customer' s specific needs.

General & self-developed chromatography process, providing diversified purification methods

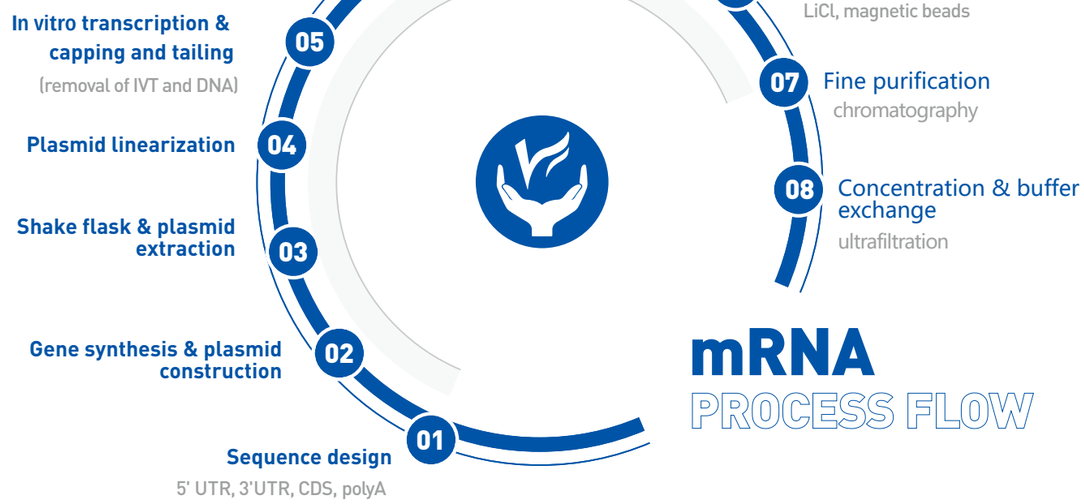
- Diversification:
  A comprehensive purification solution consisting of tangential flow filtration + multiple chromatography packing can effectively remove impurities from mRNA crude products for high quality applications;
- General & self-developed purification process:
  Well-developed and perfect LiCl precipitation + magnetic bead purification + chromatography purification solution;
  Completely self-developed, chromatography purification solution can effectively remove impurities in mRNA preparation.

Comprehensive quality control platform to meet the quality control needs of each research phase

- Meet the general QC requirements for scientific-grade concentration and purity;
- Meet the special QC needs such as mRNA translation test, capping rate, and tail distribution, etc.

One-stop Solution

ONE STOP SOLUTION >>> Sequence design and optimization >>> Gene synthesis >>> Recombinant plasmid preparation >>> Linearized template preparation >>> IVT >>> mRNA purification >>> mRNA quality control and analysis



CAPPING METHOD

Enzymatic method

Plasmid linearization, IVT, purification, capping, secondary purification

Co-transcription

Plasmid linearization, IVT (clean cap), purification

Service Details

Yaohai Bio-Pharma can not only provide various mRNA catalogue products, but also the customized synthesis service of mRNA at a scientific level, and the service content is continuously upgraded to meet different custom-tailored experimental or project needs.

Customized mRNA services

- Design and construction of mRNA template plasmids
- Classical mRNA (cap structure, PolyA tail structure) preparation
- Preparation of modified nucleotide mRNA (pseudouridine, N1-methyl pseudouridine, 5-methyl cytidine)
- Tandem expression of mRNA preparation services for two genes
- Other customized mRNA preparation services

mRNA catalogue products	Specification
mRNA-eGFP（(Transfection Control)	10μg/100μg/500μg
mRNA-1273 (Moderna Vaccine)	10μg/100μg/500μg
mRNA-162b2(Pfizer Vaccine)	10μg/100μg/500μg
mRNA-Luciferase（(Transfection Control)	10μg/100μg/500μg
mRNA-mCherry（(Transfection Control)	10μg/100μg/500μg
mRNA-IL2 (growth factor)	10μg/100μg/500μg
mRNA-IL4 (growth factor)	10μg/100μg/500μg
mRNA-IL22 (growth factor)	10μg/100μg/500μg
mRNA-OVA (Immune adjuvant)	10μg/100μg/500μg
mRNA-Cas9 (gene-editing tool)	10μg/100μg/500μg

QC standard

Supercoiled Plasmids

Test items	Test Method	Quality Specification
Plasmid concentration	UV detection	≥1mg/ml
Purity	UV260/280	1.8-2.0
Plasmid identification	Enzyme digestion	Matching the restriction enzyme fragments
Supercoil ratio	CE	≥85%
Endotoxin	USP<85>	＜10EU/mg
Residual host protein	ELISA	≤1%
Residual host genomic DNA	Q-PCR	≤1%
Residual host RNA	RT-PCR	≤1%

Linearized plasmids

Test items	Test Method	Quality Specification
pH	pH USP<791>	7.0±0.5（TE）
Appearance	USP<1>，USP<790>	Clear, and colorless
Plasmid oncentration	UV spectrometry	0.5-1mg/ml
Purity	UV260/280	1.8-2.0
Plasmid identification	Plasmid sequencing	Consistent with the reference sequence
Linearized plasmid ratio	CE	≥90%
Residual host protein	ELISA	＜10EU/mg
Residual host genomic DNA	Q-PCR	≤1%
Residual host RNA	RT-PCR	≤1%
Endotoxin	USP<85>	≤1%

mRNA

	Test items	Test Method	Quality Specification
Identification	pH	USP<791>	7.0±0.5（TE）
	Appearance	USP<1>, USP<790>	Clear, and colorless
	Sequencing	sanger	Consistent with the reference sequence
	RNA length	AGE	Molecular weight marker alignment
	RNA length	Capillary electrophoresis (CE)	Molecular weight marker alignment
Purity	A260/A280	UV detection	1.8-2.1
	Capping Efficiency	CE	＞95%
	Purity	CE	＞95%
	dsRNA	ELISA	＜0.006%
	Endotoxin	USP<85>	＜10EU/mg
	Residual Protein	CDE	≤1%

Service Advantages

01 Integrated service process

From front-end sequence design and optimization, Gene synthesis to terminal mRNA synthesis and quality control analysis

02 High quality structural design and optimization platform

Professional mRNA structural design and optimization, Facilitate efficient mRNA expression

03 Well-developed purification platform

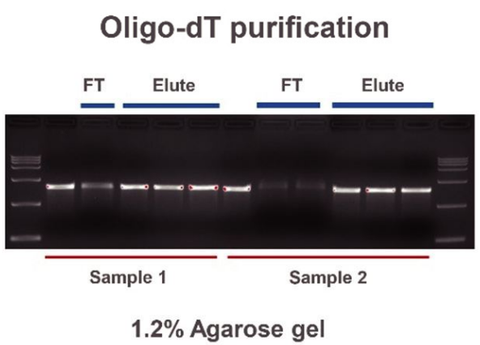
General & self-developed combination purification process Provide high quality mRNA preparation services

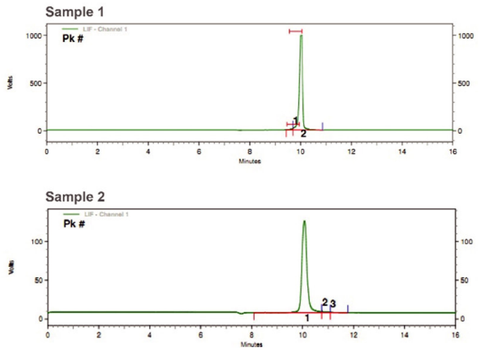
04 Catalogue products / customized mRNA

Flexible and diverse options, Meet the needs of different experiments/projects

mRNA Purification Cases and Cell Evaluation

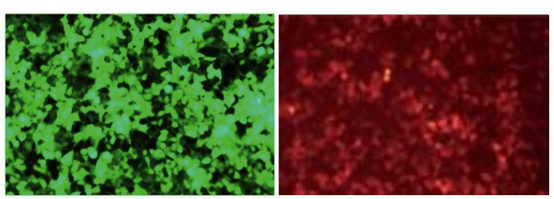
Provide various purification methods, including Yaohai Bio-Pharma's well self-developed chromatography purification process to prepare mRNA products with high quality and high purity according to the different project needs of customers for mRNA. The catalogue mRNA products of Yaohai Bio-Pharma are well expressed in cells.

