Risks, classifying management and technical requirements for pharmaceutical excipients

National Institutes for Food and Drug Control (NIFDC), CFDA
中国食品药品检定研究院

Institute for Packaging Materials and Pharmaceutical Excipients Control
包装材料与药用辅料检定所

Director & Professor, Huimin Sun
孙会敏

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总结
About NIFDC

• NIFDC was founded in 1950. It is a subordinate agency of China Food and Drug Administration (CFDA) and there are 29 internal institutions within NIFDC.
• Currently, there are more than 1326 employees, around 50% employees with higher education background of Master or PhD degree, 70 experts entitled to take the Government Special Allowance.
• There are more than 13754 modern testing instruments and equipment in NIFDC.

In September 2015, NIDFC moved to new site with the area of 100,383 square meters.

But some institutes are still on the old site, including the Institute for Packaging Materials and Pharmaceutical Excipients Control (my institute).

Missions

1. To undertake relevant registration testing of drug and medical devices and technical evaluation, and for the testing of healthy food, cosmetics apply for approving, and for the testing and specification evaluation of imported drugs.

2. To carry out the post market surveillance testing, contract testing, sampling testing, and safety evaluation of drug, medical devices, healthy food, cosmetics, and restaurant food, and responsible for the drug testing at port of entry.

3. To organize the Re-testing and technical evaluation of drug and medical devices.

4. Be responsible for the lot release of biological products.

5. To undertake the technical review and verification of the specification, guidelines and testing procedures regarding with drug, medical devices and restaurant food.

6. To carry out the registration testing, post market surveillance testing, contract testing, sampling testing, and re-testing of pharmaceutical excipients, primary packaging materials and container. And be responsible for the technical review and verification of specification of pharmaceutical excipients and packaging materials.

7. To take charge of research, development, testing, distribution and administration of the National Reference Standards of drug and medical devices.

8. To take charge of the testing of bacterial (viral) strains, take charge of collection, identification, preservation, distribution and management of medical standard bacterial (viral) strains and cell strains.
Missions

9. To take charge of the preservation, breeding and supplying of experimental animals and the quality control of experimental animals.

10. To take charge of the technical supervision of advertisements regarding drugs, medical devices and healthy products and internet information related with drugs.

11. Be responsible for providing technical assistance and guidance regarding laboratory testing technology for the food and drug quality control institutes nationwide; also be responsible for organizing the activities to provide technical assistance to the scientists within the drug quality control institute around the nation.

12. To organize the specification research and new method/technology research regarding the drug, medical devices, healthy food, cosmetics and restaurant food.

13. Be responsible for the technical administrative affair of China Food and Drug Administration (CFDA), be responsible for the routine work of the experts committees related with healthy food, cosmetics, and restaurant food safety.

14. Be responsible for the research and lab investigation of the server side effect (ADR) regard with drug and medical devices.

15. To organize the international collaboration and cooperation in the field of testing and analysis of drug, medical devices, healthy food, cosmetics, and restaurant food safety.

16. Undertake others tasks assigned by CFDA.

Organization Structure

14 Institutes

- Institute of Food Control
- Institute for Cosmetics Control
- Institute of Chemical Drug Control
- Institute for Biological Product Control
- Institute for Medical Devices Control
- Institute for Control of Chinese Traditional Medicine and Ethnic Medicine
- Institute for Control of Packaging Material and Pharmaceutical Excipients
- Institute for Laboratory Animal Resources
- Institute for Reference Standard and Standardization
- Institute for Food and Drug Safety Evaluation
- Institute for In Vitro Diagnostic Reagents
- Institute for Medical Device Standardization Administration, NIFDC
- Food and Drug Technical Supervision Center
- Generic Drugs Quality Research Center

15 Administration departments (……)
Missions of Institute for Control of Packaging Material and Pharmaceutical Excipients

- To carry out the registration testing, post market surveillance testing, contract testing, imported testing, and re-testing of packaging materials and pharmaceutical excipients related with drugs.
- Be responsible for the National Standard and technical review and verification of specification of excipients and packaging materials and container.
- To take charge of researching and Standardisation of Reference Substances of excipients, packaging materials and container.
- To organize testing, quality control, new method/technology research and compatibility testing regarding excipients, packaging materials and container.
- Undertake others tasks assigned by CFDA.
Pharmaceutical excipients are important material foundations for ensuring the production, development and application of pharmaceutical preparations.
### Homology of medicine and pharmaceutical excipients

