# COMPARISON OF CHINA DMF WITH EU & US

**Accestra Consulting**

www.accestra.com

# AGENDA

1. Speaker & Company Introduction
2. Regulatory Framework & Registration Pathways
3. Comparison of China DMF with EU & US
4. Technical Requirements: Pitfalls & Tips

Q & A

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# 01

# INTRODUCTION

SPEAKERS INTRODUCTION

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## Mr. Raymond Ng

Regulatory Affairs Manager

- Business Development Director at Accestra Consulting
- Master's Degree from the University of Nottingham
- Extensive knowledge of Chinese Pharmaceutical Import & Export regulations
- In-depth insight and practical experience in dealing with Chinese market access requirements
- Successful track record of supporting international pharma companies with market entry into China

SPEAKERS INTRODUCTION

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## Ms. Helen Ye

Regulatory Affairs Director

- Regulatory Affairs Director at Accestra Consulting
- Dedicated to Regulatory Affairs for 15 years
- Degree in Pharmacy at Zhejiang University
- Specialist in regulatory compliance for China with successful track record for obtaining market approval for drug products, APIs, Excipients, Packaging Materials and medical products

# ACCESTRA CONSULTING

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Accestra Consulting is a specialist China Regulatory affairs outsourcing partner for the pharmaceutical, medical device and food industries.

- ✓ A strong technical team with over 15 years of experience
- ✓ Proud to serve clients from over 23 countries
- ✓ Strong communication with multilingual capability to serve international clients

## Services

Regulatory Affairs Services

Local Representative Agent

Pharmacovigilance in China

GMP Auditing & Compliance

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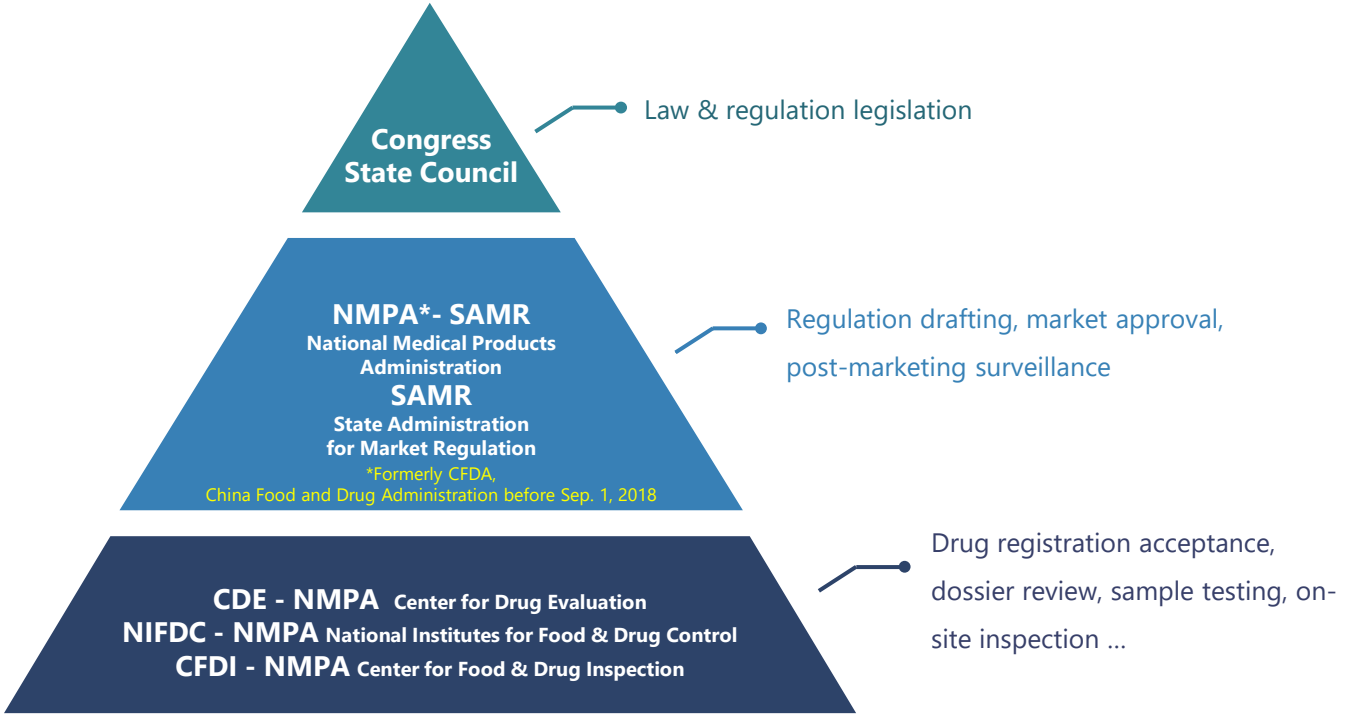
# 02