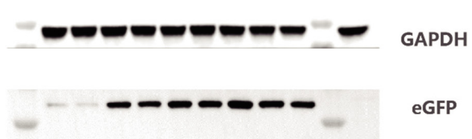




Removal of various small-molecule process-related impurities using Oligo-dT purification, with a catalogue mRNA product purity of >95%

The dsRNA in the catalogue mRNA products detected by the dsRNA detection kit (ELISA) is <0.006%





The well-expression of the catalogue mRNA product transfected with 293T in Yaohai Bio-Pharma

CircRNA Innovative Therapy CRO Services Platform

The CircRNA innovative therapy CRO services platform of The well-expression of the pre-made mRNA transfected with 293T in Yaohai Bio-Pharma contains four major technology modules: RNADes (CircRNA structural design and optimization platform), RNASyn (CircRNA synthesis and modification platform), RNAPur (CircRNA purification platform), and RNAQua (CircRNA quality analysis and control platform), which can realize an efficient preparation and purification of CircRNA, and provide the CRO services of CircRNA in vitro preparation with the whole process and high quality for universities and research institutions, etc.

CircRNA Scientific Research Level Sample Preparation

CircRNA structural design and optimization platform

- Cutting-edge “PIE” ring-forming technology, efficient intron and exon combination
- CDS, IRES optimization design

CircRNA synthesis platform

- CircRNA template plasmid design and construction
- CircRNA synthesis solution with a ring-forming rate of >80%

CircRNA purification platform

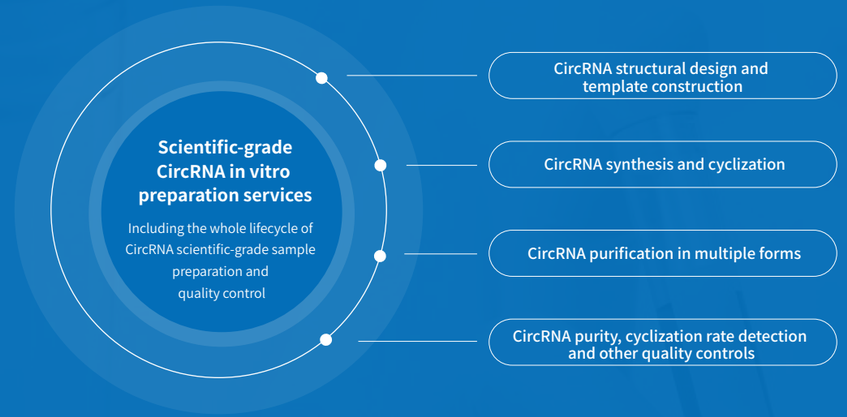
- Conventional experimental purification solutions
- Self-developed chromatography column purification process

CircRNA quality analysis and control platform

- Multiple purity testing solutions
- Testing solution with efficient ring-forming rate

Services

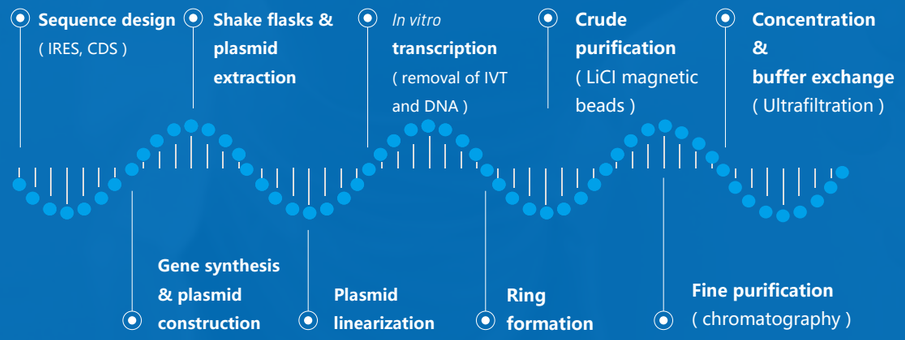
Customers provide gene sequences or amino acid sequences, and we will provide CircRNA customized services according to the actual needs of customers, including CircRNA sequence structural design and optimization, in vitro transcription template construction, CircRNA cyclization and purification, dimensionality, and cyclization rate identification, as well as catalogue CircRNA products with high quality and technical services for the researchers.



Catalogue CircRNA Products

Catalogue CircRNA Products	Specification
Circ-eGFP	10μg/50μg/100μg
Circ-luciferase	10μg/50μg/100μg
Circ-mCherry	10μg/50μg/100μg
Circ-OVA	10μg/50μg/100μg
Circ-IL2	10μg/50μg/100μg
Circ-Cas9	10μg/50μg/100μg

CircRNA Process Flow



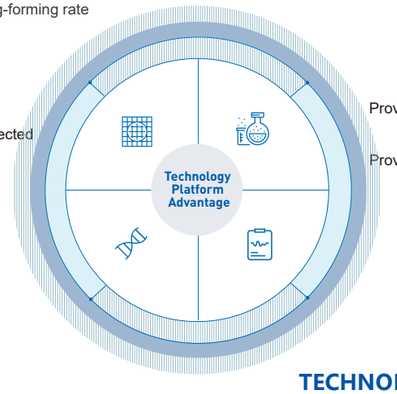
Technology Platform Advantage

STRINGENCY
Stringent quality control methods
Detection solutions with highly efficient ring-forming rate

STABILITY
One week after transfection of cells
Fluorescent protein expression can be detected
With high stability

HIGH EFFICIENCY
HPLC method
Validated by RT-PCR and other methods
With a cyclization rate of >80%

FLEXIBILITY
Well self-developed chromatography purification process
Diversified purification methods
Meet the needs of different experimental applications



STRONG PROCESS
CircRNA preparation service
with a size of 50-3000 nt

OMNI-DIRECTIONAL
Provide one-stop service from sequencing
to finished product
Provide linearized RNA cyclization service

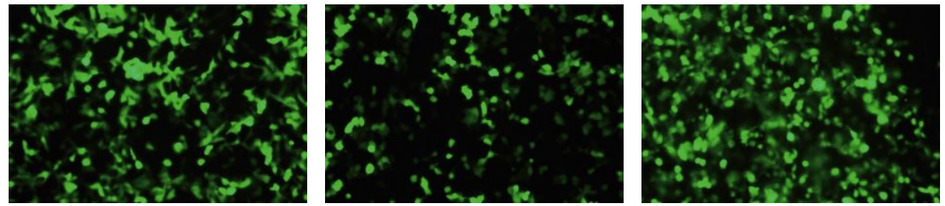
CUSTOMIZATION
Customized RNA cyclization service
according to customer requirements
Customization

TECHNOLOGICALLY ADVANCED
PhD-led senior technical team
Advanced experimental equipment and strict quality assurance team
Fast response to meet customer's delivery requirements

Case Study

Cellular Evaluation

CircRNA-eGFP prepared in vitro is efficiently and stably expressed, and strong fluorescence signal can still be detected one week after transfection of cells.



CircRNA - eGFP (24h)　　CircRNA - eGFP (48h)　　CircRNA - eGFP(72h)

Nano-antibodies CRO Services Platform

Yaohai Bio-Pharma's nano-antibodies CRO service platform is dedicated to provide customers with one-stop nano-antibodies R&D and production services from strain construction, multifunctional nanobodies expression and purification to large-scale production, which are efficient and flexible to meet customers' different experimental or project needs.

