Considerations for Production and Quality Control of Animal Derived Pharmaceutical Excipients

Chinese Pharmacopoeia Commission

Comprehansive Division
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Main Contents

- Relevant Background
- Compendial Requirements
- Key Points for Quality Control
- Working Progress
Importance of Pharmaceutical Excipients

The management provisions for nonactive materials are derived from the specifications for use of pigments in foods and drugs.

- **1906, Pure Food and Drug Act**
  
  Seven (7) synthetic organic pigments may be used in an appropriate range.

  Any one using a pigment other than the 7 pigments will be prosecuted.

- **1937, The “Sulfonamide Elixir Event” made the United States Congress to pass the "Food, Drug, and Cosmetic Act”**

  (To facilitate oral administration in children, Harold Wotkins, a chief pharmacist in a company in the United States, used diglycol as solvent instead of alcohol, leading to renal failure in 358 persons, and deaths of 107 persons)

Animal source excipients in Chinese Pharmacopoeia

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Species</th>
<th>Source</th>
<th>Serial No.</th>
<th>Species</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Taurine</td>
<td>Separated from bezoar; Terrestrial mammals have higher levels of liver and bile; marine animals such as cuttlefish, octopus, fish, and shellfish such as oysters and clams</td>
<td>11</td>
<td>shellac</td>
<td>Animal-derived fatty resin</td>
</tr>
<tr>
<td>2</td>
<td>Lanolin-free lanolin</td>
<td>Wool</td>
<td>12</td>
<td>Sodium caseinate</td>
<td>Cow, sheep</td>
</tr>
<tr>
<td>3</td>
<td>shellac</td>
<td>Animal-derived fatty resin</td>
<td>13</td>
<td>Sulfuric acid fish egg</td>
<td>Fish</td>
</tr>
<tr>
<td>4</td>
<td>Egg yolk lecithin</td>
<td>Egg</td>
<td>14</td>
<td>Lactose for inhalation</td>
<td>Animal milk</td>
</tr>
<tr>
<td>5</td>
<td>Cetyl</td>
<td>Whale</td>
<td>15</td>
<td>Heparin sodium</td>
<td>Pig</td>
</tr>
<tr>
<td>6</td>
<td>Egg yolk lecithin (for injection)</td>
<td>Wool</td>
<td>16</td>
<td>glycerin</td>
<td>Natural animal and vegetable fat refining</td>
</tr>
<tr>
<td>7</td>
<td>Cholic acid, sodium cholate</td>
<td>Pig bile</td>
<td>17</td>
<td>Lactic acid</td>
<td>Fermentation</td>
</tr>
<tr>
<td>8</td>
<td>cholesterol</td>
<td>Fresh animal offal, bone marrow and brain, wool grease</td>
<td>18</td>
<td>Capsule gelatin</td>
<td>Bovine bone, pork bone</td>
</tr>
<tr>
<td>9</td>
<td>Squalane</td>
<td>Shark liver (botanical)</td>
<td>19</td>
<td>Squalane</td>
<td>Shark liver (botanical)</td>
</tr>
<tr>
<td>10</td>
<td>Bovine serum</td>
<td>Fetal calf, newborn calf</td>
<td>20</td>
<td>Human albumin</td>
<td>Human plasma</td>
</tr>
</tbody>
</table>
### Safety Events of Animal Derived Raw materials/Excipients

<table>
<thead>
<tr>
<th>Time</th>
<th>Country</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>China</td>
<td>Capsules with out-of-limit Chromium</td>
</tr>
<tr>
<td>2008</td>
<td>China</td>
<td>Strengthen supervision and examination of Cerebroprotein Hydrolysate Injection</td>
</tr>
<tr>
<td>2008</td>
<td>American</td>
<td>“Heparin Sodium” Event</td>
</tr>
<tr>
<td>2010</td>
<td>Europe/ American</td>
<td>Porcine circovirus DNA was detected in oral rotavirus vaccine (Rotarix and RotaTeg)</td>
</tr>
<tr>
<td>2015</td>
<td>China</td>
<td>Deproteinized Calf Extract Injection was manufactured was not complies with the approved process</td>
</tr>
<tr>
<td>2016</td>
<td>China</td>
<td>CFDA stopped import of Cerebroprotein Hydrolysate Injection manufactured by a manufacturer</td>
</tr>
</tbody>
</table>

### Legal requirements for control of animal-derived materials in China

<table>
<thead>
<tr>
<th>Year</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Technical Guideline of Live Vaccine Products for Prevention, with Virus as Vector</td>
</tr>
<tr>
<td>2008</td>
<td>Technical Methods for Viral Removal/Inactivation of Blood Products, and Technical Guidelines for their Validation</td>
</tr>
<tr>
<td>July 10, 2002</td>
<td>- Notice for Further Strengthening Supervision and Management of Bovine-derived Materials and Relevant Drugs, State Drug Supervision Registration No.(2002)238</td>
</tr>
<tr>
<td>March 20, 2003</td>
<td>- Technical Guideline for Production and Quality Control of Bovine Serum for Cell Cultivation</td>
</tr>
</tbody>
</table>
Gelatin for Capsules

- **Chinese Pharmacopoeia edition 2015 vol.II and vol.IV**
  - Products from Purification after Incomplete Acid Hydrolysis, Alkaline Hydrolysis, or Enzymatic Degradation of Collagens in Animal Skin, Bone, Tendon, and Ligament

- **General Rules for Empty Capsules (draft)**
  - