Guidance on Pharmaceutical Excipient Suitability Studies (PESS) with Chinese Pharmacopeia （Volume 4）: Basics and Examples

Professor Jiasheng Tu, Ph. D.
France
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Introduction

- Background: CHP 2015 increased monographs to 270 (vs 2010ed only 135), including 23 excipients for injection use.
- China FDA (now NMPA) published new China DMF based registration of pharmaceutical excipients and packaging materials, which permit the excipients comply to CHP monographs submit DMF with a brief manufacturing documents.
- PESS allow stakeholders (regulatory agency, excipient provider, and user) correctly justify whether claimed excipients suitable to the claims.

Objectives

- The PESS is the basis for selecting pharmaceutical excipients. The principle of PESS is critical material attributes (CMA) based material analysis and final product (FP)-related researches.
- To guide to verificate the suitability of CHP monograph to the claimed pharmaceutical excipients with:
  - Different manufacturing processes
  - Different sources of raw materials
  - Physical, chemical properties of pharmaceutical excipients
  - For injection, inhalation and ophthalmic, safety issues
- To guide the user to validate the excipient suitability in the FP. Validation will be based on formulation, usage and dosage and also drug-excipients interaction
1. Verification of excipient to CHP monograph: same manufacturing process under GMP, comply with the monograph requirement.

2. Verification CHP excipient suitability to claimed FP: whether the excipient suitable to FP need to evaluate based on the safety, functionality of the excipient itself, and interaction of drug-excipient, sometimes economy.

FP related researches on CMC, efficacy and safety.
Basic framework for 《Guideline on suitability of pharmaceutical excipients》:

a) Foreword
b) Monograph suitability to the Chinese Pharmacopoeia on claimed excipient
c) Consideration of sources and methods of preparation for pharmaceutical excipients
d) Application of pharmaceutical excipients and dosage considerations
e) Study on safety suitability of pharmaceutical excipients
f) Documentations for the suitability study of pharmaceutical excipients

### Verification of CHP monograph

<table>
<thead>
<tr>
<th>Factors</th>
<th>Basic requirements</th>
<th>Guidance</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural excipients</td>
<td>Plant sources: structural composition, genetic modification, pesticide residues, allergenic substances, heavy metals, etc. should comply with relevant regulations</td>
<td>CHP&lt;251&gt;</td>
<td>Affirmation, COA and verification report should be submitted</td>
</tr>
<tr>
<td>Source and preparation methods</td>
<td>Animal sources: composition, TSE, viruses, genetically modified organisms, pesticide residues, allergenic substances, heavy metals, etc. should comply with relevant regulations</td>
<td>Guidance on animal excipients&gt;Drafting&gt;</td>
<td>Affirmation, COA and verification report should be submitted</td>
</tr>
<tr>
<td>Semi-synthetic excipients</td>
<td>Provide chemical composition, structure, preparation process, quality requirements and quality standards</td>
<td>CHP&lt;251&gt;</td>
<td>Affirmation, COA and verification report should be submitted</td>
</tr>
<tr>
<td>Synthetic excipients</td>
<td>Structure, molecular weight, related substances, impurities should meet the requirements</td>
<td>CHP&lt;251&gt;</td>
<td>Affirmation, COA and verification report should be submitted</td>
</tr>
</tbody>
</table>

COA report should be submitted.
Only applicable to excipients manufactured under GMP

<table>
<thead>
<tr>
<th>Specification</th>
<th>Vendor and user agreement to develop FRCs methods and limits</th>
<th>Examination report for FRCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosafety</td>
<td>New excipients, high-risk excipients changing the route of administration, excipients increasing the dosage of...</td>
<td>Guidance on the biosafety of excipients - Drafting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verification Report of GLP Lab</td>
</tr>
<tr>
<td>Compatibility with drug</td>
<td>Compatibility of drugs and pharmaceutical excipients and their effects</td>
<td>Guidance on the compatibility of pharmaceutical excipients and drugs - Drafting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compatibility study report</td>
</tr>
<tr>
<td>Prescription screening</td>
<td>Screening prescriptions and processes, determining the type, grade, specification, dosage of pharmaceutical excipients, and preparation process</td>
<td>ChP(2013)-9601, ICH Q8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optimization of formulation and validation report</td>
</tr>
</tbody>
</table>

**Scheme of PESS**

The selection or change of excipients

- Sources
- Production structure
- Is the name suitable? No → Not suitable to ChP
  - Yes → Is it suitable to the standard in ChP?
    - Yes → Safety compatibility stability function route dosage
    - No →
The application route and dosage of pharmaceutical excipients should be studied combined with specific formulation studies. If the pharmaceutical excipients in the preparation exceed the application route and exceed the dosage, the corresponding evidence for the application of the excipients (safety study, etc.) should be validated.

According to administration, the pharmaceutical excipients may have different levels, i.e. high risk, medium risk and low risk. Different LEVEL excipients usually have large differences in internal quality. Excipients for injection use, for inhalation use, et al, are high risky level. Excipients with high risky monographs are recommend to the corresponding preparation. If high risky preparation use lower level one, validation need to perform.

Grade of excipients

- Pharmaceutical excipients can be divided into different grades according to particle shape, particle size and density. The same excipients with different grades often have different functional related characteristics. Excipient suppliers should correctly label (including functional related characteristics). Suitability studies should include the selection and screening of grades. Pharmaceutical production and formulation prescriptions should validate the suitability of the grades of the used excipients.
Basic principles of selecting excipients

The suitability study of pharmaceutical excipients is the basis for scientific selection of medicinal excipients, including the suitability of pharmaceutical excipients for different types of formulation, different production processes, different usages and dosages, and different sources of raw materials.

- Full understanding of the characteristics of excipients
- Understand the active substance itself
- Choose excipients according to the process developed by the dosage form
- Choose excipients based on the dose of the drug
- Choose excipients according to the dosage form
- Select excipients according to drug-release characteristics
Examples

Starch:
- Sources of raw materials: wheat, potato, cassava, corn
- Functions: bulking agent, disintegrating agent, binding agent, glidants
- Different manufacturers

Polysorbate 80:
- Grades: injection grade, normal grade
- Solubilization and stability ability to different drugs: complex components of traditional Chinese medicine, single poorly soluble drugs
- Different manufacturers, different production techniques

Lactose:
- Route of administration: oral, inhalation
- Different manufacturers, different production techniques: Meggle Group vs made in China

The starch type and the content of starch in the formulation significantly affects dissolution behavior. Hydrochlorothiazide tablets
The release behavior using cornstarch from Weifang Shengtai company and Anhui Sunhere Pharmaceutical Excipients Co. and roquette co.

The release behavior using cornstarch from Weifang Shengtai company and Anhui Sunhere Pharmaceutical Excipients Co.

High moisture affects the disintegration efficiency of starch, making dissolution of tablets slower.
**For injection**

- Bacterial endotoxin
- Microbial limits (2015 Chinese Pharmacopoeia, General Principles 1105 and 1106)
- Sterility requirements (2015 Chinese Pharmacopoeia, General Principles 1101)

**Oral formulation**

Requirements on microbes are lower than that of injection

**External formulation**

Requirements on microbes are lower than that of oral formulation

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**Examples**

**The suitability study of pharmaceutical excipients with different viscosity**

- HPMC (low viscosity)
  - Binding agent for tablet
  - Porogen for sustained or controlled release tablets

- HPMC (high viscosity)
  - Retarding agent and controlled release agent for hydrophilic gel matrix sustained release tablets
The suitability study of pharmaceutical excipients with different doses

- The functions of HPMC with different concentration in formulation

<table>
<thead>
<tr>
<th>Functions</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding agent, disintegrants for Granules, tablets, pills</td>
<td>1.5%-4.0% solution</td>
</tr>
<tr>
<td>Film-forming material for film coating</td>
<td>2.0%-4.0% solution</td>
</tr>
<tr>
<td>Thickeners for colloidal preparations and suspending agent for suspensions</td>
<td>0.5%-15% solution</td>
</tr>
</tbody>
</table>

The suitability of excipients with different molecular weight

<table>
<thead>
<tr>
<th>PEG</th>
<th>PEG(200,400,600)</th>
<th>PEG-4000, PEG-6000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function in formulations</td>
<td>Solubilizer in injection</td>
<td>Baes used in ointments and suppositories</td>
</tr>
</tbody>
</table>
**Incompatibility**

- Mixing time affects tablet dissolution
- The formulation with the same dose of magnesium stearate in direct tableting is more hydrophobic than the granulation formulation.