Full ecological recombinant expression system

E.coli prokaryotic expression system
Yeast eukaryotic expression system
Mammalian cell expression system

Diversified nano-antibodies types

Monodomain nanobodies
Bivalent nano-antibodies
Multivalent nanobodies

Well-developed and perfect purification platform

Complete purification platforms
Combination purification methods
Highly efficient and flexible

From μg to kg

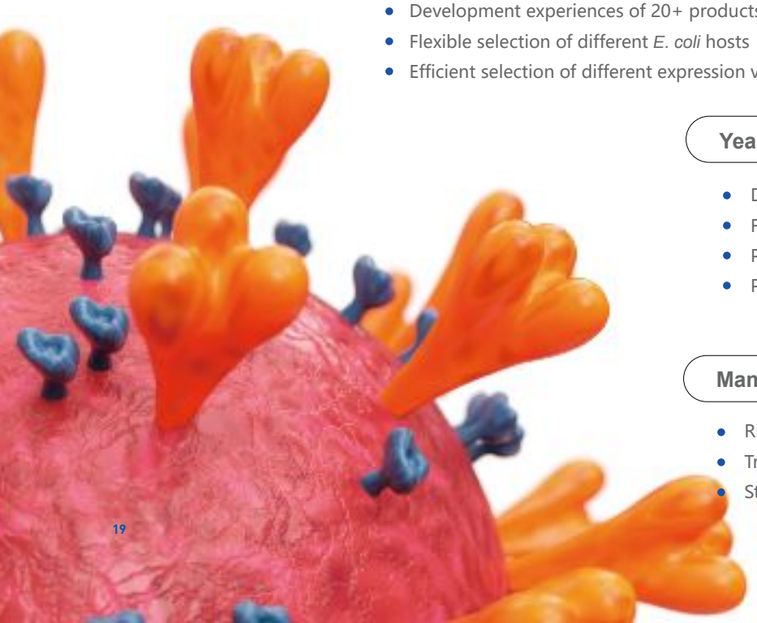
Nano-antibodies with a high expression of 10g/L
Production at a scale of 7-2000L

Full ecological recombinant expression system

At present, Yaohai Bio-Pharma has established a full ecological recombinant expression system for nano-antibodies. The existing expression systems include: *E.coli* prokaryotic expression system, yeast expression system (*pichia pastoris*), and mammalian cell expression system, and are skilled in using a variety of expression host strains to provide nano-antibodies with high quality according to the actual needs of customers.

E.coli prokaryotic expression system

- Development experiences of 20+ products
- Flexible selection of different *E. coli* hosts
- Efficient selection of different expression vectors



Yeast expression system *(pichia pastoris)*

- Development experiences of 20+ products
- Flexible selection of different *pichia pastoris* hosts
- PAOX1 methanol induced expression system
- PGAP constitutive expression system

Mammalian cell expression system

- Rich experience in nano-antibodies development of 5+ products
- Transient expression nano-antibodies
- Stable transformation strain expression nano-antibodies

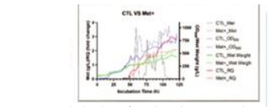
Nano-antibodies Expression CRO Services

The customer provides the gene sequence (or amino acid sequence) of the nanobodies, selects the expression host cells, and Yaohai Bio-Pharma provides one-stop gene synthesis to nano-antibodies expression, purification and production of a full range of customized nano-antibodies services.

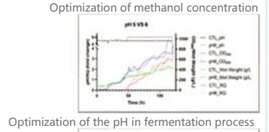
Steps	Service content	Period	Deliverables
Construction of nano-antibodies expressed engineering strains (selection from *B. aeruginosa, E. coli or* mammalian cells)	*E. coli* expression system (cytoplasmic or periplasmic space expression) *Pichia pastoris* expression systems (either methanol-induced expression system PAOX1 or constitutive expression system PGAP) Mammalian cell expression system (nano-antibodies expression by transient or stable transfection)	1 week - 2 weeks for *Escherichia coli* (excluding gene synthesis period) 2 weeks-3 weeks for *Pichia pastoris* 1 week - 2 weeks for transient mammalian cells, and about 2 months for sstable transformation strains	Purification of the obtained nano-antibodies, purification antibody assay report SDS-PAGE, SEC-HPLC (optional), RP-HPLC (optional) and CE-SDS (optional) purity analysis methods
Lab scale expression purification (labeling)	For the nanobodies expression of the constructed engineering strains, purify the protein for an expression volume of 1 L (labeling is recommended).	2 weeks - 3 weeks	
Large-scale expression purification	Large-scale fermentation of nano-antibodies samples, along with the expression purification of the fermented nanobodies.	5 weeks - 8 weeks	

Production process development » **Large-scale production** » **Purification system** » **Quality analysis system**

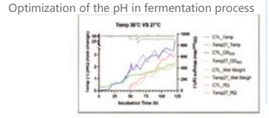
- To achieve the optimal fermentation conditions by single-factor optimization of methanol concentration and fermentation temperature and pH in the fermenter
- To achieve higher yields of expressed nanobodies fermentation liquid by optimizing the combination of optimal conditions for nanobodies fermentation.
- Rich experience in purification of nanobodies
- Flexible combination of various purification methods, such as affinity chromatography, ion chromatography, hydrophobic chromatography, etc.
- Quality analysis system assurance
- Diversified quality analysis methods
- Rich experience and purity assurance



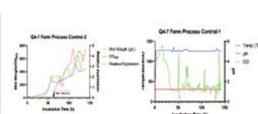
Optimization of methanol concentration



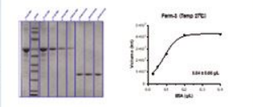
Optimization of the pH in fermentation process



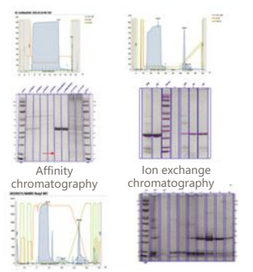
Optimization of the temperature in fermentation process



Fermentation process optimization



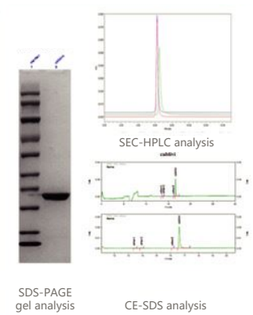
Nano-antibodies fermentation yield



Affinity chromatography

Ion exchange chromatography

Hydrophobic chromatography



SEC-HPLC analysis

SDS-PAGE gel analysis

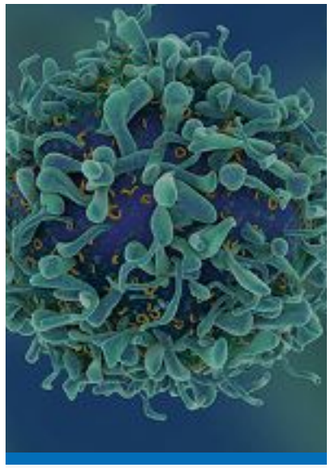
CE-SDS analysis

CDMO SERVICES

Yaohai Bio-Pharma, a CDMO services provider focusing on microbial expression system, can provide integrated one-stop biopharmaceutical end-to-end services, focalizing three major technology areas of recombinant proteins, nucleic acid drugs and nano-antibodies, with high efficiency and flexibility, provide CDMO services such as process development, IND-CMC pharmacological research, GMP production of clinical samples and registration application for global biotechnology companies, help customers to resolve the whole process from DNA to commercial production and jointly boost the process of new drug development.

Recombinant Proteins

One stop service platform for CDMO of comprehensive recombinant proteins and peptides



Nucleic Acid Drugs

Focus on plasmids, mRNA/CircRNA and other long chain nucleic acid drugs to accelerate the process from basic scientific research to clinical application

Nano-antibodies

Full domain recombinant expression system providing integrated and end-to-end nano-antibody CDMO services

One-stop CRDMO Services Platform

DRUG DISCOVERY	PRECLINICAL RESEARCH PHASE	CLINICAL RESEARCH PHASE	COMMERCIAL PHASE
Trial sample preparation services (mRNA、CircRNA、nano-antibodies)	Strain construction/ Cell bank construction Process development Process transfer Formulation development Analytical method development Preclinical sample preparation Registration application and consulting services Stability study Regulatory support	Process transfer Process scale-up Clinical sample production Stability studies Release testing Regulatory support	Process characterization Process validation Product production Stability studies Release testing Regulatory support
	・2L ・50L ・500L ・10L ・100L ・1000L ・30L ・200L ・2000L	・50L GMP ・500L GMP ・100L GMP ・1000L GMP ・200L GMP ・2000L GMP	・50L GMP ・500L GMP ・100L GMP ・1000L GMP ・200L GMP ・2000L GMP

Rich project experience

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

Professional team guarantee

With an experienced CDMO execution team, supported by gradient professionals, the entrusted project can be efficiently and collaboratively boosted.

One-stop service

Provide one-stop service from process development to commercial production

Compliance service guarantee

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

Comprehensive production line guarantee

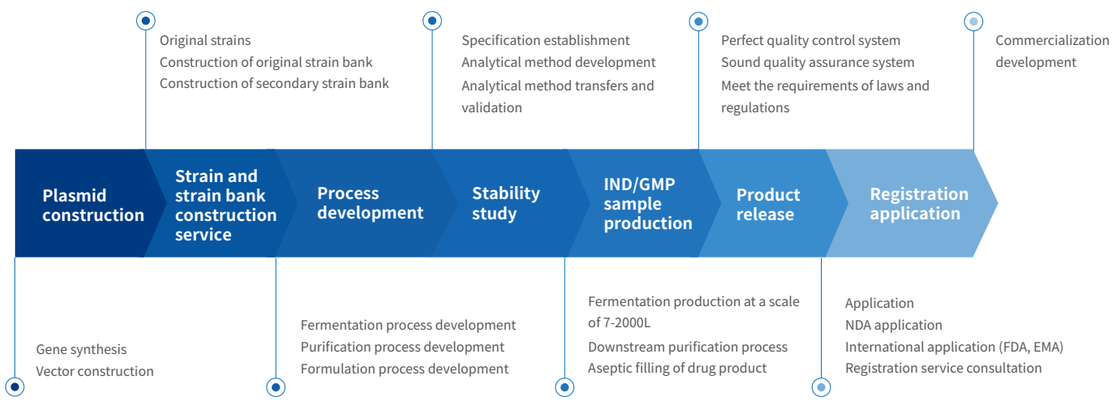
With an automatic fermentation system with a multi-scale of 2-2000L, high-quality and diversified fermentation purification services can be provided.

MICROBIAL FERMENTATION

RECOMBINANT PROTEIN CDMO SERVICES OVERVIEW

In the field of recombinant protein services, Yaohai Bio-Pharma can provide one-stop services of CMC for many types of recombinant proteins, including cytokines, vector proteins, recombinant polypeptides, enzymes, allergens, VLPs, vaccines and other types of recombinant proteins.

Recombinant Protein CDMO Services Cover The Full Cycle of Product Development



Types of Recombinant Protein Expression Services

Yaohai Bio-Pharma has an integrated CMC development and cGMP production process platform to produce recombinant proteins, plasmids, and DNA fragments using *E. coli* and yeast expression systems.

STRAIN CONSTRUCTION	LAB SCALE PROCESS DEVELOPMENT	PILOT SCALE UP AND PRODUCTION	QUALITY ANALYSIS AND CONTROL
Services	**Services**	**Services**	**Services**
• Gene synthesis • Plasmid construction • Strain construction • Vial target proteins and assays • Strain preservation and testing • Strain bank construction	• Optimization and verification of fermentation conditions • Scale-up and verification of 30L fermentation process • Purification process development, optimization and verification • Scale-up and verification of 30L purification process	• Analytical method development, validation and verification • Analysis and release testing of intermediate products and finished drug substances obtained during lab -scale • development and scale-up production Stability study • Provide release testing of strain bank and testing of raw materials and excipients	• Pilot-scale process optimization and scale-up production • Registration application batch production • Clinical phase I-III sample production • Industrialized production • Standard substance preparation
Service features	**Service features**	**Service features**	**Service features**
• Highly efficient screening of high expression strains within four weeks at the earliest • Selection of a variety of host strains and expression vectors, with codon analysis and optimization • One-stop service from gene sequencing to stable strain delivery by experienced technical team	• Provide optimization and screening of more than 10 parameters and complete fermentation process development within 1.5 month at the earliest • With various types of fermenters and bioreactors, fermentation of different vectors with high-density fermentation can be satisfied • Establish the evaluation, optimization and control strategies of fermentation and purification process parameters based on the concept of Quality by Design (QbD) • Build a high-throughput chromatography media screening platform and introduce DOE design for rapid process optimization	• With fermentation processes at a scale of 30L-50L-200L-1000L-2000L, matched by purification and drug product scale, the needs of different projects can be satisfied • 20+ pilot-scale up and production projects have been completed, including pilot-scale up, IND sample preparation, clinical phase I & II sample preparation, with extensive project experiences	• Rich experience in quality research, with several projects successfully passing on-site inspections by NMPA • The laboratory is equipped with a variety of chromatography techniques and assays to meet different types of compounds • With a perfect quality management system, the quality management and risk management throughout the whole process of experimental projects, as well as the compliance with the corresponding requirements of NMPA and FDA can be ensured

Advantages of Recombinant Protein Service Platform

01 Integrated recombinant protein process development capability

With comprehensive and diversified recombinant protein process development experience, including: recombinant polypeptides, cytokines, carrier proteins, recombinant enzymes, allergens, VLPs, vaccines, and other types of recombinant proteins.
Advanced process development concept. The critical quality attributes (CQA) of the product are studied to establish the critical process parameters (CPP) through DoE based on the requirements of QbD (Quality by Design), which are robust and meet the product quality requirements.
Well-developed platforming process. Well-developed label-free protein process development capability reduces the process steps, improves protein purity, and ensures the process impurities and residual product impurity conforming to the requirements. Platform-based process can rapidly response to the project needs and shorten the process development time.

02 Rich project experience

Rich experience in recombinant protein CRDMO services

More than 5 IND clinical approval letter.

More than 100 successfully serviced recombinant protein CMC projects

Professional team guarantee

Support by experienced and stable CRDMO services team, with extensive service experience and accumulated technical experience in multiple types of recombinant protein projects, and focus on process route innovation, quickly resolve process difficulties, and reduce R&D costs.

Professional PM project management team proficiently masters the project management of the whole life cycle of biologics development, can identify and manage the project critical path, identify, control and manage the project risks.

03 Comprehensive production capacity guarantee

Large-scale preparation service at a scale of 50L-100L, 200L, 500L, 1000L and 2000L, etc.
2 production lines of drug products (vial lyophilized powder/injection, pre-filled cartridge).

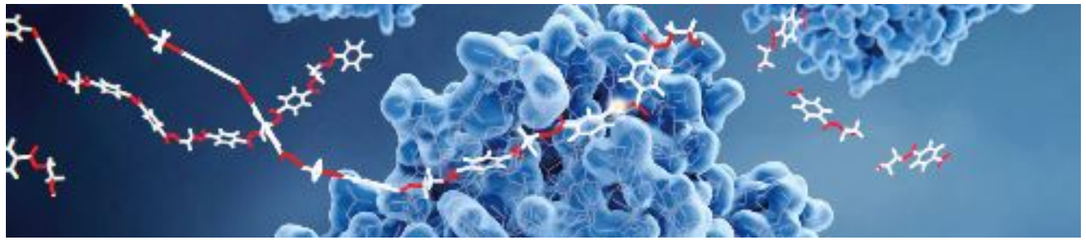
04 Perfect quality management system

Provide a full range of quality management service, with professional and standardized service guarantee system, and the whole cycle complies with the requirements of the new edition of pharmacopoeia and GMP related guidelines.

05 One-stop CRDMO services

Provide one-stop service from strain construction to commercial production, covering all stages of preclinical, clinical phase I, II, III and biologics production.

Cases of Recombinant Protein CDMO Services



Recombinant human interleukin-2 services

Target product: Recombinant human interleukin-2

Expression system: *E.coli*

Before process optimization

Before optimization, there were process problems such as low expression of the target protein, poor purification, and the result of bacterial endotoxin exceeding the requirement of pharmacopoeia (pharmacopoeia standard: it should be less than 10 EU per 1 million IU), and the in-house process was adjusted several times by the client, but still could not reach the expected target.

After process optimization

Yaohai Bio-Pharma adopted the *E.coli* prokaryotic expression system for the expression and purification of the target protein. After process optimization such as fermentation and purification:

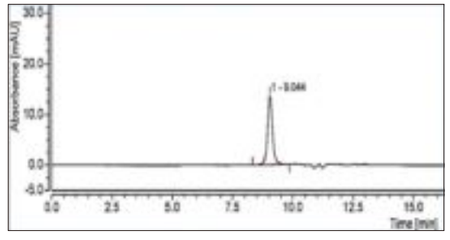
- Bacterial endotoxin <1EU/mg
- Purity>98%
- Yield of target protein>10mg/g cell

The process optimization was finally completed and successfully delivered according to the customer's requirements.

Relevant SEC-HPLC quality analysis

The results of SDS-PAGE analysis are shown in the figure

SDS-PAGE analysis



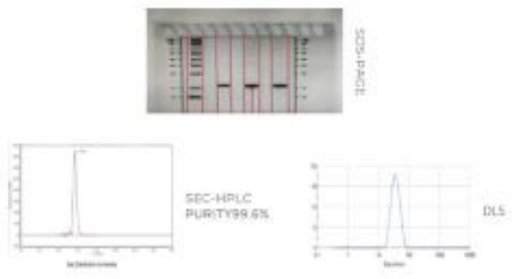
SEC-HPLC quality analysis

VLPs services

After process optimization

Based on Yaohai Bio-Pharma's well-developed recombinant protein platform-based process technology, the process optimization was completed quickly, which greatly shortened the R&D cycle and accelerated the project R&D progress, which was beyond the customer's expectation.

- Short process development cycle: process optimization can be completed within 2-4 months
- High success rate: platform-based process, with a success rate of 100%
- Bacterial endotoxin<1EU/mg
- Purity >99%

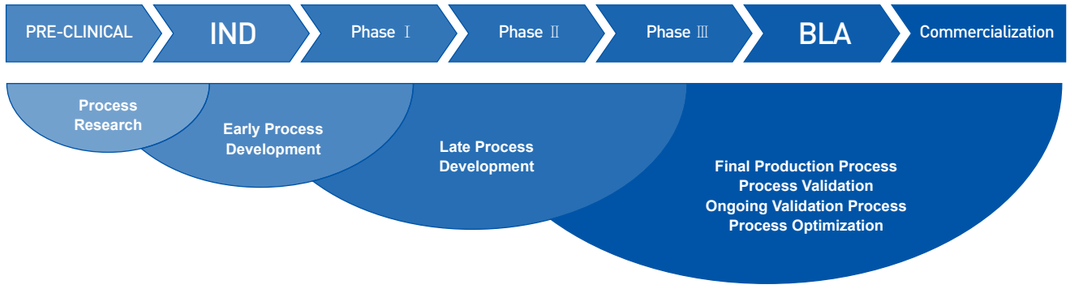


NUCLEIC ACID DRUGS

PLASMID CDMO SERVICES

Overview of Plasmid CDMO Services

Yaohai Bio-Pharma commits to provide one-stop plasmid CDMO services, has established a GMP-compliant circular plasmid production platform and a linearized plasmid production platform, with well-developed process development and GMP production experience, and can provide customers with integrated CDMO services from plasmid construction, strain bank construction, process development, quality methodology study, stability study, non-clinical research plasmid production to clinical plasmid GMP production and registration application, meeting the needs of plasmid services at different stages from 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

Plasmids at Different Levels

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

IIT

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

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

IND

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

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 plasmid process development platform of Yaohai Bio-Pharma adopts the concept of “Quality by Design (QbD)” and is equipped with comprehensive CMC process development and optimization, analytical method development and quality control capabilities, supporting the preparation of plasmid at research level under non-GMP and GMP-like conditions and providing plasmid vector services to 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/film package	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, automatic aseptic production of injection (vial), lyophilized powder and pre-filled cartridge can be achieved

02

Provide plasmid production at different scales from 30L-2,000L 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

Plasmid Process Development
GMP Production Process of Plasmids

Supercoiled plasmid process development flow

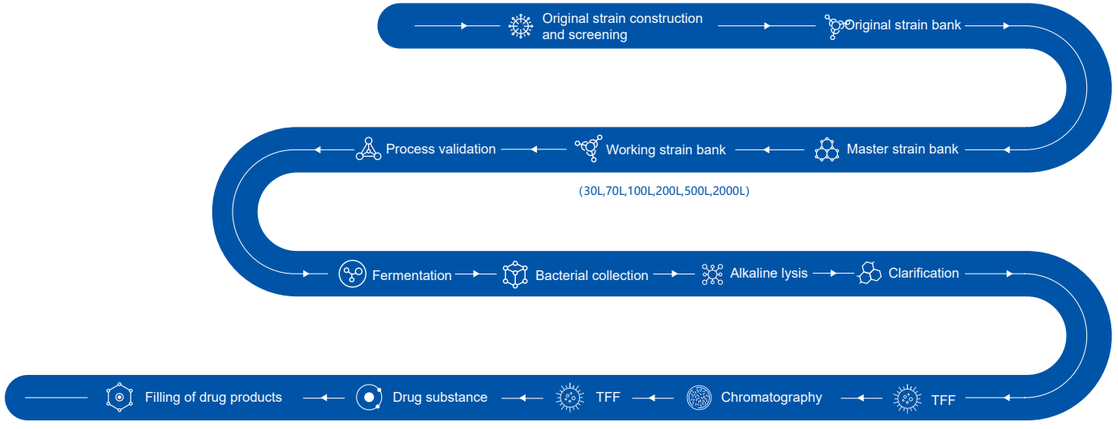
- Recombinant plasmids
- Genetically stable strain screening
- Tertiary strain bank construction
- Strain bank passaging and storage stability study
- Fermentation process development/optimization
- Purification process development/optimization
- Process scale-up study and validation

Application types bare 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

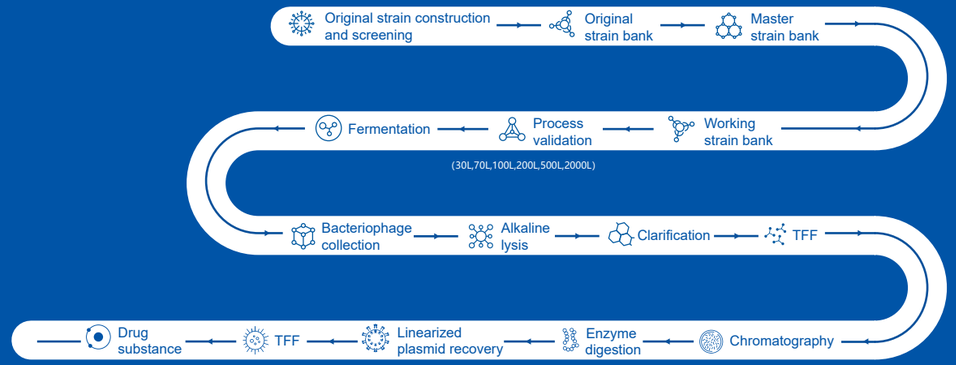
Development of plasmid project cycle	Month	1				2				3				4			
Milestones	Week	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Recombinant strain construction	4	●	●	●	●												
Tertiary strain bank construction and passaged stability	5					●	●	●	●	●							
Lab-scale plasmid development and verification	4						●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

Linearized Plasmid Process Development Flow

- Recombinant plasmids
- Genetically stable strain screening
- Three level of cell bank construction
- Cell bank passage and storage 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

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	●	●	●	●												
Tertiary strain bank construction and passaged 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

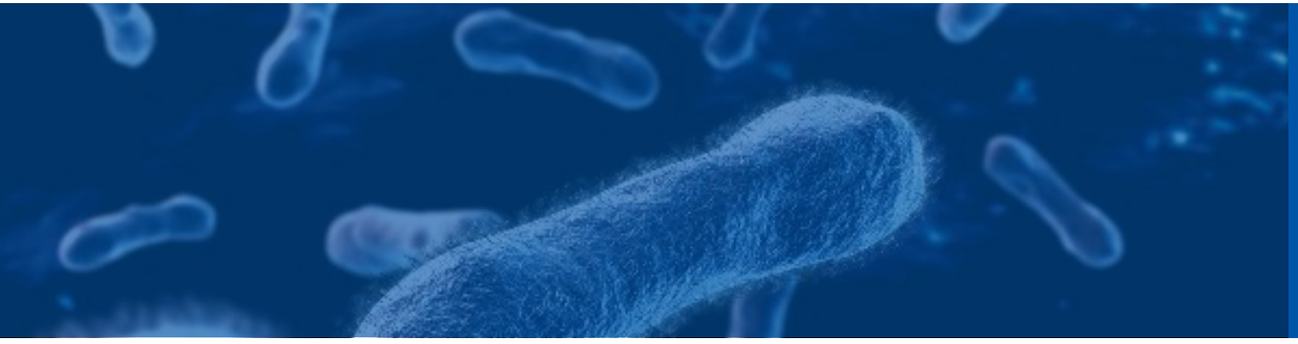
Test Items	Test Method	Specification
pH	pH determination method	7.2±0.5
Appearance	Visual method	Colorless clear liquid
Plasmid concentration	UV method	N/A
Plasmid identification	Sanger sequencing	Consistent with theoretical sequence
Plasmid assay	Restriction nuclease method	Consistent with the theoretical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

