Hitston

Hitston Oligonucleotide CDMO Services

About Hitston

Hitston Ltd., a subsidiary controlled by HitGen Inc., is an integrated service platform for the pilot-scale and commercial production of oligonucleotides. By the end of 2023, the company had invested nearly 100 million RMB to build and operationalize a dedicated oligonucleotide GMP Facility with 2,000m^2 and a dedicated quality control laboratory with 1,000m^2. Collaborating with HitGen's dedicated nucleic acid chemistry R&D laboratories with total area more than 2,000m^2, Hitston currently offers CDMO services of oligonucleotide active pharmaceutical ingredients (APIs) from preclinical to commercial production. These services meet the demands of IND filing, Phase I to Phase III clinical trials, as well as commercial production on 100g to kg scale.

Oligonucleotide GMP Facility
> 2000 m^2

Quality Control Laboratory
> 1000 m^2

Nucleic Acid Chemistry R&D Laboratories
> 2000 m^2

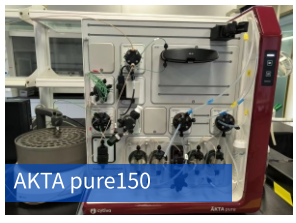
Oligonucleotide CDMO Services

Process Development and Optimization

Professional team: The oligonucleotide process development team at Hitston is more than 100 dedicated chemists. The core members hold doctoral degrees and possess more than 12 years of experience in oligonucleotide synthesis. The team have rich experience in R&D, pilot production and commercial production. The team leaders are overseas returnees with more than 12 years' experience in oligonucleotide R&D and full industrial chain operations, and have been recognized as provincial or municipal outstanding talents.

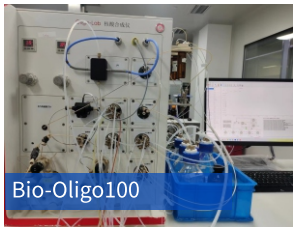
Equipment: The company have several nucleic acid synthesizers, purification systems, tangential flow filtration (TFF) desalting equipment, and UPLC/UPLC-MS. The equipment supports process development for several projects at the same time.

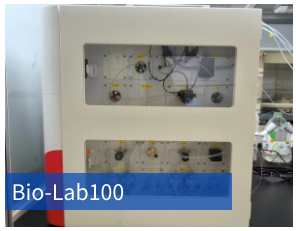

Oligopilot™ 100 plus


AKTA pure150


AKTA flux s


Acquity UPLC H-Class plus


Bio-Oligo100


Bio-Lab100


Bio-TFF100


Waters xevo G2-XS-QTof

Professional skills: Process development and production of phosphoramidite monomers (novel starting materials), supports, and bioconjugates. Process development and validation for oligonucleotides. Cover a wide range of nucleic acid molecule types, such as ASO, siRNA, aptamer, CpG, conjugation, and so on. Various modified monomers, such as 2'-H, 2'-OH, 2'-F, 2'-OMe, 2'-OMOE, 2'-C16, LNA, cEt, UNA, GNA, TNA, vinyl-phosphate, and amino/thiol/hydroxyl monomers, as well as delivery molecule, such as modified with GalNAc at 3'-position and 5'-position, cholesterol, etc.

Analytical Method Development and Validation

HitGen group has two NMRs (600 MHz and 400 MHz) and tens of HPLC, UPLC, UPLC-PDA/Qda/RI/ESLD/FIR, LCMS, MSMS, QTOF, and GC-FID/ECD/MS. These instruments enable rapid method development and validation for raw materials, intermediates and oligonucleotides. The methods cover impurity identification and quantification, purity, molecular weight, sequence confirmation and so on, which ensure the quality of the product meets the requirement in different scenarios.

The company's high-precision instruments, such as automatic potentiometric titrators, infrared spectrometers, ultraviolet spectrometers, polarimeters, and melting point apparatuses, can be used to conduct physicochemical property tests including LogD, LogP, pka, thermodynamic solubility, kinetic solubility, solution stability, content, residual solvents, elemental impurities, mutagenic impurities, moisture, pH, bacterial endotoxins, and microbial methods development and validation. Additionally, the company has a management system that includes the EMPOWER network-based electronic chromatography data management system, the UNIFI network-based electronic chromatography mass spectrometry data management and processing system, 3Q validation of precision instruments, annual third-party metrological calibration of precision instruments, online backup management of electronic data databases, specialized account login and multi-level permission management for precision instruments, and dedicated R&D QA supervision. This system complies with the regulatory requirements for both NMPA and the US FDA.

Purity analysis and structure characterization


HPLC


LC-MS


KF

Polarimeter


UPLC-MS


IR


XRD(D8)

NMR(400M,600M)


GC-MS


ICP-MS

Chiral and achiral purification on mg- g scale


Ana-SFC


Prep-SFC


Prep-HPLC


MS-directed Prep-HPLC

Impurity analysis


LC-DAD-MS-ELSD-FLD-RID


HRMS(Q-ToF)


LCMS/MS(TQS)

Stability Research

The company currently possesses four German Binder stability test chambers, which enable online real-time monitoring of temperature and light intensity, as well as remote audio-visual and mobile phone alerts for abnormalities. These chambers can meet the various temperature, humidity, and light requirements recommended by ICH guidelines, covering stability testing needs for ultra-low temperature, low temperature, room temperature, high temperature, high humidity, and comprehensive light intensity conditions.