<table>
<thead>
<tr>
<th>Name</th>
<th>API</th>
<th>Pharmaceutical excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (for injection)</td>
<td>Improve Blood Circulation, Anti-aging, etc.</td>
<td>Anti-oxygen</td>
</tr>
<tr>
<td>VC (for injection)</td>
<td>Reduce the incidence of cancer, etc.</td>
<td>Anti-oxygen</td>
</tr>
<tr>
<td>Mannitol (for injection)</td>
<td>Diuretic, dehydrant, etc.</td>
<td>Solubilizer, flavoring agents, disintegrating agent, etc.</td>
</tr>
<tr>
<td>Ethanol (for injection)</td>
<td>Sterilize</td>
<td>Solvent, sanitizer, etc.</td>
</tr>
<tr>
<td>Sorbitol (for injection)</td>
<td>Treat encephalede and glaucoma</td>
<td>Plasticizer, emulgator, filling agent</td>
</tr>
<tr>
<td>Lecithin (for injection)</td>
<td>Protect liver, Anti-aging, etc.</td>
<td>Emulgator, solubilizer, stabilizer, etc.</td>
</tr>
</tbody>
</table>

#### Pharmacological effect
- **Drug action:**
  - The action of drugs is a molecular reaction mechanism, which has its own specificity, and is the manifestation of the body's reaction to the drug. It is the basis for classifying drugs and the basis for guiding drug use and prescribing doses.

#### Toxic effect
- **Toxic effect:**
  - The toxic effect of drugs refers to the change in body function and tissue pathological changes caused by drug use, usually due to the individual differences in the body, pathological states, or the combined use of other drugs, resulting in increased sensitivity. When drug use exceeds the therapeutic dose, it is easy to cause toxic effects.

### Different understanding of pharmaceutical excipients

#### Pharmacopoeia records = No safety risk (GRAS)?

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Risk / No risk?</th>
<th>Pharmaceutical excipients risk</th>
<th>Usage risk</th>
<th>Risk level</th>
<th>Critical excipient risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Different understandings of class I, II and III changes

<table>
<thead>
<tr>
<th>Risk / Inactivity?</th>
<th>Risk level</th>
<th>Critical excipient risk</th>
<th>Macromolecule/micro molecule classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Solution
- The other one
- Someone
Sergio Canavero used PEG (聚乙二醇) as adhesive (粘合剂) in human head transplantation (换头术). It has been reported that PEG can promote nerve growth in spinal cord in animal experiments. (PEG在动物实验中，有促使脊髓的神经生长的作用)
**UPCC-MS**

Content limit set-up of polymerization degree distribution by UPCC-MS

<table>
<thead>
<tr>
<th>Polymerization (n)</th>
<th>Content limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>≤5%</td>
</tr>
<tr>
<td>5≤n≤52</td>
<td>≥90%</td>
</tr>
<tr>
<td>13≤n≤58</td>
<td>≤5%</td>
</tr>
</tbody>
</table>

**Relative deviations of average molecular weights of PEG400 samples were all less than 4.0%**

**Degree of polymerization of PEG400 and its distribution can be accurately measured by UPCC-MS**

**PEG400 Standard**

**Sample 1**

**Sample 2**

**Sample 3**

**Sample 4**

**Sample 5**

**UPCC-MS spectra of PEG400 from different manufacturers**

**PEG400 measured by UPCC-MS**

**Polyethylene glycol (PEG)**

- **PEG polymers**
  - compound of repeating units of ethylene glycol,
  - is generally considered biologically inert and safe in humans.

- **PEGylation of drugs**
  - is extensively used to improve their PK properties
  - increase therapeutic efficiency
  - diminish the potential for immunogenicity and toxicity.

- **lead to significant PEG accumulation in tissues**
  - with chronic administration
  - potentially result in adverse effects.

- **LC-MS/MS based on MRM scanning mode has excellent performance in quantitative analysis**

- **Gold standard for analysis of limited and definite drugs**

- **The drug (MW > 400Da) usually excreted by bile.**
- **Interesting, PEG-4k excrete mainly by renal excretion.**
- **PEG may be a flexible molecular.**
- **PEG can excrete through kidney.**

**The cumulative excretion of PEG4000 after intravenous administration accounted for the percentage of the dose.**

**Anal. Chem. 2017, 89, 5193-5200---SCI 6.32**
### Risk level of pharmaceutical excipients

Risks of pharmaceutical excipients themselves and risks of their use should be considered together.

### Risk level:
- **High**
- **Medium**
- **Low**

<table>
<thead>
<tr>
<th>Risk level of excipients</th>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of excipients</td>
<td>(Excipients for injection from animals/Lactose)</td>
<td>Medium risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Medium risk of excipients</td>
<td>High risk</td>
<td>Medium risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Low risk of excipients</td>
<td>Medium risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

*Characteristics: Oral solid preparations, low dosage, low safety risk*

- This is from Announcement on Associated Review and Approval of Pharmaceutical Packaging Materials and Pharmaceutical Excipients with Drugs ([2016] No.134).