# REGULATORY FRAMEWORK & REGISTRATION PATHWAYS

# COMPETENT AUTHORITIES



# REGULATIONS

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## History of Regulatory Reform

(Binding Review & Approval and Filing System)


**State Council**

Agenda for Process Simplification

**CFDA**

Implement Binding Review & Approval of Excipients and Packaging materials

**CFDA**

Announcement No. 146: Include APIs in Binding Review & Approval

**NMPA**

Announcement No. 56: Optimize Binding Review & Approval and Filing Systems

**NMPA**

Provisions for Administration of Binding Review & Approval and Filing (Draft for Comments)

**Approval System**

**Filing System**

# REVIEW & APPROVAL

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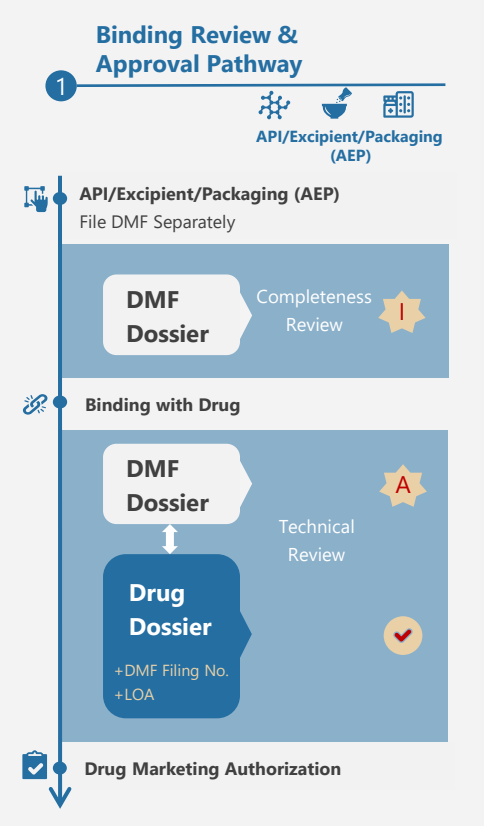


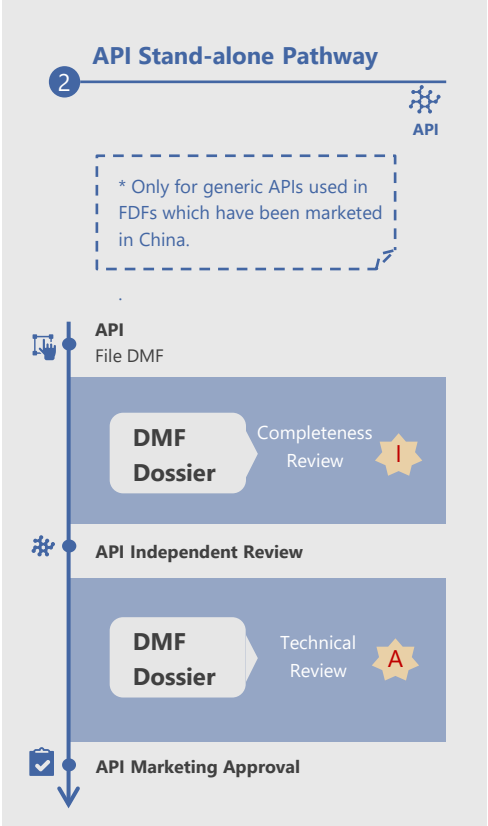


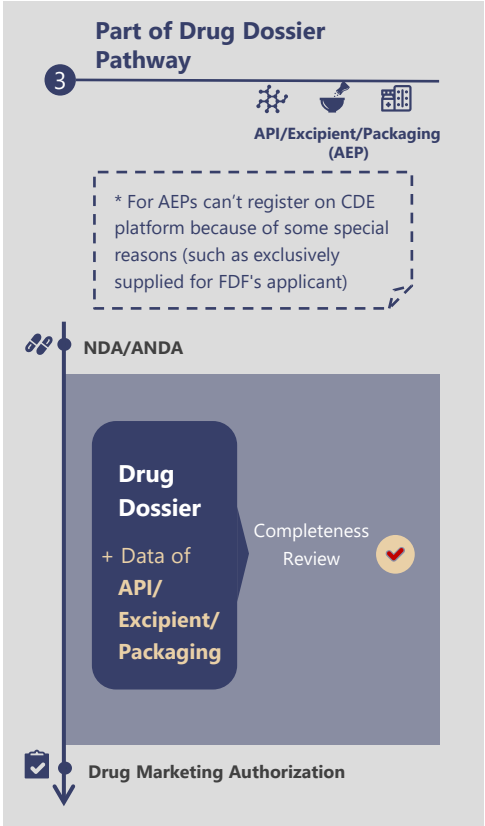


**Note:** I Inactive DMF filling no.; A Active DMF filing no.; Approval of drug.

# REVIEW & APPROVAL

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## China DMF Filing Workflow

Completeness Check

Data-gap Analysis

File DMF Dossier

Completeness Review
Application Accepted
5 workdays

Issue Inactive Filing Number I
1-2 weeks

Binding Review & Approval
(Technical Review)
Queuing time

Activate Filing Number A
5 -16Months

Total Timeline: 10-20 Months

# REVIEW & APPROVAL

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## DMF Material Checklist

### API

- ✓ ICH M4 Module 1 Administration Documents and Drug Information (including Application Form, etc.)
- ✓ ICH M4 CTD Module 2 and Module 3, mainly 2.3.S & 3.2.S
  - General information
  - Manufacture
  - Characterization
  - Control of Drug substance
  - Reference Standards or Materials
  - Container Closure System
  - Stability Study
  - …

### Excipient

- ✓ Application Form
- ✓ Applicant Information
- ✓ Product information
- ✓ Manufacturing Information
- ✓ Characterization
- ✓ Quality Control
- ✓ CoAs
- ✓ Stability Study
- ✓ Pharmacology and Toxicology Study

…

### Packaging

- ✓ Application Form
- ✓ Applicant Information
- ✓ Product information
- ✓ Manufacturing Information
- ✓ Quality Control
- ✓ CoAs
- ✓ Stability Study
- ✓ Compatibility Study
- ✓ Safety Study

…

# FILING SYSTEM

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| ✕ Approval System | Jan. 1, 2018 | ✓ DMF Filing System |
|---|---|---|
| 3-8 years +<br>2-5 years +<br>1-3 years + | - Timeline - | 1-1.5 years +<br>1-1.5 years +<br>1-1.5 years + |
| €380-5,800<br>FREE | - Administration - Fee | **€25-50k**<br>FREE |
| Approval License | - Result - | Inactive/Active Filing No.<br>API： Approval Notice. |
| NO | - Annual Report - | YES |

