



# Welcome to Hengdian!



2016



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## Location

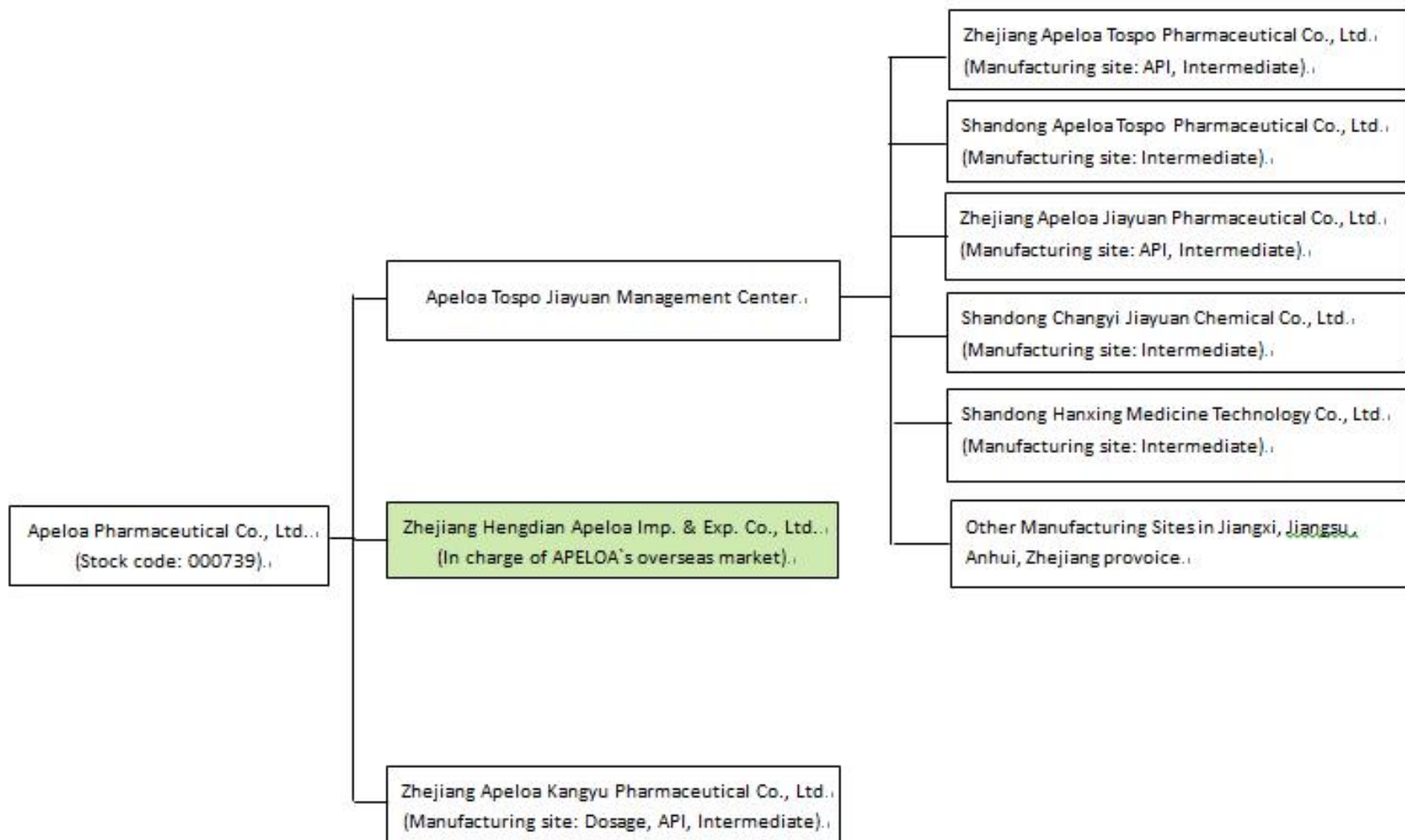


## Headquarter

- 180 km away from Hangzhou City
- 380 km away from Shanghai City



## Apeloa Organization





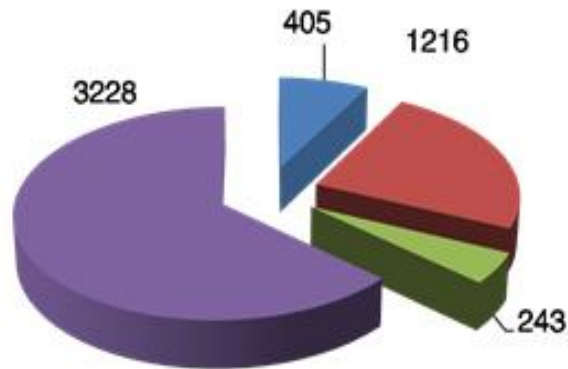
## Apeloa Tospo Jiayuan

- 5 manufacturing site approved by cGMP
- 2 API site approved by USFDA site inspection
- Some products approved by USFDA, KFDA and PMDA
- ISO9001, ISO14001, OSHAS18001 certified
- Passed several top US, European Pharmaceutical companies' EHS audits



# Human Resources

- 300 R&D, 32 Ph.D
- The Recruitment Program of Global Experts: Dr. Tang Xiaoping and Dr. Wang Xiaoju
- 30 people with oversea working experience



- Senior professional titles
- Intermediate title and technician
- licensed pharmacist
- Others



## Advantages

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- Integrated product chain
  - Intermediate — API — Finished Dosage — Sale (home and abroad)
- Various drug forms
  - API ( $\beta$ -Lactam ,tumor, and others)
  - Oral preparation (tablet, capsule , particle and etc.)
  - Injection (liquid, powder)
  - Sustained/Controlled release drugs
- Wide treatment area
  - Anti-infection
  - Cardio-cerebrovascular
  - Anti-tumor
  - Digestion





## Capacity

✓ **Total Capacity in Multi-purpose Workshop**

Apeloa Jiayuan: 367 m<sup>3</sup>

Apeloa Tospo: 534 m<sup>3</sup>

Apeloa Jiayuan		Apeloa Tospo	
Vessel Size	Amount	Vessel Size	Amount
100 L & 200 L	5	100 L	20
500 L	16	500 L	25
1000-1500 L	30	1000 L	40
2000-3000 L	94	3000 L	50
5000 L	2	5000 L	55
8000 L	7	8000 L	3
10000 L	2	10000 L	3



# Analytical Capabilities

**R&D centers**

HPLC (Waters & Agilent)	LC-MS
GC (Shimadzu & Agilent)	GC-MS
NMR (300 MHz)	DSC/TGA Others

**QC Lab**

HPLC	UV-Vis	LOD	Laser Particle
GC	Polarimeter	Sulfated Ash	Size Analyzer
IR	KF titrator	Stability Chamber	(Malvern)
TOC	Microscope	Incubator	Others

**Contract Lab**

XRD NMR (500 MHz)
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## Our Star Finished Dosage

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- Cefixime (capsule, dispersible tablet)
- Cefdinir capsule
- Amoxicillin and Clavulanate Potassium Capsules
- Cilnidipine Tablets
- Flucloxacillin sodium for injection
- Diisopropylamine ascorbate



## Our Star Product

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### ■ API

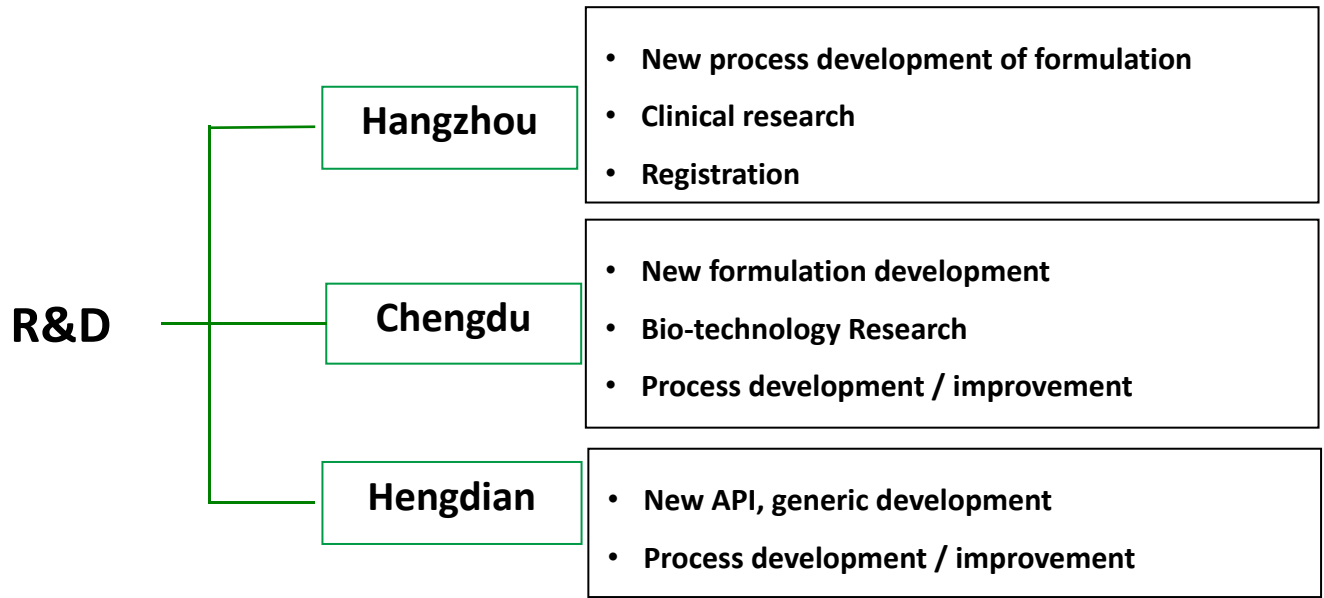
- Bupropion HCl
- Cefixime
- Cefprozil
- Cefdinir
- Florfenicol

### ■ Intermediate

- PHPG Dane Salt, PG Dane Salt, D-PG
- OTBN



# R&D Center



**Associated partner: PKU, ZJU, ZJUT, etc.**



## Hengdian R&D

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- National-recognized Enterprises Technology Center
- National Post-Doctoral Work Station
- Academician Workstation
- Develop over 30 products annually
- Own more than 20 product with independent intellectual property rights
- Own 40 invent patents