- In this slide, some sweetening agents, flavors, colorants, pH adjusters and other pharmaceutical excipients used in preparations that may not be reviewed and approved according to the requirements of Announcement No.134, because of their usage and characteristics.
Characteristics and risks of pharmaceutical excipients

**Types of DMEs**

- **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**

**What is critical excipients?**

It is dependent on their characteristics, functions, usages and dosage.

**Diverse Sources**

- **From animals** (TSE, Infectious microbial infections, viral inactivation, etc.), plants (pesticide residue, Biotoxin contamination, Transgenic species, etc.), Minerals, Chemical synthesis

**Complex Production Process**

- Extraction, Synthesis (focus on the mass of monomer, initiator, catalyst), Semi-synthesis (focus on naturals), Purification, etc.

**Different Routes of Administration**

- Oral, injection, topical, ophthalmic, nasal, otic, venous, etc. (High-risk: injection, inhalation, ophthalmic)

**Different Dosage**

- Oral tablet (Compound Aspirin Tablets: over 90% excipients), Injection (Intravenous fat emulsion: about 19% excipients)

**Classifying Management**

- Risk control should be carried out according to the route of administration and the amount of prescription. Pay attention to high-risk pharmaceutical excipients (Solubilizer, preservative in injection)
- Excipients are inert, non-toxic/safety risks; suppliers are free to change and there is the risk from quality differences.

**Different Cognition**

- Recognition is different.
According to the classification method of macromolecular excipients and micromolecule excipients, the quality status of domestic pharmaceutical excipients can be evaluated objectively from the application and quality control of excipients. The classification of pharmaceutical excipients includes:

1. **Classified by difficulty level of quality control**
   - Macromolecule/micromolecule classification
   - Pharmaceutical excipients are important for drug safety and quality. Recent drug safety incidents have shown the importance of pharmaceutical excipients in ensuring drug safety and quality.

2. **Classified by source**
   - Natural products, polynucleotides, and synthetic products
   - Classified by formulation for preparation
   - Tablets, injections, capsules, granules, plants, nasal sprays, suppositories, and pellets

3. **Classified by usage**
   - Solvents, suspension agents, solvents, emulsifiers, colorants, adhesives, disintegrants, lubricants, wetting agents, osmotic pressure regulators, stabilizers, free-flowing agents, antistatic agents, and antiadhesive agents

4. **Classified by route of administration**
   - Oral, injectable, mucosal, dermal, topical, nasal, and ocular administration

### Recent Safety Incidents

- **Qi Er Yao accident (65 cases, 9 deaths)**
- **Plasticizer, PVC accident**
- **“地沟油代替大豆油制作抗生素中间体”事件**
- **“铬超标胶囊事件”**
- **“地沟油代替大豆油制作抗生素中间体”事件**
- **Multistate Outbreak of Fungal Meningitis from NECC, 64 deaths**

### Chinese Pharmacopeia records

<table>
<thead>
<tr>
<th>Country</th>
<th>Actual use</th>
<th>Pharmacopeia records</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>543 kinds</td>
<td>270 kinds</td>
</tr>
<tr>
<td>USA</td>
<td>1500 kinds</td>
<td>525 kinds</td>
</tr>
<tr>
<td>Europe</td>
<td>3000 kinds</td>
<td>280 kinds</td>
</tr>
<tr>
<td>Japan</td>
<td>1000 kinds</td>
<td>131 kinds</td>
</tr>
</tbody>
</table>

Classification of pharmaceutical excipients

- QB. P  
  - Classified by source: natural products, polynucleotides, and synthetic products
  - Classified by formulation for preparation: tablets, injections, capsules, granules, plants, nasal sprays, suppositories, and pellets
  - Classified by usage: solvents, suspension agents, solvents, emulsifiers, colorants, adhesives, disintegrants, lubricants, wetting agents, osmotic pressure regulators, stabilizers, free-flowing agents, antistatic agents, and antiadhesive agents
  - Classified by route of administration: oral, injectable, mucosal, dermal, topical, nasal, and ocular administration

Pharmaceutical excipients are important for drug safety and quality. Recent drug safety incidents have shown the importance of pharmaceutical excipients in ensuring drug safety and quality.

Safety accidents caused by pharmaceutical excipients

- Qi Er Yao accident (65 cases, 9 deaths)
- Plasticizer, PVC accident
- "地沟油代替大豆油制作抗生素中间体" event
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Pharmaceutical excipients are important for drug safety and quality. Recent drug safety incidents have shown the importance of pharmaceutical excipients in ensuring drug safety and quality.
On Jun 21, 2011

- The plasticizer diisodecyl phthalate (DIDP) in the Libatin (for children's preparation) PVC cap volatilizes and spreads into the drug.

- Qualitative Analysis of Libatin PVC Caps by IR

![PVC Standard IR](image1)

![PVC Sample IR](image2)

In September 2012, fungal meningitis broke out in USA, which resulted in 64 deaths in 9 states. The reason was that they received methylprednisolone acetate (MPA) steroid injections contaminated by fungal from the New England Compounding Center (NECC) in Framingham. In January 2015, The United States Department of Justice has decided to sue 14 employees of NECC for second-degree murder.
The quality risks of pharmaceutical excipients exist throughout the production, distribution and usages. Mainly in the following aspects:

- **Safety**
  - Source and Method (animals, plants, minerals, chemical synthesis)
  - Manufacturing process (Extraction, Synthesis, Semi-synthesis, Purification)
  - Detrimental impurity

- **Functionality**
  - Batch stability (sustained-release preparations)
  - Supplier quality variance
  - Route of administration (Oral, injection, topical, ophthalmic, nasal, otic, venous, etc.)
  - Macromolecule: composition, molecular weight and its distribution, degree of polymerization, catalyzer, monomer

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02 Risks of pharmaceutical excipients
03 Classifying management of pharmaceutical excipients
04 Technical requirements of pharmaceutical excipients
05 Conclusion
### Comparison of Pharmaceutical Excipients Review & Approval System in China and ICH

#### Regulation Management

<table>
<thead>
<tr>
<th>USA</th>
<th>EU</th>
<th>Japan</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacetical excipient management system</td>
<td>DMF</td>
<td>CEP certification</td>
<td>Provide dossier with preparaons</td>
</tr>
<tr>
<td>Review &amp; Approval</td>
<td>Dependent, review &amp; approval with preparations, Pharmaceutical excipient unapproved</td>
<td>Independent (EDQM)</td>
<td>Dependent, review &amp; approval with preparations, Pharmaceutical excipient unapproved</td>
</tr>
<tr>
<td>Critical excipient</td>
<td>Excipients collected in EP, COS certification</td>
<td>Excipients not collected in EP</td>
<td>New excipients, generic drug and coprocessed excipient</td>
</tr>
<tr>
<td>Range</td>
<td>Type II DMF</td>
<td>EDMF&amp;COS: EDMF applies to all APIs. COS certification can handle substances collected in EP, including APIs and pharmaceutical excipients.</td>
<td>Only after the MF registration information is replaced with a formal registration number, the review of drug marked applications will start.</td>
</tr>
</tbody>
</table>

---

**What is critical excipients?**

It is dependent on their characteristics, functions, usages and dosage.

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**FDA—DMF**

- Manufacturers provide DMF application
- FDA accepts and carries out formal examination
- Approve: receive DMF number
- DMF holder sends authorized value
- Drug Manufacturers provide IND, NDA, ANDA applications
- Associated review by CDER
- Proposed Pharmaceutical excipients / Packaging Material defect with preparations
- Update / Charge Activate DMF
- Proposed Reference Information

**Types of DMF**

1. **Type II Drug Substance, Drug Substance Intermediate and Material Used in Their Preparation, or Drug Product**
   - Key excipients, key materials or drugs in the product
   - Associated review by CDER

2. **Type III Packaging Material**
   - Associated review by CDER

3. **Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation**
   - Associated review by CDER

---

**Type II DMF**

- EDMF&COS: EDMF applies to all APIs. COS certification can handle substances collected in EP, including APIs and pharmaceutical excipients.
- Only after the MF registration information is replaced with a formal registration number, the review of drug marked applications will start.
**Situation of standards of pharmaceutical excipients for injection in Ch.P 2015 edition**

**Monograph Management**

<table>
<thead>
<tr>
<th>Name</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxymethylcellulose sodium</td>
<td>崩解剂</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>抗氧剂</td>
</tr>
<tr>
<td>Maltose</td>
<td>稀释剂</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>碱化剂</td>
</tr>
<tr>
<td>Putaamine</td>
<td>崩解剂</td>
</tr>
<tr>
<td>Glycine</td>
<td>酸化剂</td>
</tr>
<tr>
<td>Sodium dihydrogen phosphate</td>
<td>缓冲剂</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>抗菌剂</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>防腐剂</td>
</tr>
<tr>
<td>Sodium sulfite</td>
<td>治疗剂</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>酸化剂</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>填充剂</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>防腐剂</td>
</tr>
<tr>
<td>Steroid base</td>
<td>软膏基质</td>
</tr>
<tr>
<td><strong>Monograph Management</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Pharmaceutical excipients for injection in Ch.P 2015 edition**

- Compared with the global pharmacopoeia, pharmaceutical excipients for injection in Ch.P 2015 edition is up to 23. But it still can not reach the number of injectable excipients (about 140 kinds).

![Figure 1. 23 kinds of pharmaceutical excipients for injection recorded in Ch.P 2015](image)
### Excipients for injection

#### Overview

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Phosphate Dihydrogen Trihydrate**

**Egg Yolk Lecithin for injection**

**Egg Yolk Lecithin for injection**

**Water for Injection**

**Cholesterol for Parenteral Use**

**Soybean lecithin for injection**

**Dextran 1 for injection**

**PLGA (50/50)**

**PLGA (75/25)**

**PLGA (85/15)**

**Pregelatin**

**PEG300**

**PEG400**

**PEG3000**

**Soya lecithin**

**Carbohydrate**

**Purified water**

**Technical requirements of pharmaceutical excipients**

**Conclusion**

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05 Conclusion
### Technical Requirements for Pharmaceutical Excipients Standards for Injection

#### Items of Pharmaceutical Excipient Monograph

<table>
<thead>
<tr>
<th>Name</th>
<th>Molecular Formula</th>
<th>CAS Number</th>
<th>Source &amp; Method</th>
<th>Structure</th>
<th>Characteristic</th>
<th>Impurities</th>
<th>Test</th>
<th>Content</th>
<th>Type</th>
<th>Storage</th>
<th>Depressor Substances or Pressor Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate80</td>
<td>Poloxamer 188</td>
<td>[CAS] 20500-00-0</td>
<td>Ethylation of glucose</td>
<td>Poly(oxyethylene) polymer</td>
<td>Detergent behavior</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

#### Items that should be paid attention to in Pharmaceutical Excipients for Injection Monograph

<table>
<thead>
<tr>
<th>Source</th>
<th>Manufacturing Process</th>
<th>Impurities</th>
<th>Macromolecule</th>
<th>Route of Administration (for Injection)</th>
<th>Excipients Absorption and Potential Toxicity</th>
<th>Bacterial Endotoxin/Sterility</th>
<th>Abnormal Toxicity</th>
<th>Osmotic Pressure</th>
<th>Depressor Substances or Pressor Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Technical Requirements for Pharmaceutical Excipients Standards for Injection

23(in Ch.P 2015) / 270(Total)

For example, Polysorbate80(for injection), Lactose, Lecithin, Activated carbon, Hydroxypropyl-β-cyclodextrin, Povidone, Benzalkonium chloride.

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### Polysorbate80 (for injection)

Polysorbate80 (Tween80) 聚氧乙烯脱水山梨醇单油酸酯，属于亲水型非离子型表面活性剂，可广泛应用于药品、食品、化妆品等。

#### Complex ingredient 组分复杂性：

1. **parent nucleus** (sorbitan/一失水; isosorbide/二失水)

2. fatty acids (oleic acid, linoleic acid, palmitic acid, stearic acid, etc.)

3. esterification of oleic acid (monoester, diester, triester, tetraester)

4. polymerization of ethylene oxide

#### Theoretical structure of polysorbate80

\[ x + y + z + w = 20 \]

---

#### 2006年6月1日鱼腥草注射液系列药品由于发生严重不良反应，被国家食品药品监督管理总局紧急叫停。
### Comparison of production process of polysorbate80

<table>
<thead>
<tr>
<th>No.</th>
<th>Traditional process</th>
<th>Modern process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>聚山梨酯80成品中聚乙二醇含量高</td>
<td>聚山梨酯80聚乙二醇含量未检测出</td>
</tr>
<tr>
<td>2</td>
<td>成品色度是APHA≤400#</td>
<td>成品色度是APHA≤60#</td>
</tr>
<tr>
<td>3</td>
<td>选用的油酸含量≥70%</td>
<td>选用的油酸含量≥90%</td>
</tr>
<tr>
<td>4</td>
<td>生产过程较难控制，指标波动大</td>
<td>生产过程容易控制，指标稳定</td>
</tr>
<tr>
<td>5</td>
<td>成品中含有油酸聚氧乙烯醚</td>
<td>成品中有微量的油酸聚氧乙烯醚</td>
</tr>
<tr>
<td>6</td>
<td>环氧乙烷，二氧六环杂质超标</td>
<td>环氧乙烷，二氧六环杂质减少</td>
</tr>
<tr>
<td>7</td>
<td>乙二醇，二甘醇杂质更多</td>
<td>乙二醇，二甘醇杂质少</td>
</tr>
</tbody>
</table>

### Polysorbate80 for injection monograph in 2015 Ch.P

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>性状</td>
<td>本品为淡黄色至橙黄色的黏稠液体；微有特臭，味微苦略涩，有温热感</td>
<td>本品为淡黄色至橙黄色的黏稠液体；微有特臭，味微苦略涩，有温热感</td>
</tr>
<tr>
<td>溶解性</td>
<td>在20°C时应为1.06-1.09</td>
<td>在20°C时应为1.06-1.09</td>
</tr>
<tr>
<td>黏度</td>
<td>在25°C时（毛细管内径为2.0<del>2.5mm）为350</del>550mm²/s</td>
<td>在25°C时（毛细管内径为2.0<del>2.5mm）为350</del>450mm²/s</td>
</tr>
<tr>
<td>酸值</td>
<td>不得过2.0</td>
<td>不得过1.0</td>
</tr>
<tr>
<td>皂化值</td>
<td>45~55</td>
<td>45~55</td>
</tr>
<tr>
<td>羟值</td>
<td>65~80</td>
<td>65~80</td>
</tr>
<tr>
<td>碘值</td>
<td>18~24</td>
<td>18~24</td>
</tr>
<tr>
<td>过氧化值</td>
<td>不得过10</td>
<td>不得过3</td>
</tr>
</tbody>
</table>
| 鉴别         | (1) 取本品的水溶液（1→20）5ml，加氢氧化钠试液5ml，煮沸数分钟，放冷，用稀盐酸酸化，显乳白色浑浊。
(2) 取本品的水溶液（1→20），滴加溴试液，溴试液即褪色。
(3) 取本品6ml，加水4ml混匀，呈胶状物。
(4) 取本品的水溶液（1→20）10ml，加硫氰酸钴铵溶液（取硫氰酸钴铵17.4g与硝酸钴2.8g，加水溶解成100ml）5ml，混匀，再加三氯甲烷5ml，振摇混合，静置后，三氯甲烷层显蓝色。 | (1) 取本品的水溶液（1→20）5ml，加氢氧化钠试液5ml，煮沸数分钟，放冷，用稀盐酸酸化，显乳白色浑浊。
(2) 取本品的水溶液（1→20），滴加溴试液，溴试液即褪色。
(3) 取本品6ml，加水4ml混匀，呈胶状物。
(4) 取本品的水溶液（1→20）10ml，加硫氰酸钴铵溶液（取硫氰酸钴铵17.4g与硝酸钴2.8g，加水溶解成100ml）5ml，混匀，再加三氯甲烷5ml，振摇混合，静置后，三氯甲烷层显蓝色。 |
| 酸碱度       | pH5.0~7.5 | pH5.0~7.5 |
| 颜色         | 取本品10ml，与同体积的黄色2号标准液比较（附录IX A），不得更深 | 取本品10ml，与同体积的黄色2号标准液比较（附录IX A），不得更深 |
| TEG          | NMT 0.01% | NMT 0.01% |
| 水分         | 不得过3.0% | 不得过0.5% |
| 炽灼残渣     | 不得过0.2% | 不得过0.1% |
| 重金属       | 不得过10ppm | 不得过10ppm |
| 砷盐         | 不得过2ppm | 不得过2ppm |
| Fatty Acid Composition | NLT 58.0%，含肉豆蔻酸、棕榈酸、棕榈油酸、硬脂酸、亚油酸与亚麻酸分别不得大于5.0%、16.0%、8.0%、6.0%、18.0%与4.0% | NLT 98.0%，含肉豆蔻酸、棕榈酸、棕榈油酸、硬脂酸、亚油酸与亚麻酸分别不得大于0.5%、1.0%、1.0%、1.0%、1.0%与0.1% |
| Bacterial endotoxin | Aldehydes? | Aldehydes? |
| Sterility     | 取本品，依法检查（附录XI H），应符合规定 | 取本品，依法检查（附录XI H），应符合规定 |
Composition differences of Polysorbate80 from different manufacturers

Composition of polysorbate80 synthesized from different oleic acid purity

- Different factory products in composition 1 (PEG/PS/PI), composition 2 (PSM) and composition 4 (PSD) have relatively large differences.
- The peak area sum of the polyethyleneglycol components of brands 2-7 is significantly less than the peak area sum of the reference component. This indicates that these different manufacturers' polyethyleneglycol 80s contain other unknown substances or impurities.

Conclusion

The composition of Polysorbate80 produced by different factories and different processes is obvious different, which indicates that its functional and biological effects are also different.

Modern process

Traditional process

Comparative chromatogram of polysorbate80 products from different manufacturing processes

Discrete distribution of the relative content (%) of polysorbate80 components from different manufacturers

Composition differences of Polysorbate80 from different manufacturers

Different factory polyethyleneglycol 80 products have obvious differences in composition, indicating that their functional and biological effects are also different.

Allergic impurities in injectable excipients — protein in lactose

The residual protein in lactose is a risk factor for the safety of injections.

Residual protein in lactose %

- α-Lactalbumin (α-乳糖蛋白): 19.7%
- β-Lactoglobulin (β-乳球蛋白): 43.6%
- BSA (牛血清白蛋白): 4.7%
- Ig (免疫球蛋白): 3%
- Other proteins (其他蛋白): 29%

The residual protein in lactose is a risk factor for the safety of injections.

Acute Allergic Reaction due to Milk Proteins Contaminating Lactose Added to Corticosteroid for Injection

The residual protein in lactose is a risk factor for the safety of injections.

