MEDICILON

20 Years of Excellence

High Quality Integrated Drug R&D Services

www.medicilon.com

COMPANY PROFILE

From its inception in 2004, Medicilon Inc. (STAR Market, stock code: 688202.SH) has been committed to providing comprehensive research and development (R&D) services to biopharmaceutical companies, research institutions, and other organizations working in the preclinical space, with the primary objective of supporting and accelerating pharmaceutical, biopharmaceutical and medical device R&D worldwide.

A Comprehensive CRO for Pre-Clinical Pharmaceutical R&D

- End-to-end services and solutions covering the entire spectrum of preclinical biopharmaceutical R&D. Supporting everything from target discovery, candidate development, preclinical screening and drug safety evaluation through IND submission
- Focus on communication and collaboration with clients in a variety of target indication areas such as neoplasms, neurological diseases, diabetes, inflammation, etc

State-of-the-Art Facilities

- Three R&D centers with 910,000+ square feet of lab space in Shanghai, China
- AAALAC accredited animal facilities
- GLP/GMP compliant facilities and instrumentation operated in accordance with both FDA and NMPA regulations

High-Performance Teams

- 2,000+ scientists and service personnel
- Led by internationally trained scientists with Ph.D. degree and/or with 10+ years of R&D and management experience
- Provide timely support and consultations through one-on-one communication

IP Protection

- Strict adherence to rigorous internal policies and an excellent historical track record

Medicilon (Zhangjiang) High-tech Park

Medicilon (Chuansha) Headquarters

Medicilon (Nanhui) Bio-tech Park

Medicilon (Hangzhou)

Medicilon (Baoshan)

Medicilon USA (Lexington MA)

SERVICE SCOPE

Drug Discovery

Chemistry
Biology
Early DMPK

Preclinical Research

Pharmacology
Pharmacodynamics
Pharmacokinetics
Drug Safety Evaluation
Bioanalysis

Drug Development & CMC

DS/API/DP
CMC Research

IND Filing

FDA
NMPA
EMA
TGA

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Global Headquarters: No. 585, Chuanda Road, Pudong, Shanghai, 201299, China

US Laboratory: 20 Maguire Road, Suite 103, Lexington, MA 02421, USA

DRUG DISCOVERY

Medicilon's Discovery Chemistry and Biology divisions have established a strong track record assisting thousands of clients worldwide with the discovery and development of small molecules and biologics as well as cell- and gene-therapies. Combining the most cutting-edge instrumentation with high-performance, experienced scientists, Medicilon has the expertise, capabilities and capacity to support projects of any size.

Chemistry Service Model

Full-Time Equivalent (FTE)

Fee For Service (FFS)

Chemistry Service Scope

Medicinal Chemistry

- Compound Library
- Activity Screening
- Conventional/AI drug design
- Structure activity relationship (SAR) studies
- Lead compound identification
- Preclinical Candidate Compound (PCC) Identification

Custom Synthesis

- Preparation of special reagents, intermediates and molecular fragments
- Preparation of standards
- Synthetic design and preparation of impurities or metabolites
- Synthesis of stable isotope internal standards
- Synthesis of deuterated compounds

Scale-up Synthesis

- Reference compound synthesis
- Hundred-gram scale high purity compound synthesis for animal studies
- Process development of target compound
- Synthesis of kilogram-scale compound

New Drug R&D Services Platform

- PROTAC R&D service platform
- ADC R&D service platform
- Small nucleic acid R&D service platform
- AI-enabled drug discovery platform
- Photoreduction platform
- Electrochemistry platform
- Green chemistry platform
- Catalyst screening platform

Service Advantages

> 80%
FFS on-time delivery rate

> 85%
Chemical reaction success rate

> 12
Number of reactions completed per person/week

Biology Services

Recombinant Protein Expression & Purification

- *E. coli* expression system
- Yeast protein expression system
- Baculovirus expression system
- Mammalian cell protein expression systems
- Recombinant kinase preparation
- Recombinant antibody expression

Structural Biology Platform

- Protein crystallization screening
- Protein-small molecule co-crystallization condition screening
- FBDD service
- Three-dimensional structure analysis
- Protein crystallization, co-crystallization with ligands, and structure determination
- Selenomethionine (SeMET) medium

In Vitro Biology

- Enzyme-based assays
- Cell-based assays
- PROTAC molecular screening
- High throughput screening
- siRNA and mRNA drug discovery
- Gene therapy/cell therapy drugs
- Radioisotope analysis (^{3}H, ^{33}P, ^{32}P, ^{35}S, ^{125}I, ^{14}C)
- Intermolecular interaction force detection/assay (Biacore 8K based)

Antibody Discovery Platform

- Hybridoma screening platform
- Phage display platform
- Single B-cell sequencing platform
- ADA positive antibody preparation
- Antibody engineering modification
- Expression cell line construction

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CMC DEVELOPMENT

Process & Scale-up Services

- Process development and optimization
- Pharmaceutical process scale-up
- Formulation process scale-up
- Chemical project R&D outsourcing

CMC Services

Formulation Form

- **Solid:** tablets, capsules, granules
- **Semi-solid:** ointments, creams, gels
- **Liquid:** injections, eye-drops, suspensions, tinctures
- **New forms:** slow-releaser, spray, inhalation, emulsion

Stage of Service

- Investigational new drug (IND) application (China-U.S.)
- New drug clinical trial phase II/III
- New drug application (NDA)
- New drug post-market changes

Content of Service

- Pre-formulation study
- Formulation process development
- Scale-up
- Quality and stability study
- Preparation of application materials

Filing Category

- Class 1 new drugs
- Class 2 improved new drugs
- Class 3, 4 generic drugs
- Consistency evaluation
- Supplementary application

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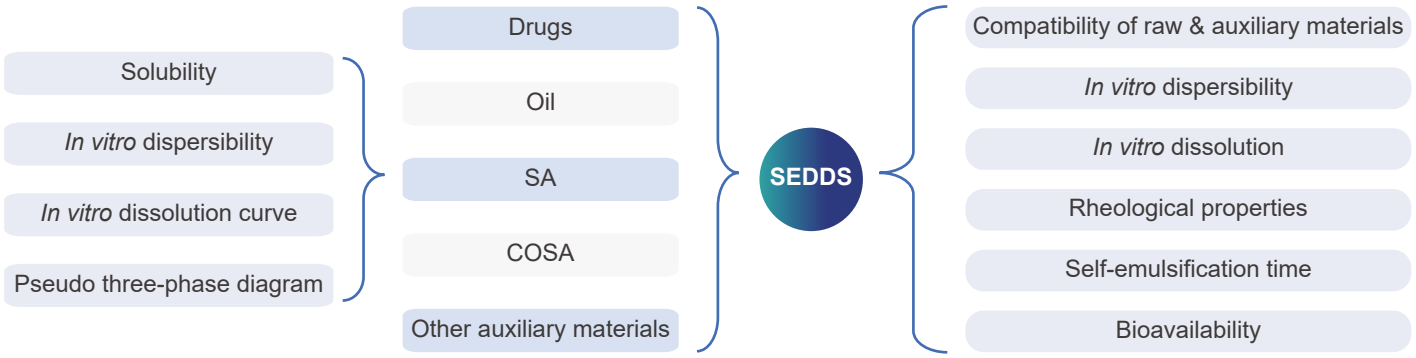
Formulation Department R&D Platform

Self- Emulsifying Drug Delivery System (SEDDS)

- SEDDS is a solid or liquid formulation consisting of a drug, an oil, a surfactant (SA) and a co-surfactant (COSA). It is usually formulated as a soft or hard capsule. Due to the low free energy of emulsification, SEDDS can generate emulsion spontaneously by peristaltic action of the gastrointestinal tract. Subsequently, the emulsion formed is absorbed via the lymphatic route. The oral bioavailability of SEDDS drugs is increased due to bypassing the first-pass effect in the liver. Therefore, SEDDS has become an important strategy to improve the oral bioavailability of poorly water-soluble drugs.
- Typically, SEDDS include self-emulsifying drug delivery systems (SNEDDS), self-microemulsifying drug delivery systems (SMEDDS), and conventional self-emulsifying drug delivery systems (CSEDDS). SNEDDS (< 100 nm), SMEDDS (100 nm - 250 nm), and CSEDDS (> 300 nm) are often judged by the size of the emulsion particles formed after the addition of water.



GMP Workshop of Formulation Department

GMP workshop (Class D cleanroom), GMP analysis laboratory, perfect QA system

- GMP standard
- 10,000+ square feet oral solids workshop
- Fully functional & flexible production
- Especially suitable for the preparation of Phase I clinical study samples
- GMP workshop for oral solid formulation
- GMP workshop - Topical semi-solid formulations
- Managed according to GMP regulations
- 10,000+ square feet GMP analysis lab
- Release testing, analytical method validation, stability study

PRECLINICAL RESEARCH

Medicilon's Preclinical Research Division services include pharmacology, pharmacodynamics, DMPK, drug safety evaluation and bioanalysis for small molecules, biologics, and medicinal herbs. Medicilon maintains a large in-house library of animal disease models to meet the research demands in different therapeutic areas. Medicilon can also assist clients in the preparation of a preclinical safety evaluation package.