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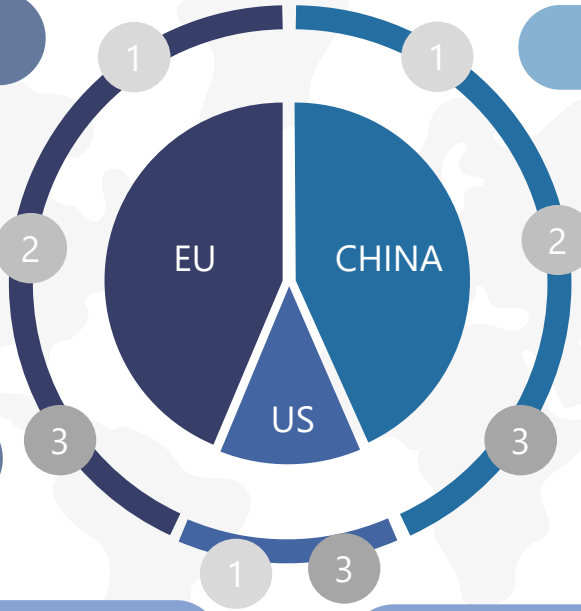
# 03

# COMPARISON OF CHINA DMF WITH EU & US

# PATHWAYS




ASMF (APIs)

CEP (APIs and Excipients)

APIs and excipients (Listed in Ph.Eur)

Part of Drug Dossier Pathway

DMF (AEP, but excipients are not mandatory)

Part of Drug Dossier Pathway

Binding Review & Approval Pathway (AEP)

Stand-alone Pathway (APIs)

Only for generic APIs used in FDFs which have been marketed in China.

Part of Drug Dossier Pathway

For AEPs can't register on CDE platform because of some special reasons (such as exclusively supplied for FDF's applicant)

# SCOPE

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**ASMF & CEP** VS **CHINA DMF** VS **US DMF**

ASMF
- APIs (except biological active substances)

CEP
- APIs and excipients (Listed in Ph.Eur)

- APIs
- Pharmaceutical excipients
- Pharmaceutical packaging materials

- **Type II** - Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation; or Drug Product
- **Type III** - Packaging Material
- **Type IV** - Excipient, Colorant, Flavor, Essence, or Material Used in their Preparation
- **Type V** - FDA-Accepted Reference Information

# SCOPE-CHINA DMF

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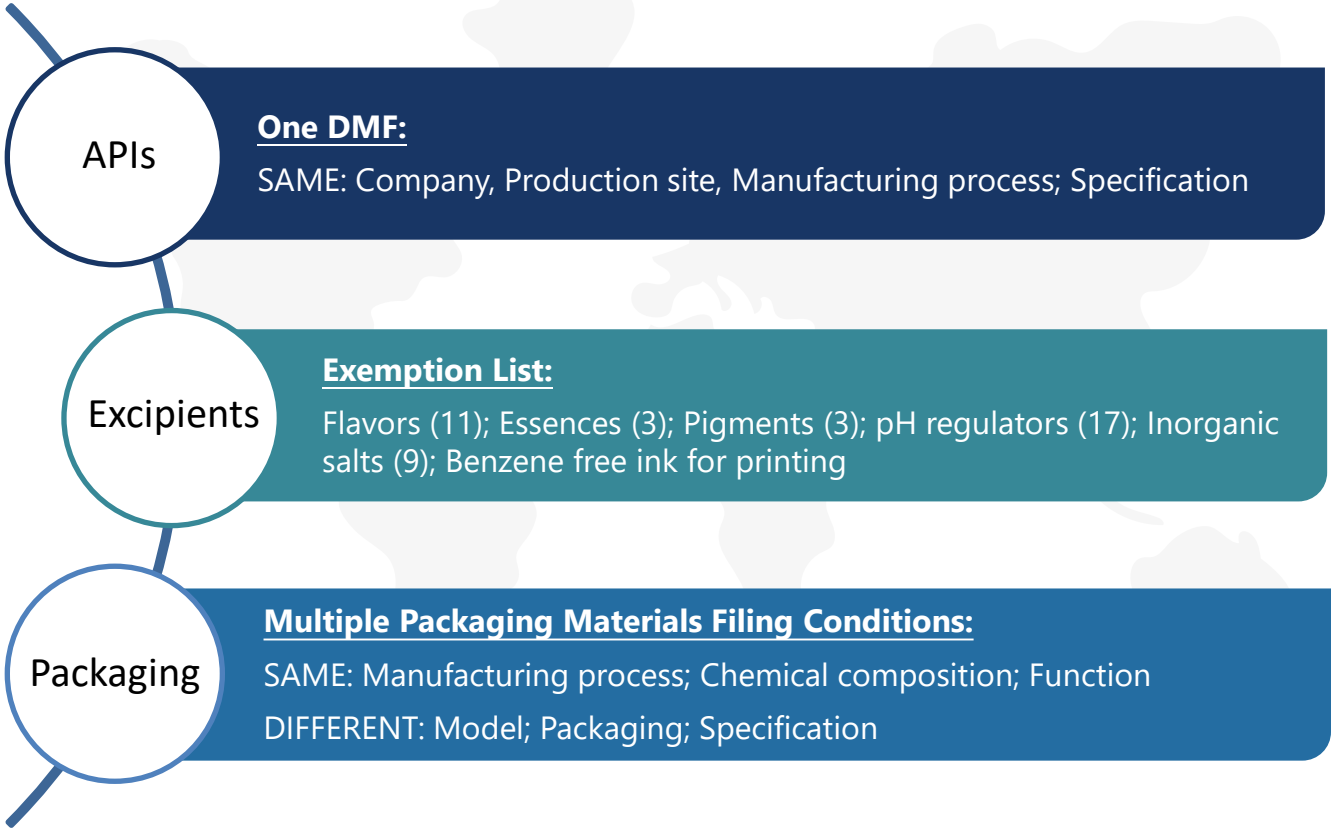