## Expertise

### Reaction Type:

★ Chiral synthesis and resolution

Grignard

High vacuum Distillation

Oxidation

★ Fermentation and Enzyme Catalyzed Reactions

★ Fluorination/Halogenation

Cyanogenation

Alkylation

Impurity Study

Polymorphism Study

### Temp. range:

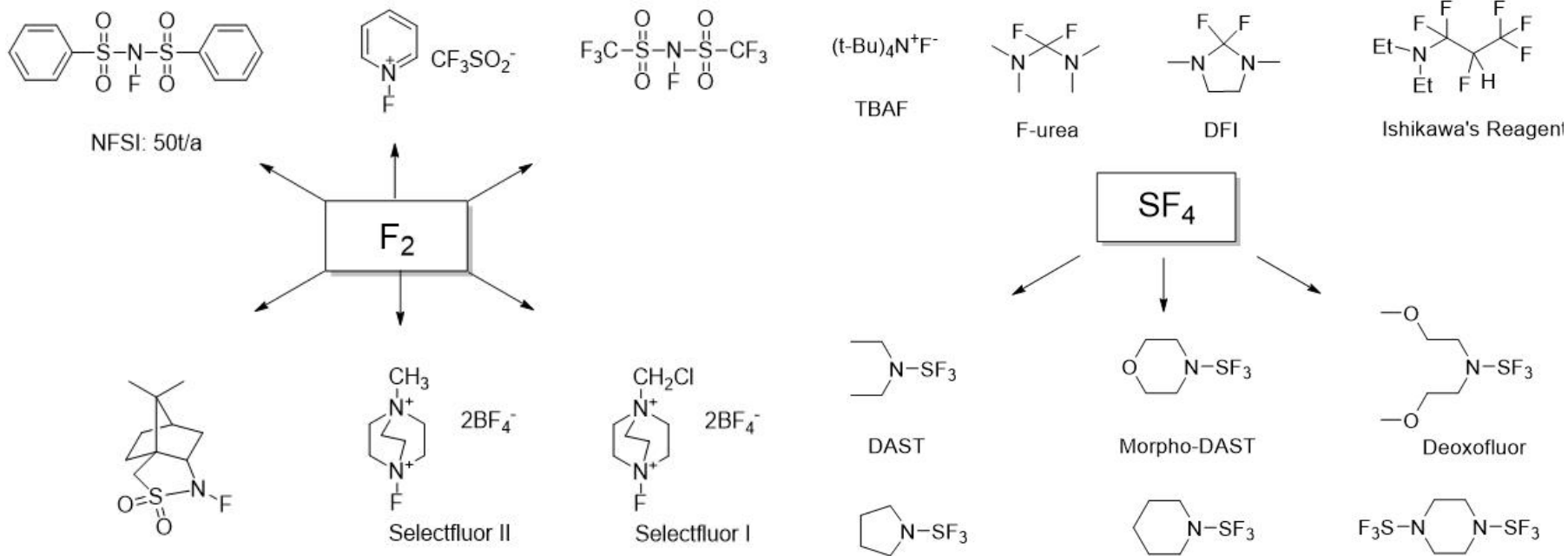
-80~250°C

### Pressure range:

-0.1~5×10<sup>6</sup> pa



## Fluorination

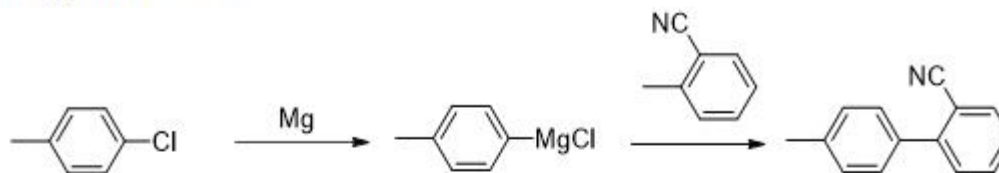




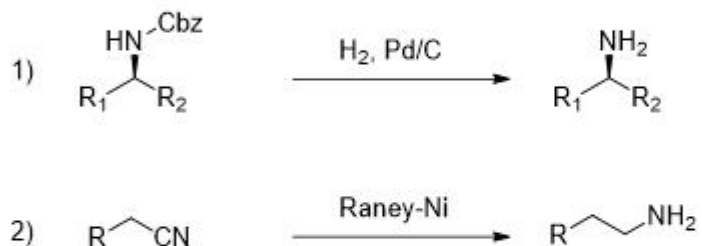


# Other technologies

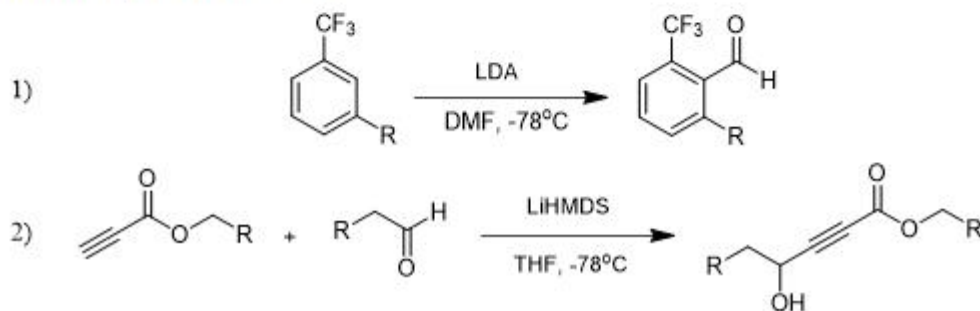
## \*Grignard Reaction



## \*Hydrogenation

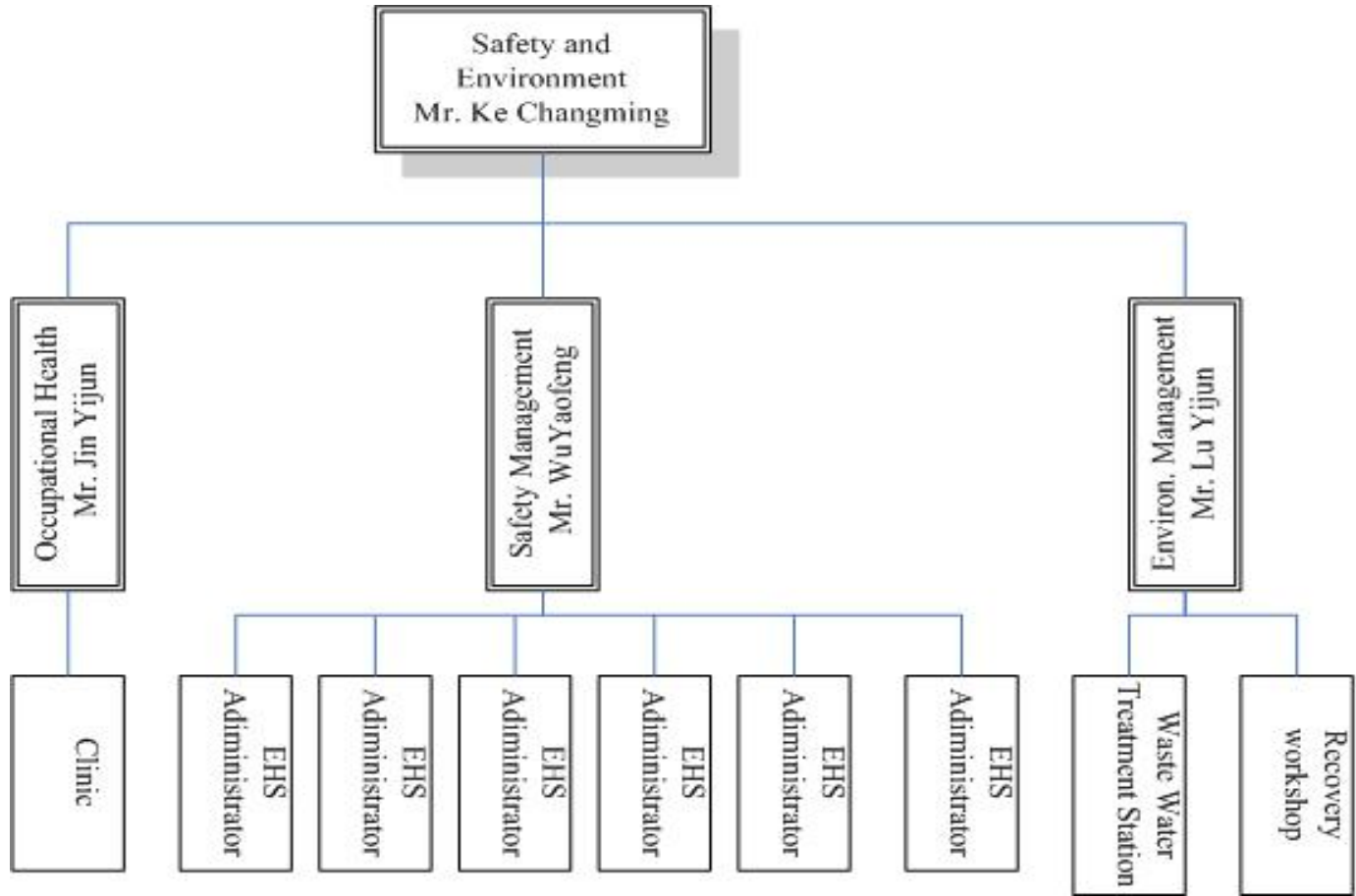


## \*Low temperature Reaction



# EHS System

# EHS Organization Chart





## EHS Targets

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- **No Severe Injury ;**
- **No Major fire and explosion accidents;**
- **No Occupational disease;**
- **Year Rate of slightly wounded cost working day  $\leq 0.3\%$ ;**
- **No Major Environmental Pollution Accident and No Government Warning;**
- **Discharge Waste Gas and Water after Meeting the Standard;**

## EHS Management System

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- ◆ Spillover control
  - ◆ Chemical management
  - ◆ Special work permit
  - ◆ VOC
  - ◆ LOTO
  - ◆ Accident
  - ◆ PPE
  - ◆ Emergency issue
- ◆ New product
  - ◆ Contractor
  - ◆ Staff training
  - ◆ ...