19
39批乳糖中残留蛋白氮含量在11.5ppm-99.3ppm之间，按照口服级标准，39批样品都合格，由于本次抽样39批乳糖样品大多来自注射剂生产厂家，这些批次的乳糖用在注射剂中，则会有一定的风险。国内外尚无注射级乳糖的法定标准，国外肺部给药吸入乳糖的残留蛋白氮含量规定为32ppm，国家食品药品监督管理局在《新药用辅料非临床安全性评价指导原则》中将注射用辅料与肺部给药辅料的安全性归为一类，故本次抽验注射级乳糖残留蛋白氮含量限量定为32ppm。按此标准，39批样品中有14批不合格，不合格率为36%，值得关注的是并不是所有国外产品的残留蛋白氮含量都合格，提示企业不能完全迷信国外产品的质量，如果乳糖用于注射，买回原料后，企业应先提纯降低残留蛋白后再使用。
Different sources of lecithin have different compositions

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Soya Lecithin</th>
<th>Egg Yolk Lecithin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC/PC20:20</td>
<td>57.8%</td>
<td>73.0%</td>
</tr>
<tr>
<td>PE/PE20:20</td>
<td>13.3%</td>
<td>15.0%</td>
</tr>
<tr>
<td>PI/PI22:1</td>
<td>2.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>LPC/LPC18:1</td>
<td>3.2%</td>
<td>5.8%</td>
</tr>
<tr>
<td>LPE/LPE18:1</td>
<td>0.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Others/Other</td>
<td>22.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Different fatty acid ester chains

Measure: Establish four monographs (different sources and routes of administration) separately

Substances cause Haemolysis or agglutination
—lyso phosphatide in lecithin

Unqualified rate was 22%

http://www.nicpbp.org.cn

Christoph Wabel (1998), Ph. D. thesis

18批卵磷脂国家抽验样品中有4批样品不符合规定，溶血磷脂酰乙醇胺的不合格率为22%——2013年抽验
Activated carbon (For injection)
活性炭（供注射用）

About 1.5 billion bags of activated carbon are used each year.
每年115亿袋的大输液使用量/其他

Adsorption is the CMA of activated carbon. The requirement in Ch.P 2015 edition is higher than in 2010 edition, which is consistent with that in the USP.
吸附力是主要功能性指标，2015版标准比2010版标准高，但与USP标准一致

Function: To adsorb endotoxin, which is not allowed to contain in activated carbon. Otherwise it will pollute drugs.
作用是吸附内毒素，但本身不允许含有，否则会污染药物

Adsorption is the critical function attribute of activated carbon.
吸附力是活性炭的主要功能性和质量评价指标

Quality control research is being carried out for the risk control of nanoparticles below 200nm that cannot be filtered in activated carbon.
对于活性碳中无法过滤的200nm以下纳米微粒的风险控制，正在进行质控研究

Activated carbon (For injection)
活性炭(供注射用)

Ch.P 2015版标准

Adsorption is the CMA of activated carbon. The requirement in Ch.P 2015 edition is higher than in 2010 edition, which is consistent with that in the USP.
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### Hydroxypropyl - β - cyclodextrin

**Item** | **Year** | **Acceptability (%)** | **Pharmacopoeia Criterion**
--- | --- | --- | ---
Propylene oxide (PO) | 2016 | 66.7 | USP 1ppm
Residual protein | | 58.3 | Nitrogen content ≤ 0.01%

**Risks**
- Not set Bacterial endotoxin, Microbial limit and Sterility items
- No restrictions on propylene oxide residues
- No residual protein control

**Measures**
- It is recommended to add bacterial endotoxin, microbial limit, sterility, propylene oxide, residual protein, conductivity, etc.
- It is recommended to measure the degree of substitution by NMR.

### Povidone——2-pyrrolidone

**Comparison of N-vinylpyrrolidone, aldehyde and hydrazine in povidone from different national pharmacopoeia**

<table>
<thead>
<tr>
<th>Pharmacopeia</th>
<th>N-Vinyl-2-pyrrolidone Limit (200 times)</th>
<th>≤ 0.2%</th>
<th>USP35/NF30</th>
<th>≤ 0.001%</th>
<th>BP2013/EP7.0</th>
<th>≤ 0.001%</th>
<th>JP16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>100%</td>
<td></td>
<td>≥ 0.02%</td>
<td></td>
<td>54.2% (其中超标的样品都是国产样品)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldehyde</td>
<td>Limit (40 times)</td>
<td>≤ 0.2%</td>
<td>≤ 0.05%</td>
<td>≤ 0.05%</td>
<td>≤ 0.05%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>100%</td>
<td></td>
<td>68.7% (超标的样品也都是国产样品)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrazine</td>
<td>Limit</td>
<td>未规定</td>
<td>≤ 0.0001%</td>
<td>≤ 0.001%</td>
<td>≤ 0.001%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>批国产样品合格</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Manufacturing process of povidone to remove 2-pyrrolidone**

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-filtration membrane filtration</td>
<td>Low material loss and short time</td>
</tr>
<tr>
<td>Adsorption</td>
<td>High cost and more polluted water</td>
</tr>
<tr>
<td>Disintegrant, adhesive, etc</td>
<td>Time consuming and large material loss</td>
</tr>
</tbody>
</table>

Disintegrant, adhesive, etc
Toxicity of 2-pyrrolidone impurities

According to the European Chemicals Agency (ECHA), the no observed adverse effect level (NOAEL) of 2-pyrrolidone is 207mg/kg/d. And based on ICH Q2C, the acceptable daily intake (ADI) of 2-pyrrolidone is calculated to be 41.4mg/d.