- Magnesium stearate: aspirin, iron salts, some vitamins, alkaloids, and drugs sensitive to magnesium ions, strong organic acid salts
- Lactose compatibility: Pharmaceutical preparations containing aspirin, theophylline, penicillin, and phenobarbital should avoid the use of lactose.

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**Examples - Excipients**

### Different functional excipients and its key standard

<table>
<thead>
<tr>
<th>Functions</th>
<th>Excipients</th>
<th>Key standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent</td>
<td>Lactose, sucrose, kaolin, basic calcium carbonate, calcium carbonate, calcium phosphate</td>
<td>Color, particle size, particle size distribution, heavy metals, moisture, microbial limits</td>
</tr>
<tr>
<td>Binders</td>
<td>Water, alcohol, starch slurry, gelatin solution, xanthan gum, sodium alginate, carboxymethyl cellulose, polyethylene glycol, pyrrolidone</td>
<td>Viscosity, foreign matter, residue on ignition, pH, microbial limit</td>
</tr>
<tr>
<td>Lubricant</td>
<td>Magnesium stearate (calcium), talc, stearic acid, mineral oil, sodium chloride, sodium benzoate, polyethylene glycol</td>
<td>Particle size, water, melting point range, microbial limit</td>
</tr>
<tr>
<td>Disintegrating agent</td>
<td>Corn starch, methyl cellulose, sodium carboxymethyl cellulose, alginic acid, microcrystalline cellulose</td>
<td>Foreign matter, moisture content, viscosity, microbial limits</td>
</tr>
<tr>
<td>Pigment</td>
<td>Dyes and shades specified by FD&amp;C and D&amp;C</td>
<td>Identification, volatile organic content, color grade</td>
</tr>
<tr>
<td>Flavor</td>
<td>Volatile oil, dry spices</td>
<td>Refractive index, specific gravity, solubility, alcohol content</td>
</tr>
<tr>
<td>Sweetening agent</td>
<td>Mannitol, lactic acid, sorbitol, saccharin, aspartame</td>
<td>Water content, heavy metals, residues on ignition, specific rotation</td>
</tr>
</tbody>
</table>
### The microbial limit study for different route of administration

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Total amount of microorganisms (cfu/g, ml)</th>
<th>The total amount of mold and yeast (cfu/g, ml)</th>
<th>Colonies not allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet/Capsule</td>
<td>1000</td>
<td>100</td>
<td>Escherichia coli, Salmonella</td>
</tr>
<tr>
<td>Oral liquid formulation</td>
<td>100</td>
<td>10</td>
<td>E.coli</td>
</tr>
<tr>
<td>Suppository</td>
<td>1000</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Nasal medications</td>
<td>100</td>
<td>10</td>
<td>Staphylococcus aureus, Pseudomonas</td>
</tr>
<tr>
<td>Inhalation</td>
<td>100</td>
<td>10</td>
<td>Staphylococcus aureus, Pseudomonas aeruginosa, gallbladder-tolerant Gram-negative bacteria</td>
</tr>
<tr>
<td>Vaginal medication</td>
<td>100</td>
<td>10</td>
<td>Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans</td>
</tr>
<tr>
<td>Transdermal preparation (each piece)</td>
<td>100</td>
<td>10</td>
<td>Staphylococcus aureus, Pseudomonas</td>
</tr>
</tbody>
</table>
Summary

- Excipient PESS is aim to guide:
  1. Excipient provider to verify the applicability of the CHP monograph to the claimed excipient. Only manufactured under GMP can be validated.
  2. Drug product manufacturer to validate the suitability of excipients comply with CHP monographs.
  3. NDA and ANDA researcher to validate the excipients when choose CHP monograph excipients.

THANKS