# CONFIDENTIALITY

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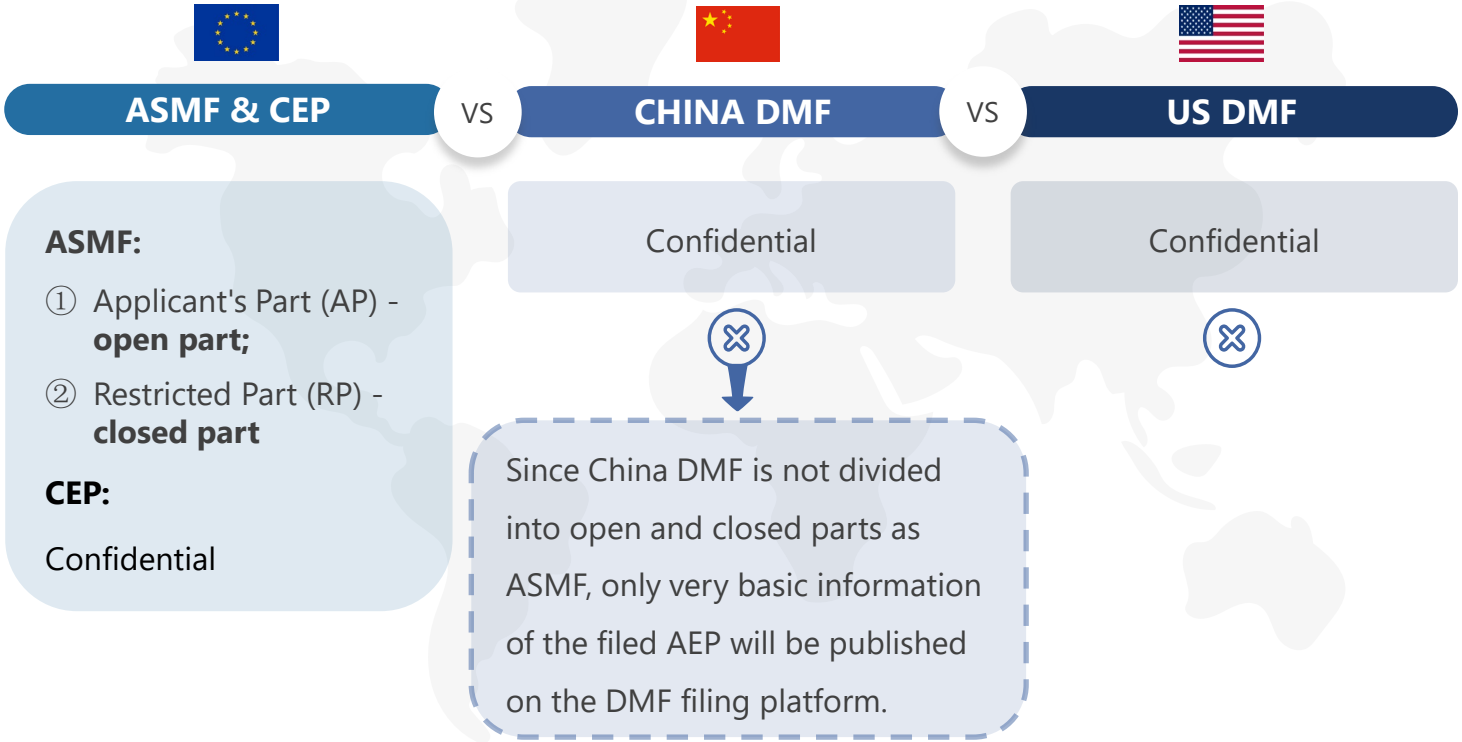