Test Items	Test Method	Specification
Residual host genomic DNA	Q-PCR	＜0.2%
Host pre-white residue	ELISA	＜0.1%
Residual host genomic RNA	qRT-PCR	＜50μg/mg
Endotoxin	Gel method	＜10EU/mg
Antibiotic residues	ELISA	＜50ng/mg
Sterility	Direct inoculation/ film filtration	Meet the requirements

Linearized plasmids

Test Items	Test Method	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%

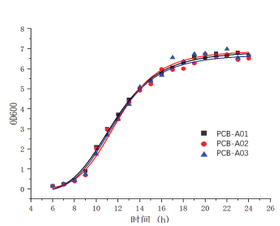
Test Items	Test Method	Specification
Residual host genomic DNA	Q-PCR	＜0.2%
Host pre-white residue	ELISA	＜0.1%
Residual host genomic RNA	qRT-PCR	＜50μg/mg
Endotoxin	v	＜10EU/mg
Antibiotic residues	ELISA	＜50ng/mg
Microbial limits	Direct inoculation method/film filtration method	Conformity
Poly A length(Optional)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



Plasmid Case Study

Good strain stability

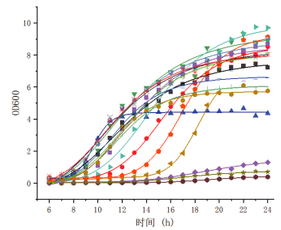
Primary Cell Bank (PCB) growth curve



PCB growth curve

Achievable DoE design of fermentation process

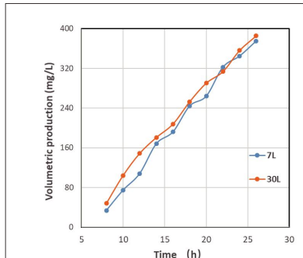
DoE design of medium screening



fermentation strain growth curve

Good stability and scalability

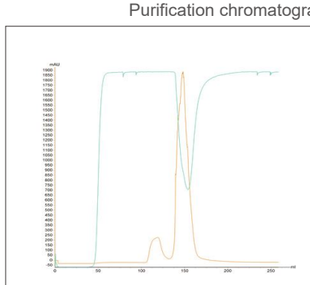
3 batches of plasmid yield at different fermentation scale of 7L and 30L



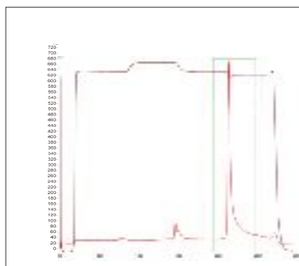
fermentation plasmid yield

Three-step / Two-step Purification Process

Purification chromatogram



plasmid purification:
Bastarsose 6FF chromatogram



plasmid purification:
PlasmidCap HP chromatogram

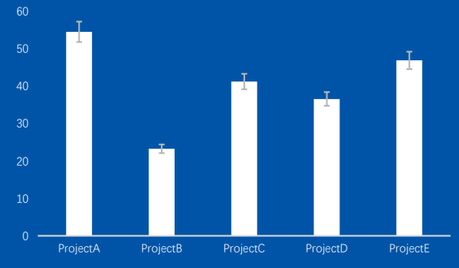
Plasmid Purification Platform

Recovery 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

NANO-ANTIBODIES

CDMO SERVICES

Nano-antibodies Full Ecological Recombinant Expression CDMO Services Platform

Yaohai Bio-Pharma has a complete one-stop technology platform and CDMO overall solution for nanobodies, which can provide customers with the whole life cycle services from genetically engineered strain construction, establishment of strain bank, lab-scale process development/optimization, pilot process scale-up, IND application and clinical sample preparation, quality specification establishment, analytical method development/verification, quality management system establishment, NDA registration application and commercial production. Life cycle services, supported by the production platform from lab-scale, pilot-scale to large-scale, with a series of services such as process and method development and verification, equipment verification and quality control, and quality research, etc., can meet the cooperation needs of customers from early drug findings, clinical research to marketing at commercial scale.




Plasmid Construction

Gene synthesis
Vector construction

Strain and Strain Establishment Services

Original strains
Original strain bank construction
Secondary strain bank constructio

Process Developmen

Fermentation process development
Purification process development
Drug product process development

Stability Study

Specification establishment
Analytical method development
Analytical method transfers and verification



Registration and Application

IND application
NDA application
International application* (FDA, EMA)
Registration service consultation

Product Release

Perfect quality control system
Sound quality assurance system
Meet the requirements of laws and regulations

IND/GMP Sample Production

Fermentation production at a scale of 7-2000L
Downstream purification process
Aseptic filling of drug product

Advantages of Nano-antibodies Services

Advanced Process Development Concept

- A stable process with high output and yield can be achieved by determining the critical process parameters (CPP) with CQA (critical quality attribute) as the starting point obtained through DoE based on the concept of quality by design (QbD).

Rich project experience

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

Professional team guarantee

- Support by experienced and stable CDMO services team, with rich service and accumulated technical experiences in multiple categories of recombinant protein projects, and focus on process route innovation, quickly resolve process difficulties and reduce the R&D costs
- Professional PM project management team proficiently masters the project management of the whole life cycle of biologics development, can identify and manage the project critical path, identify, control and manage the project risks

Comprehensive production capacity guarantee

- Large-scale preparation services at a scale of 50L-100L, 200L, 500L, 1,000L and 2,000L
- 2 production lines for drug products (vial lyophilized powder/injection, pre-filled cartridge)

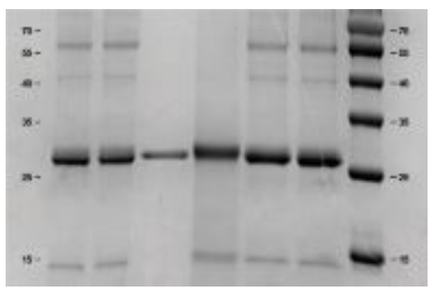
Perfect quality management system

- Provide a full range of quality management service, with professional and standardized service guarantee system, and the whole cycle can comply with the requirements of the new edition of the pharmacopoeia and the GMP related guidelines, to continue to deliver products with stable quality for customers.

One-stop CDMO services

- Deliver one-stop service from strain construction to commer-
cial production, covering all stages of preclinical research,
clinical phase I, phase II, phase III and biologics production.

Nano-antibodies Case Study



Objective

Purity ≥95%; endotoxin <50EU/mg protein.

Developed a two-step chromatography method

Affinity chromatography: affinity using A3, with a purity of up to 94.1%;
Anion exchange chromatography: using 50HQ, with a yield of 73.9%,
and a purity of 98.1%

The process target requirements were met after testing the endotoxin.

DRUG SUBSTANCE

PRODUCTION

Service Capacity Guarantee

Industrial Scale Guarantee

Production services of drug substances at a scale of 50L-100L, 200L, 500L, 1,000L, and 2,000L to meet the needs of different projects

Rich Technology Transfer Experience

Comprehensive and perfect technology transfer process and risk control system

Compliance Assurance

Well-established quality management system in compliance with the requirements of NMPA/FDA and EMA, and experienced quality management team

Powerful Data Management

More than 80% of production lines are intelligently operated

GMP Production and Quality Control Service Platform — Overview of Drug Substance Production

With the capability of one-stop entrust manufacturing service, Yaohai Bio-Pharma can provide customers with the services of preclinical, clinical and marketed drug production. There are five production lines of drug substance designed based on QbD, and in compliance the GMP requirements of NMPA, FDA and EMA, which can provide bioreactors at various sizes of 50 L-100 L, 200 L, 500 L, 1,000 L and 2,000 L to support customers' production needs at different stages of development. Relying on the international advanced production equipment, flexible production line configuration, and high standard quality system, the new drug development process of the customers can be efficiently promoted.