Equipped with Ph.D. level scientists as well as the most innovative technology and platforms, Medicilon is committed to providing high-quality customer-oriented service support and delivering high-quality results.

Professional Qualifications

AAALAC Certificated

NMPA GLP Certificated
(2011, 2012, 2015, 2019, 2023)

US FDA GLP listed
(2017)

International RQAP-GLP

Clinical Pathology SCCL Certificated

Bioanalysis Lab NCCL Certificated

Bioanalysis Lab NIFDC Certificated

Radiation Safety License

PHARMACOLOGY

The Pharmacology department combines strong technical expertise with extensive experience in consulting, conducting, and evaluating efficacies of small molecule and biologic drugs using a wide variety of *in vitro* and *in vivo* research models. Our focused therapeutic areas include, but are not limited to oncology, CNS, cardiovascular and metabolic diseases, inflammation, immunological diseases, and digestive diseases.

Experimental Animal Capacity

- NHP
- Rodent
- Dog
- Mini-pig
- Rabbit

Tumor Animal Models (400+)

190+	CDX models
110+	PDX models
30+	Humanized models
30+	Syngeneic models
50+	Orthotopic models

Data as of 2024.08

Non-tumor Animal Models (270+)

72	Inflammatory & immune diseases models
65	CNS diseases models
46	Metabolic diseases models
25	Cardiovascular diseases models
18	Digestive diseases models
45	Others diseases models

Data as of 2024.08

Oncology Research Center
Pharmacology Equipment & Facilities

DMPK & BIOANALYSIS

Medicilon's DMPK&BA department offers our clients a broad spectrum of high quality services in the areas of *in vitro* ADMET, *in vivo* DMPK & BA, non-GLP Tox, and bioanalysis services for both small and large molecule drugs, such as proteins, antibodies, oliogonucleotides, ADC and new modalities. We have available all common laboratory animal species such as non-human primates, canines, minipigs, mice, rats, rabbits, etc.

In Vitro ADMET

- Liver microsomes / S9 / Hepatocyte metabolic stability
- CYP450 enzyme inhibition & TDI
- CYP450 enzyme induction
- Enzyme phenotype analysis
- Plasma protein binding
- Plasma (serum) stability
- *In vitro* MetID and metabolic pathways
- GSH-trapping
- Whole blood / plasma distribution
- Permeability and efflux
- Transporters
- (P-gp/BCRP/OATs/OCTs/OATPs/MATEs/BSEP/MRPs)
- BBB penetration,Kp,uu
- hERG
- Mini-Ames, Ames

In Vivo PK & Tox

- Species: Mouse (ICR, C57, balb/c, SCID, Nude mouse), Rat (SD, Wistar), Guinea pig, Mini-pig, Rabbit, Canine (beagle dog), Cynomolgus monkey
- Administration Routes: Intravenous (IV), Oral (PO), Subcutaneous (SC), Intramuscular (IM), Intraperitoneal (IP), Topical, Transdermal, IT etc.
- Dose Strategies: Single, multiple and cassette dosing
- Serial blood microsampling
- *In vivo* metabolite identification and quantitation
- Tissue distribution
- Mass balance with excretion
- Pre-formulation screening
- PK/PD & human PK modeling
- Tox, MTD, DRF
- $^{125}I/^{14}C/^{3}H$ labeled isotope drug metabolism and mass balance studies
- Surgical techniques: Venous cannulation, biliary cannulation, infusion pump, liver/muscle biopsy and implantation

Bio-analytical Services (BAS)

The Bioanalysis Department of Medicilon provides comprehensive bioanalytical services which includes PK/PD, ADA and NAB assay development and sample analysis for small molecule, biologics and vaccine bioanalytical development. Our lab implements a comprehensive management system for sample accessioning and experimental data processing, tracking and storage. All of our bioanalysis studies are in compliance with FDA/OECD/NMPA GLP regulations.