# **Environmental Management**

**The waste water treatment daily capacity: 3000mt**

**Daily incoming waste water: 2100mt**

**Releasing standards: COD≤800ppm**

**Ammonia Nitrogen ≤35ppm**



**Waste water treatment station**



# **Environmental Management**

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**Incinerator capacity:  
300kg/h(solid), 200kg/h(liquid)**



**More than 10 suits of waste Gas  
treatment facilities at present.**



# Safety Management



Cover the sewage tank

**当心**  
**CAUTION**

维修前，  
请断开电源并上锁  
DISCONNECT POWER  
AND LOCK OUT  
BEFORE SERVICING



**危险**

**不准操作**

此吊牌及锁具  
只准以下人员移除：  
姓名 \_\_\_\_\_  
部门 \_\_\_\_\_  
预计完成时间 \_\_\_\_\_

Lock out

# Safety Management



PPE training



Emergency drill

# Safety Management



Emergency material



# Safety Management

## Training



**Newcomers:** safety education of three-degree level

**Staffs:** periodically safety training

**EHS staff:** technical examination



# Safety Management

**Special Work Permit**

**Hot Work**

**Work in high place**

**Work in Confined Spaces**

**Excavation Work**

**Hoisting Work**

**Circuit Work**

**Work of Blocking Blind Board**

When everything is considered and approved, the operation can be permitted



# Quality System



# Health Authority Audits

✓ TOSPO site:

Time	Audit organization	Audit content	
2008.08	SFDA	GMP Audit	APIs
2011.11	Ministry of Agriculture	GMP Audit	APIs for veterinary use
2012.06	SFDA	GMP Audit	APIs (New version GMP)
2012.08	PMDA	GMP Audit	Advanced Intermediates
2013.04	SFDA	GMP Audit	APIs
2014.03	FDA	GMP Audit	API starting material, intermediate and veterinary API

# Health Authority Audits

✓ Jiayuan site:

Time	Audit organization	Audit content	
2007.05	FDA	GMP Audit	APIs
2009.01	FDA	GMP Audit	Advanced Intermediates
2009.12	SFDA	GMP Audit	APIs
2012.01	SFDA	GMP Audit	APIs (New version GMP)
2012.05	FDA	GMP Audit	APIs
2012.08	SFDA	GMP Audit	APIs
2014.03	Korean FDA	GMP Audit	APIs
2014.05	FDA	GMP Audit	APIs

All of the audits passed without 483.

# Quality Assurance

## Main Responsibilities

- **Material Release and Rejection**
- **Documentation Management**
- **GMP Training**
- **Supplier Management**
- **Change Control Management**
- **Deviation Management**



- **Validation Management**
- **Customer Complaint Management**
- **Stability Management**
- **Reserve Samples Management**
- **Audit Management**
- **Quality System Review**

# Quality Control

## Main Responsibilities

- Test of raw materials, intermediates and final products
- Stability Test
- Environmental Monitoring
- Purified Water Monitoring



- Standards Management
- Calibration





## Main SMPs

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- **Documentation Management**
- **Suppliers Audit**
- **OOS**
- **Deviation and CAPA**
- **Change Control**
- **GMP Self-audit**
- **Stability Test**
- **Validation Management**
- **Customer Complaint**
- **Recalls and Returns**

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**Zhejiang Apeloa Tospo Pharmaceutical Co. Ltd.**

- Established Year: 1990
- Site Area: 166,500 M<sup>2</sup>
- Employees: 810
- Product Area: Intermediates, Veterinary, Formulation, CMO
- Regular product: Cephalosporin intermediates

- Established Year: 1991
- Site Area: 477,000 m<sup>2</sup>.
- Employee: Around 2400
- Product areas: APIs, Advanced intermediates, CMO
- Regular product: Metoprolol, Bupropion, etc.

Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd

- Established Year: 1993
- Site Area: 460,000m<sup>2</sup>
- Employee: Around 1300
- Product areas: Bio-fermentation, chemical drugs, Intermediates
- Regular product: Colistin sulfate, etc



Thank You!