Formulation, Sterile Filling and Lyophilization

The formulation development and production of Hitston is part of a one-stop oligonucleotide drug CDMO platform. There are 3 cGMP-compliant sterile formulation production workshops, which have passed the audits by NMPA, US FDA, and EMA.

- The facility employs a single-use liquid preparation and filling system, equipped with both vial filling and pre-filled syringe filling production lines. The vial filling and stoppering machine are operated in a B+A grade environment. And the filling and stoppering in isolators.
- The production line can flexibly adjust batch sizes meeting different requirements and the minimum batch size is ~ 500 mL.
- The liquid preparation system is equipped with one 100 L of preparation tank, one 60 L of transfer tank, and one 100 L of sterile receiving tank. Each tank can be performed online weighing, temperature control, and nitrogen protection, and can also be used sterile feeding methods to meet different processes.
- The filling machine is equipped with six pump heads, with a production speed of up to 120 vials per minute, and a general filling control range of ±3%.
- The pre-filled syringe filling machine is equipped with 10 filling needles and sampling-type online weighing, with a general filling control range of +5%, and a filling range of 1~ 10 mL, meeting the production needs of oligonucleotide formulations in vials or pre-filled syringe packaging.

Also, a grade C clean workshop with a water-for-injection (WFI) system was built, which ensure the environment under good control during production.

- Additionally, the company has invested over ten million yuan in a customized integrated filling system with an isolator. This system enables lyophilization and filling of APIs to be conducted under grade A conditions, meeting the sterile requirement. Furthermore, due to the strong hygroscopicity of oligonucleotide, the system can perform filling according to customer's specifications, avoiding the quality risks associated with repeated opening and use of APIs.
- The system is also capable of aseptic filling of drug product for early-stage clinical trials and the batch size of filling is approximately 3,000 vials per batch.

The integrated sterile filing and lyophilization system

IND Dossiers Preparation

- Preparation of CTD IND dossiers of Module 2 (quality overall summary, QOS) and Module 3 (quality) under the guidance of ICH M4Q (R1).
- Prepare the Summary of CMC Research Information of Chemical Drug for Phase I Clinical Trial Applications.
- Prepare other CMC related dossiers.

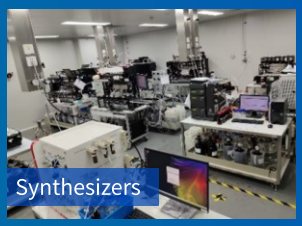
Oligonucleotide Manufacturing Services

Hitston's dedicated oligonucleotide cGMP workshop offers customized production of nucleotide ranging from milligrams to kilograms scale. The facility has successfully passed several on-site inspections by China's NMPA and the US FDA, as well as numerous client audits from Japan, the United States, and Europe. The site has implemented integrated management of environment, health, and safety (EHS), and has obtained certifications including ISO 14001 Environmental Management System, OHSAS 18001 Occupational Health and Safety Management System, and the Level III Safety Standardization Certificate for Enterprises Handling Hazardous Chemicals, and so on.

The professional team at Hitston's oligonucleotide platform is capable of efficiently providing clients with pre-clinical samples, dose range-finding study samples and toxicology samples, GMP products for clinical trials, and commercial production.

Pre-clinical R&D, μg~ g scale

The company has established nearly 100m^2 of dedicated synthesis labs with constant temperature and humidity. There are 8 microgram-scale 192-channel high-throughput DNA/RNA synthesizers, 2 milligram-scale 12-channel DNA/RNA synthesizers, and 6 gram-scale DNA/RNA synthesizers. The capacity is ongoing expansion. Additionally, there are dozens of nucleic acid purification instruments on various scales. Currently, the company has achieved an annual delivery capacity of hundreds of thousands of oligonucleotide products purified with pre-HPLC.


Synthesizers


Reverse-phase purification system

Phase I to Phase III Clinical Trials, GMP, 100g~ kg

The company has installed and put into operation one internationally renowned nucleic acid production equipment, one ion purification system, two tangential flow filtration (TFF) systems, one lyophilization system, and three quality control (QC) instruments. The batch size can reach to kilo scale, with an annual designed production capacity of ~ 10kg. The workshop is currently undergoing expansion.


Cytiva's Oligo pilot


Cytiva's Pilot 600R


Cytiva's AKTA flux6


Waters's UPLC/ UPLC-MS


Isolator lyophilization system

Commercial Scale, GMP, 100g~ kg

Currently, Hitston's oligonucleotide production platform can meet the demands of oligonucleotide active pharmaceutical ingredient (API) and drug product for early stages of commercialization. Additionally, a pilot production line with a scale of tens of kilograms will be built timely based on development of the products.

Collaborations

Since its commissioning in April 2023, Hitston has established strong collaborative relationships with several well-known domestic pharmaceutical companies and biotech firms, and several projects were successfully delivered.

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