# TIMELINE & COST

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| ASMF & CEP | VS | CHINA DMF | VS | US DMF |
|---|---|---|---|---|

**– Registration Timeline –**

| ASMF & CEP | CHINA DMF | US DMF |
|---|---|---|
| **CEP**: 18-24 months<br>**ASMF**: Depend on the associated drug product | **Inactive(AEP)**: 5 workdays (1-2 weeks);<br>**Active(AEP)**: 5-16 months after starting review. | **Completeness Assessment (API):** 60days<br>**Technical review stage (API)** : 10 months |

**– Administration Fee –**

| ASMF & CEP | CHINA DMF | US DMF |
|---|---|---|
| **CEP**: €3-9K<br>**ASMF**: Depend on EU member country | **API**: €~25-50k (183.6-367.6k RMB)<br>**Excipients and packaging**: Free | **Type II API: $78,293 (2023)**<br>**Other DMF types:** Free |

# SUBMISSION


**ASMF & CEP:**
eCTD

**API:**
CTD, digital dossier in one CD

**Excipients and packaging:**
Not CTD, digital dossier in one CD

eCTD

# APPROVAL STATUS

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## ASMF & CEP

**ASMF**

Reference No.

**CEP**

CEP Certificate

VS

## CHINA DMF

I A Notice

**Inactive:** The DMF dossier of API, excipient or packaging is complete but not approved.

**Active:** API, excipient or packaging is approved for Binding Review & Approval pathway or Stand-alone Pathway (API only).

**Notice**: APIs approved for the first time or upon renewal.

VS

## US DMF

I A List Letter

**Inactive:** The DMF has been closed, either by the holder or by the US FDA.

**Active:** The DMF was found acceptable for filing, administratively, and has not been closed.

**List of Type II DMFs Available for Reference:** The DMF has undergone a successful Completeness Assessment (APIs only).

**First Adequate Letter/No Further Comments Letter** (API only)

# API Renewal & Responsibilities

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| ASMF & CEP | VS | CHINA DMF | VS | US DMF |
|---|---|---|---|---|
| **– API Renewal Cycle –** | | | | |
| **ASMF**: N/A<br>**CEP**: 5 years | | 5 years | | N/A |
| **– Responsibilities–** | | | | |
| **ASMF:**<br>• Notice required for Changes;<br>• Inform MAH of drugs;<br>• Annual report<br>**CEP:**<br>• Notice required for Changes;<br>• Inform MAH of drugs;<br>• Annual report<br>• Re-registration | | • Changes application;<br>• Inform MAH of drugs;<br>• Annual report;<br>• Re-registration | | • Notice required for Changes to DMF;<br>• Inform MAH of drugs;<br>• Annual update;<br>• LOA |