Guidance for Industry

QIC Impurities: Residual Solvents

In summary, it is scientific and reasonable that 2-pyrrolidone limit is NMT 0.5%.

In the FDA’s 1978 announcement, all products used in intravenous injection or containing PVP were recalled. Because PVP interferes with the coagulation process and affects the identification of blood type in blood transfusion or distribution.

The limit of 2-pyrrolidone is an urgent problem

The limit of 2-pyrrolidone is NMT 0.5% in Copovidone monograph from USP, EP and BP. Both povidone and copovidone are water-soluble substances with similar uses and the routes of administration, so the limit of 2-pyrrolidone should be the same, ‘NMT 0.5%’.

Ophthalmic excipient——Benzalkonium chloride

Benzalkonium chloride

No. Batch No. Manufactures Proportion of composition

<table>
<thead>
<tr>
<th>No.</th>
<th>Batch No.</th>
<th>Manufactures</th>
<th>Proportion of composition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n-C_{12} (%)</td>
<td>n-C_{14} (%)</td>
</tr>
<tr>
<td>Y1</td>
<td>20150618</td>
<td>A</td>
<td>100</td>
</tr>
<tr>
<td>n-C_{14} monomer</td>
<td>C1520084</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>n-C_{16} monomer</td>
<td>D1514040</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

MIC (最小抑菌浓度)

<table>
<thead>
<tr>
<th>样品名称</th>
<th>金黄色葡萄球菌</th>
<th>大肠埃希菌</th>
<th>白色念珠菌</th>
<th>黑曲霉</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{12}单体</td>
<td>1.23</td>
<td>48.83</td>
<td>24.41</td>
<td>3.05</td>
</tr>
<tr>
<td>C_{14}单体</td>
<td>3.05</td>
<td>6.19</td>
<td>6.10</td>
<td>12.21</td>
</tr>
<tr>
<td>C_{16}单体</td>
<td>3.05</td>
<td>24.41</td>
<td>3.05</td>
<td>6.19</td>
</tr>
</tbody>
</table>

每种单体和不同烷基组成比例的样品，对金黄色葡萄球菌、大肠埃希菌、白色念珠菌和黑曲霉等4种细菌的MIC明显不同。
Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation stinging or pain in the eye after using this medicine, talk to your doctor.

苯扎氯铵可能会引起眼睛刺痛，尤其是眼睛干涩或者患有眼部疾病时。用药后一旦感到眼睛不适、肿胀或者疼痛，应咨询医生后再用药。

HPLC-MS can separate C_{10}, C_{12}, C_{14} and C_{16}, and analyze them accurately and quantitatively.

- HPLC-MS: ACQUITY UPLC H-Class PDA-QDa system; Column: Intersil CN column, 3um, 4.6X100 mm; Temperature: 35℃; Injection volume: 5-8uL; Detection wavelength: 215nm; QDa detection: ESI+, Scan, SIR mode; Mobile Phase A: acetonitrile; mobile phase B: 100 mM NH4Ac in water (pH = 5.0); Flow rate: 1.00 ml/min; Isocratic elution: A/B = 50:50
The toxicity of C_{10}, C_{12}, C_{14} and C_{16} increased in turn, and C_{12} should be used when used in eye preparations.

C_{10}, C_{12}, C_{14}和C_{16}的毒性依次递增，当用于眼用制剂时，应使用C_{12}苯扎氯铵。
Pharmaceutical excipients are important components of drugs, which quality could affect the quality and safety of drugs directly, especially the pharmaceutical excipients for injection. A quality problem with a drug can only affect one point, but if a quality problem with a kind of excipient affects all drugs that use the excipient, then drug will be affected in whole.

For many years, China attaches great importance to the quality of excipients and implement review and approval management, which guarantees overall quality of excipients.

Furthermore, on the one hand, the quality and safety of excipients for injection, interaction with API, influence of preparations on absorption and effectiveness ought to be paid more attention. On the other hand, it is necessary to strengthen the study of Critical Quality Attributes of excipients, which could help manufactures find out the difference between domestic excipients and original excipients and guide them to select excipients scientifically. It could enhance the quality of domestic excipients and promote the industrialization level fundamentally in order to improve the safety of drugs.
Thank You!

010-67095721
sunhm@126.com
010-67052750