Service Items

Strain construction under GMP system	Pilot process optimization and scale-up production
Preparation batch production ofsamples for IND registration and application	Production of samples at clinical phase I-III
Industrialized production	Preparation of standard substances

GMP production of drug substances with high productivity and flexibility

- GMP-compliant production area for drug substances at an area of more than 10,000 square meters
- GMP-compliant fermentation service platform at a various scale of 50L-100L, 200L, 500L, 1,000L and 2,000L
- Independent upstream and downstream production areas, supported by fully functional upstream and downstream process equipment
- Upstream: 5 production lines for drug substances, with a production capacity of 7,500L, and equipped with fermenters at different specifications
- Downstream: 5 purification production lines, equipped with low, medium and high chromatography and ultrafiltration systems, covering a wide process scale
- The plant has been reasonably designed, with qualified air conditioning system and water system (4Q) to deliver a GMP-compliant production workshop
- Advanced equipment (sourced globally) is all qualified (3Q), with PQ available; the instruments and gauges are all completely calibrated
- Supported with compliance QA, operation QA and verification team to ensure efficient implementation of quality system

DRUG PRODUCT **PRODUCTION**

GMP Production and Quality Control Services Platform

—— drug product production

Production Services of Sterile Drug Products

For the production of sterile drug products (DP, Drug Product), Yaohai Bio-Pharma has built a production workshop for drug product at an area of 2000 ㎡, which can provide automated production services for sterile drug products in accordance with GMP requirements, and is a high-tech automatic production line integrating multiple processes such as vial washing, oven, sterilization (depyrogenation), filling, lyophilization and capping. The production line meets the requirements of sterile drug products for China NMPA, EU EMA and US FDA. Yaohai Bio-Pharma is experienced in the production of sterile biological drug products and delivers high quality production services from clinical sample production to commercial production of vials and pre-filled cartridges.

For vial injections, the maximum annual output is 10 million
For vial lyophilized powder, the maximum annual output is 5 million

For pre-filled vials and cartridges, the maximum annual output is 8 million

IND, clinical phase I/II/II and commercial production

Comprehensively designed production line for injections, lyophilized powder and pre-filled vials

Category of products to be filled: recombinant proteins, polypeptides, plasmids, antibodies, vaccines and other mainstream biological products

Production line of vial injection and sterile lyophilized powder drug product

Filling Range

- 1ml-25ml

Aseptic Production Line

- Product (and package material) exposure area are equipped with O-rabs system under Grade A environment protection
- Fully automatic loading and unloading system
- Fully automatic SIP/CIP system for the lyophilizer
- Equipped with online ammonia applying system for nitrogen protection
- PMS online monitoring system

Filling Accuracy

- Filling with a very high accuracy: (the filling medium is water for injection) ±0.25%

Filling Speed

- Take an example of 2 mL of vials, the maximum production speed is 300 vials/min, and the maximum lyophilized powder batch size is 37,800 vials/batch

Production line of pre-filled sterile drug product

Filling Process

- Equipped with plunger pump, peristaltic pump, and double pump system, different process needs can be satisfied.

Filling Range

- Pre-filled vials, 1 mL and 3 mL, cartridge, 3 mL

Filling Accuracy

- The filling accuracy is within ±3% for 0.2 mL to 0.5 mL
- TThe filling accuracy is within ±2% for 0.5 mL to 3 mL

Aseptic Filling

- A variety of filling methods (typical filling, filling by applying nitrogen, vacuum filling)
- Vacuum stoppering method, suitable for multiple types of stoppering process requirements
- O-rabs system is applied in the product exposure areas (and packaging materials) with Grade A environment protection
- Ergonomic glove port settings can minimize the impact of interventions on the product
- With PMS online monitoring system, the production environment status can be real-time monitored and the environmental abnormalities can be rapidly detected.

Production Capacity

10 Million Vials	5 Million Vials	8 Million Vials
(annual production)	(annual production)	(annual production)
Specification 1ml-25ml	Specification 1ml-25ml	1ml-3ml
Vial Injection	Vial lyophilized powder	Pre-filled Vial/cartridges

QUALITY RESEARCH PLATFORM-QC

QC-Quality Control System (GMP)

Based on the rich experience in GMP quality management, Yaohai Bio-Pharma provides customers with continuous and stable quality services through a close cooperation among the quality control (QC) team, the production and quality assurance (QA) team in the areas of testing of raw materials and excipients, intermediate process control, stability study and product release testing of biological drug product. Meanwhile, Yaohai Bio-Pharma established a sound quality control system, in compliance with the regulatory requirements, with certified quality system throughout all phases of QC testing

Service Content

Analytical method transfer/ verification/validation

Strain bank release testing, passaging stability, and storage stability

Raw materials and excipients release testing

Testing and standardization of self-made standard substances

Releasing testing of intermediate products, drug substances, semi-finished products, and finished products

Stability study

Service Features

- Equipped with advanced quality analysis testing instruments
- The QC team has undergone strict GMP training and guidance and is familiar with the newly revised GMP requirements
- Skilled in physical, chemical, biological and microbiological quality control testing methods
- Rich experience in project execution
- In addition to the current scope of testing, the testing capabilities is continuing to be expanded

Bioanalytical Testing Services

At present, Yaohai Bio-Pharma has established a perfect quality testing platform in terms of physicochemical, microbiological and biochemical testing, with well-established quality control methods for different products according to their physicochemical characteristics, which can meet the release testing of biological products (recombinant proteins, polypeptides and plasmid products) and support the analysis and quality control needs of the life cycle of biological drug products.

Classification	Biochemical Testing Items	Physical And Chemical Testing Items	Microbial Testing Items
Testing items	Expression of target product	Appearance	Plasmid loss rate
	Plasmid restriction digestion mapping	PH	Seeding LB plate
	Protein content	Visible foreign matter	Staining microscopy
	Purity	Loading	Viable bacteriocins
	Molecular weight	Particulate matters	Antibiotic resistance
	Activity test	Osmolality	Biochemical reaction
	Exogenous DNA residue	Water	Residual antibiotic
	Residual host bacterial proteins	Density	Bacterial endotoxin
	Isoelectric point	Residual organic solvent	Microbial limits
	UV spectroscopy	Optical rotation	Sterility
	Polypeptides mapping		
	Identification		

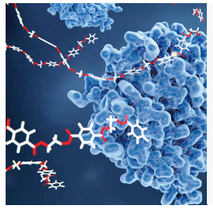
Testing Capability

At present, a variety of conventional items can be tested, with about 30 testing items, and 50 testing methods available, and the testing service capabilities is continuing to be improved.

30+ Test Items

50+ Test Method

Service Capacity Guarantee



Recombinant Protein Project Service Experience

100+ recombinant protein projects have been successfully served, including several PEG-modified protein projects and enzyme-based product projects, with extensive experience in the full testing of recombinant protein projects.

VLPs Vaccine Project Experience

VLPs vaccine testing on multiple projects have been successfully implemented, with proficiency in the quality specification and test items of VLP particles.

Stability Study

Dozens of individual stability study projects have been successfully conducted.

Experience In Plasmid Projects

Many projects with therapeutic plasmids and viral vector products have been served, with accumulated extensive experience in HCD and HCR assays for critical projects.

Analytical Method Verification/Validation

150+ analytical method transfer/verification/validation activities have been completed.

QUALITY RESEARCH PLATFORM - QA

Service Capability Guarantee

Quality management is the lifeline of Yaohai Bio-Pharma. Yaohai Bio-Pharma provides a full range of quality management service, adheres to the goal of customer satisfaction, establishes a quality policy of “quality-oriented, perfect compliance, simple efficiency, unity and cooperation” , and is committed to providing sample preparation of IND and clinical phases to meet the requirements of FDA, EMA, and NMPA, and satisfies the comprehensive quality management services for the commercial production of drug products required by NMPA.