Sample Analysis
Analytical Method Validation
Analysis Method Development

Small Molecule Bioanalysis

- DMPK *in vitro* & *in vivo* screening
- Preclinical GLP pharmacokinetic assays
- Global clinical trials
- Generic bioequivalence (BE) trials

Equipment

- Sciex Triple Quad 7500
- Sciex Triple Quad 6500+
- Sciex Triple Quad 5500
- Sciex Triple Quad 4000
- Shimadzu MS 8050
- Thermo Orbitrap Exploris 240
- Sciex API 4000
- Waters Acquity UHPLC
- Shimadzu UHPLC
- Thermo Vanquish UHPLC
- Waters Acquity UPLC Xevo TQ-XS
- Thermo Q Exactive HF-X

Large Molecule Bioanalysis

- For proteins, antibodies, ADCs, polypeptides, vaccines, and various cell and gene therapies
- More than 200 bio-analytical methods for various macromolecules, CAR-T, CAR-NK, lytic virus, etc. have been developed and validated
- PK/TK/ immunogenicity (Total ADA, Nab)/ biomarker/cytokine analysis was supported
- Comprehensive support for bioassays from early screening through preclinical and clinical stages

Equipment

- MSD Sector Imager 6000/SQ120
- Molecule Devices M4/M5e/i3X Plate Reader
- BioTek ELx405 Plate Washer
- Gyrolab xPlore
- CytoFlex FACS
- CTL ELISPOT
- QIAcuity One 5 Plex ddPCR
- Nanodrop NP-80
- Vi-CELL XR Cell Counter
- PE Envision Plate Reader
- Luminex
- Biacore 8K
- ABI7500 qPCR


Biacore 8K


BD LSRFortessa Flow Cytometer


MSD electrochemiluminescence analyzer

Bioanalytical Platform

- Nucleic Acid Drugs
- ADC Drugs
- Metabolite Identification

PRE-CLINICAL TOXICITY EVALUATION

Medicilon's state-of-the-art preclinical facilities hold full AAALAC accreditation. With advanced platforms and experienced scientists, Medicilon guarantees the utmost professionalism in drug efficacy and safety assessments services, adhering to global regulatory standards. Offering services from stand-alone preclinical studies to comprehensive IND-enabling packages, Medicilon provides flexible solutions to efficiently support biotech and pharmaceutical clients in reaching their developmental milestones.

Toxicology Services (GLP & Non-GLP)

- Single and repeated-dose toxicity studies
- Reproductive/developmental and juvenile toxicity studies
- Genotoxicity studies
- Toxicokinetic studies
- Safety pharmacology research
- Immunogenicity studies
- Local tolerance studies
- Carcinogenicity studies

Histopathology Studies

- H&E staining
- Special staining
- Immunohistochemistry (IHC)
- Tissue cross-reactivity (TCR)

Clinical Pathology Studies

- Hematology analysis
- Urinalysis
- Clinical biochemistry analysis
- Hemocoagulation analysis
- Lymphocyte phenotyping

New Drug Delivery Technology

Inhalation formulation safety assessment

Ophthalmology safety assessment

IND Enabling Services

Medicilon provides the IND application for the preclinical services. Medicilon is one of the leading CRO that fulfills both the Chinese and US GLP standards. Since 2004, we have successfully helped our clients submit hundreds new drug application to FDA and NMPA and met the requirements of the FDA and NMPA. We have undergone several inspections and passed all of them. Medicilon has provided an efficient, cost-effective and professional service to help our clients achieve their goals.