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# 04

# TECHNICAL REQUIREMENTS: PITFALLS & TIPS

# COMMON TECHNICAL PITFALLS

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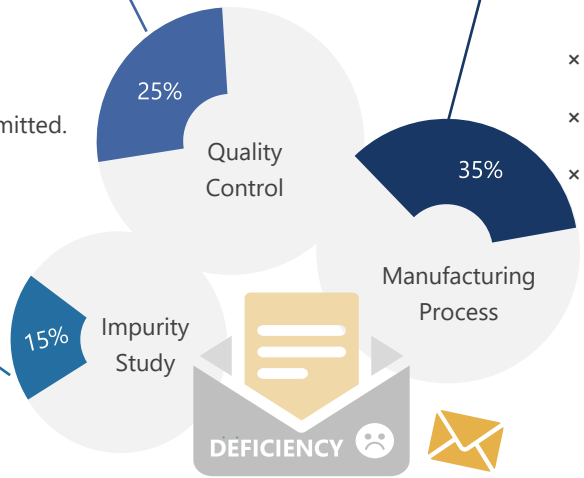
## Quality Specification

- × Lack of test items in the specification
- × Not in compliance with Chinese Pharmacopoeia or its general principles without giving justified reasons (such as heavy metal and microbial limit)
- × The types of residual solvents are incomplete, the possibility of benzene in the solvent is commonly omitted.
- × Microbial limit and endotoxin test

## Impurity Study

- × Elemental impurities
- × Genotoxic impurities
- × Impurity structural formula




## Manufacturing Process

- × Production process flowchart and reaction equation are incomplete, or the information of reaction conditions, catalysts, solvents is missing
- × Process description is incomprehensive
- × Production equipment information list is not provided
- × The starting materials are not properly selected

# COMMON TECHNICAL PITFALLS

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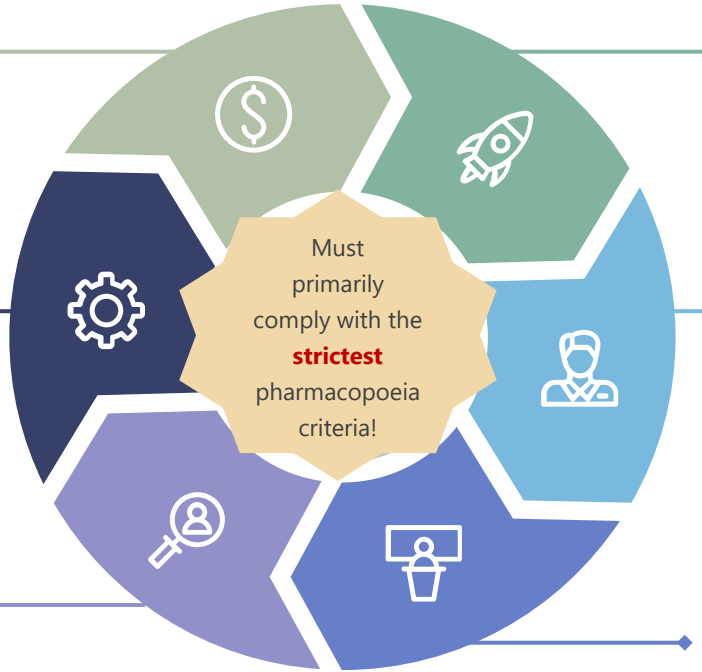
- The production process and/or quality research of new product is insufficient with significant technical defects
- The quality specification (especially safety-wise) is below Chinese Pharmacopoeia or national standards without any convincing reasons
- Cannot provide valid supporting documents, or have not notarized them in time




- For high-risk excipients, lacking safety study, or the quality control research is incomplete (Case Study 1)
- For high-risk pharmaceutical packaging materials, lacking complete safety and compatibility research (Case Study 2)
- Packaging materials with different raw materials for different product models or codes are required to be registered separately (Case Study 3), and for many cases stability studies are inadequate or even missing (Case Study 4)