Establishment of Comprehensive Documentation System for Ten Systems

quality management	organization and personnel	premises and facilities	equipment management	materials and products
validation and verification	document management	production management	quality assurance	laboratory management

Establishment Principles of Quality System

The quality system covers the whole life cycle of a drug product from development to commercial production.

The quality system is based on the existing laws and regulations at home and abroad, and complies with the laws and regulations requirements of CMC (Chemistry, production and control) activities.

Meanwhile, it is combined with the characteristics of CDMO business to maintain a certain degree of flexibility and meet the high expectations of customers for contract manufacturing.

Document Assurance System

Yaohai Bio-Pharma establishes a comprehensive document assurance system, which is based on GMP requirements and closely follows the company's business model to ensure that all GMP activities of the Company are covered.

Management Policy	POL
Standard Operating Procedure	SOP
Process flow, specification, inspection procedure	STP
Record, the numbering follows therequirements of SOPs and STPs, with independent review and approval process	Form

Regulatory Support

The Company engages a well-known third-party GMP consulting company at home and abroad at irregular intervals according to the business needs, to perform consulting and improvement activities on the Company’ s quality system to ensure continuous improvement. In addition, the Company has employed experts with FDA background as consultants to assist in resolving issues arising during the operation of the quality system in a timely manner.

Global

Measures for Administrative of Drug Registration, Good Laboratory Practice for Pharmaceuticals, ICHQ5, Q8, Q9, Q10, Q12, Good Clinical Laboratory Practice, and Good Manufacturing Practice

Globalized

REGISTRATION & APPLICATION SERVICES

Service Overview

01 With an extensive drug registration and application team, high-quality, efficient and accurate registration support can be provided, including domestic and international IND/BLA application services.

02 The comprehensive registration and application services include CMC consulting services, guidance on registration and application strategy, assistance in completing the writing and submission of CMC-related CTD documents, assistance in communication with official agencies, guidance on site verification for development and research, organization of drug registration regulations training and conference guidance, etc.

03 With in-depth research and understanding of domestic and foreign registration-related regulations, comprehensive guidance on regulatory strategies for clients throughout the product development lifecycle can be provided.

Service Content

Registration Services

- Dedicated to CMC regulatory consulting services
- Provide guidance on CMC strategy development and gap analysis for domestic and international registration applications
- Assist in communication with regulatory agencies, assist in response to approval comments and submission of supplemental information
- Convene scientific consultation meetings

Regulatory Support Matrix

- Global regulatory research for drug regulatory agencies
- Regulatory strategy & implementation guidance
- Sorting and interpretation of general regulations and special regulations
- Routine regulatory consultation throughout the year
- One-on-one regulatory consulting
- Project management

Writing of CMC Registration Dossier

- Writing of IND and NDA registration dossier
- Flexible and customized writing services of registration dossier

On-site verification

- Guidance on preparation of verification materials
- Guidance on the development of on-site verification

Other value-added and Special Services

- Project demonstration in the process of technology development or transfer
- Process analysis on IND/NDA registration strategy
- Research and evaluation of case-by-case drug product

Service Advantages

Professional Team Guarantee

Core members have more than ten years of experience in drug registration and project management, with multi-module expertise, rich professional operation experience, and strong professional support guarantee from domestic and foreign experts.

Rich Project Operation Experience

More than 200 clients have been served, covering a wide range of project types, with rich project experience, accurate grasp of regulatory guidelines, review requirements and critical points of drug registration, to predict the important and difficult points of the project in advance, which greatly enhances the project efficiency.

Real-time Information Sharing

Through familiarity with the perfect communication channels with official authorities, grasping the latest regulatory trends in real time, and fully understanding the laws and regulations of regulatory agencies, the real-time information sharing can be realized with customers based on sufficient information integration and analysis with a powerful database of regulations and document templates.

Full Life-cycle Service Management

With a one-stop service chain advantages of establishment of R&D system, registration and application of IND and NDA projects, and project management, the management concept of the whole life cycle of drug products is applied throughout the project.

Perfect Project Management Services

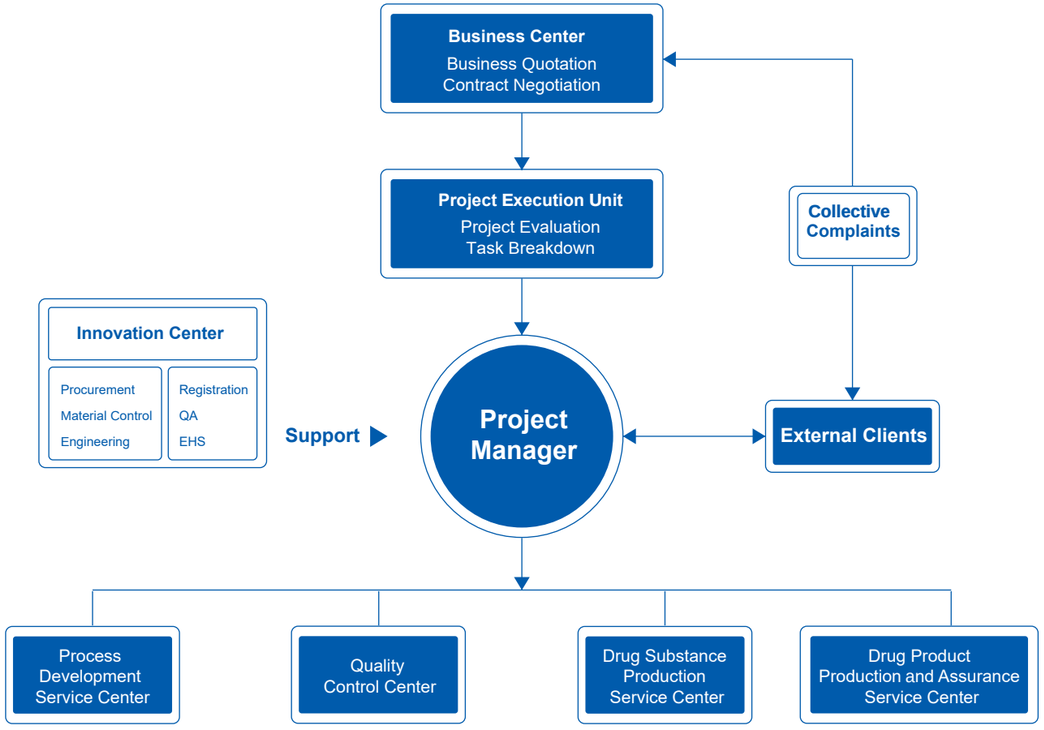
Provide planning and guidance services for the whole life cycle of each overall project, put forward feasible suggestions, focus on risk management and control budget, closely integrate with the actual situation of the project, develop implementable solutions and ensure the quality of the project.

Project Management & Service Process

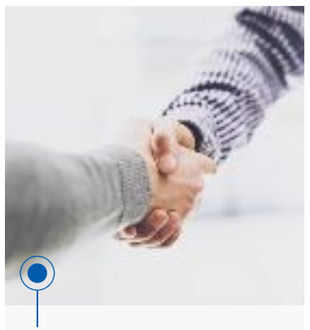
313 SERVICE SUPPORT MODEL

“313 service support model” is adopted to provide strong implementation guarantee for project operation
Implement three-cycle supply chain guarantee based on procurement center, material control center, and engineering center
Strengthen the innovation center to support technical guarantee
Three-cycle compliance guarantee based on registration department, QA and EHS
Thus to jointly maintain the project with high quality.

Service Guarantee

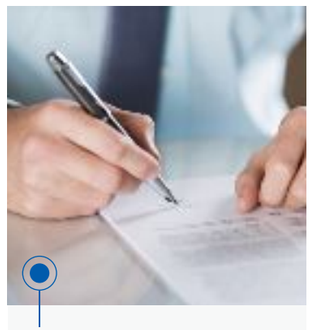


Service Process



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

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

CHOOSE YAOHAI BIO-PHARMA

Rich 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 Guarantee

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 2-2000 L.

Compliance Service Guarantee

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

Provide customized services to meet the needs of different types of projects and provide quality and efficient services to clients.

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