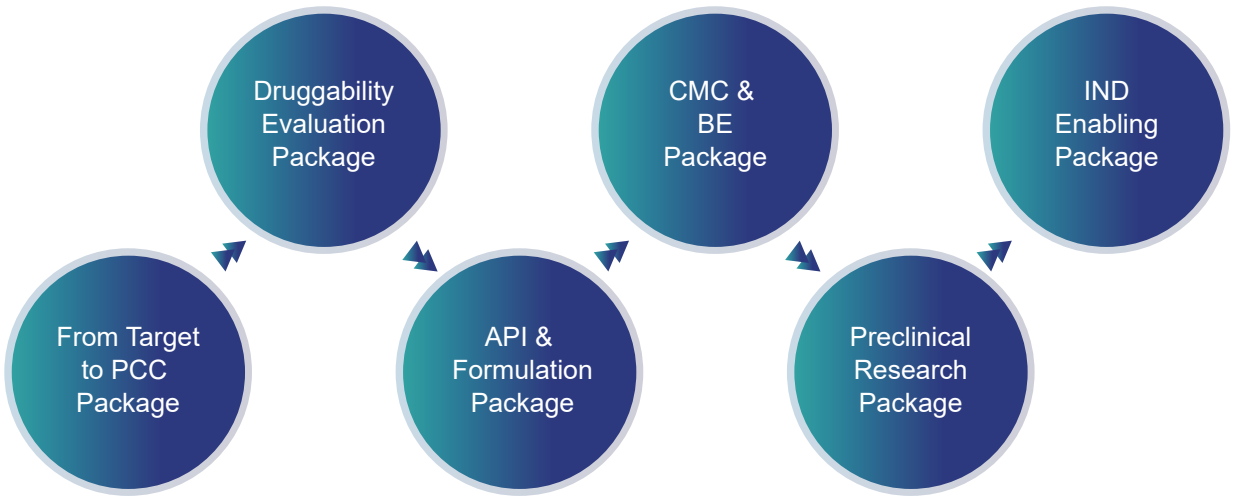
From Target to IND

Cooperation Model: Risk-sharing

- Medicilon is responsible for the overall progress of the project (chemistry, biology, pharma-codynamics, DMPK, CMC, preclinical studies, filings).
- Payment by milestone
- Medicilon does two projects at the same time, one official and one as backup; to ensure the completion of at least one project.

4 ~ 6 Mths	6 ~ 9 Mths	~ 3 Mths	12 ~ 15 Mths
Discovery of lead compounds	Optimization of lead compounds	Identification of candidate compounds	Preclinical studies and IND filings for candidate compounds

Chemical & Biologics Drug Development

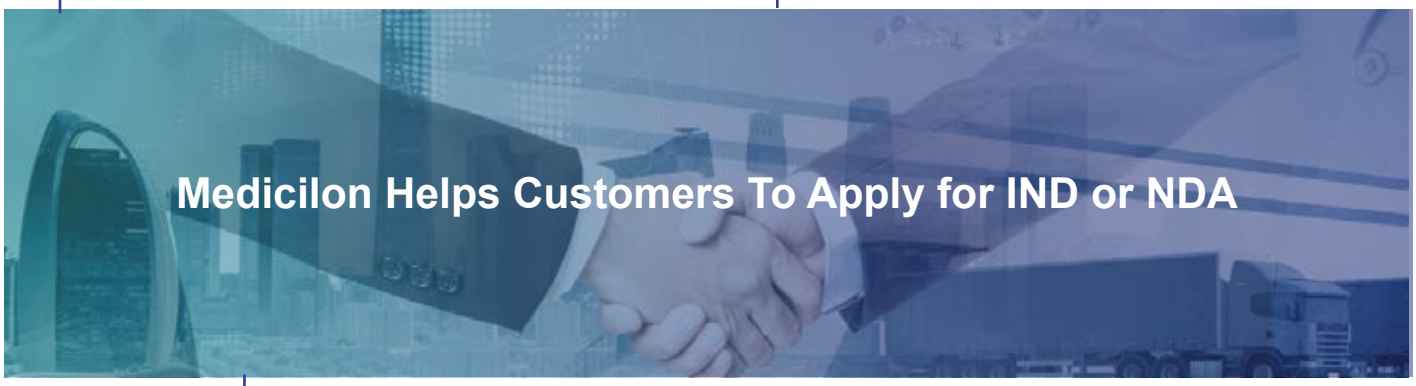


Medicilon Helps Customers To Apply for New Drugs

In-depth understanding of Chinese and US regulatory environments and their requirements for IND application, able to provide IND/ANDA application services for NMPA and US FDA for domestic and foreign clients

With professional IND and NDA research teams, we can provide one-stop research, full project management and filing services

With rich resources of NMPA and FDA review experts, we can provide targeted technical, regulatory and application strategy advice



Medicilon's IND filing service platform can provide customers with customized registration strategies, avoid potential registration risks, ensure timely and accurate submission of filings, and track the progress of reviews

Case: Lead Compound → Preclinical Candidate Compounds

Cooperation Type: FTE

Project Background:

Clients: US-based biopharmaceutical company

Project Team: 38 FTEs (32-24 chemical researchers + 6-14 biological researchers) + preclinical researchers

Starting Point: 2-3 novel targets in metabolic diseases, starting with HTS lead compounds

Results: 5 preclinical candidates over ~2 years, 1 of which is in clinical testing

Chemistry

- **Medicinal chemistry**: lead compound screening and optimization
- **Efficiency**: 1 compound/week/FTE, total of ~2000 compounds synthesized
- **Process development & Scale-up synthesis**: Synthesis of 1 Kg compounds to support US non-GLP and GLP toxicology studies

Biology

- **Gene vector construction**:
  3 assays, 3 lentiviral vectors, 8 adenoviral vectors, 2 stable cell lines
- **Analysis of 1 novel crystal structure, 8 co-crystalline structures with ligands**
- **Production of 20-30 mg protein for testing**

Preclinical

- PK testing of 65 compounds
- *In vivo* activity studies of 9 compounds
- Non-GLP toxicity screening of 9 compounds

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