## For Excipient & Packaging Products

# TIPS

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**01**

Follow regulatory updates

**02**

Strategic plan & research quickest pathway options to China

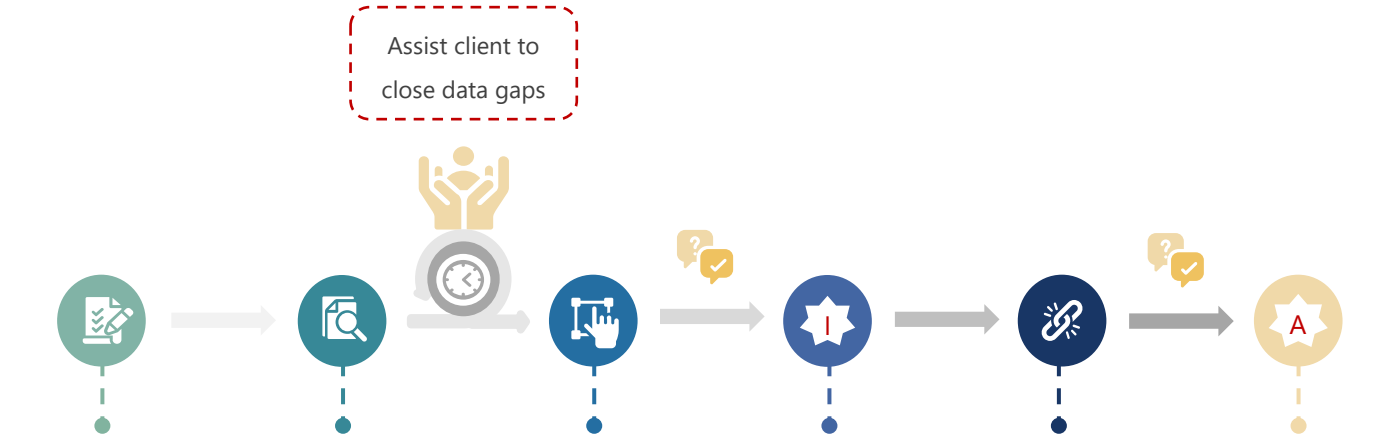
**03**

Mind the gap, close the gap to meet China requirements

**04**

Appoint independent local agent/partner

# OUR SERVICE




Assist in dossier preparation

Follow up with CDE

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# Q&A SESSION

# Q&A #1

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**Question:**

Can the drug product applicant submit a DMF for an excipient or packaging material, if the supplier is not prepared to do so?

**Answer:**

Yes, as we've shared in the presentation, the drug product applicant can submit the dossier of an excipient or packaging material with the drug product if the supplier is not prepared to register in China. This is the 3rd pathway, "part of drug dossier pathway". As the API/excipient/packaging material supplier will need to share data with the drug applicant, this pathway has a potential risk of information disclosure. For API/excipient/packaging material suppliers who are concerned about confidentiality, the recommended pathway is the 2nd pathway to file DMF separately.

Another option is, if the drug company and the AEP supplier are both overseas companies, it is currently possible for the drug company to apply for DMF filing as the DMF holder while the AEP supplier being the contract manufacturer based on a mutual agreement, and the relating administrative documents being provided to the authority in compliance with the requirements. However, this option is quite complicated, especially for APIs produced by contract manufacturers, we can help further evaluate on the feasibility according to client's situation if needed.

# Q&A #2

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**Question:**
What is the content of the annual report? Is there a template?

**Answer:**
There has been no specific regulation issued so far about the content of annual report for API/excipient/packaging material. There are only general requirements in the regulations regarding what information should be included in the annual report. We typically refer to the annual report of drug product when preparing the annual report for AEP products.

# Q&A #3

**Question:**

What is current regulation to apply for post approval change to China DMF?

**Answer:**

For AEP DMF Holders:

Step 1: Conduct research to identify the impact of AEP change on the drug quality, safety and efficacy, subsequently inform the drug MAH.

Step 2:

- For API: Assess the risk level of impact and classify the change as minor, moderate or major. According to the classification, determine whether review and approval by CDE is required. For a major change, file a supplementary application to CDE. For a moderate change, update data and submit notification on CDE's platform (database) for DMF filing. For a minor change, include information in the annual reports.
- For Excipient/Packaging: Update relating data and submit notification on the platform (database) mentioned above, which does not require CDE approval.

Step 3: Regardless of the classification of change, update the relating data on the platform (database) and submit the eversion materials to CDE, as well as in the annual reports.

For Finished Drug MAH:

Refer to the Provisions for Post-approval Changes to Drug Registration (NMPA [2021] Decree No. 8).

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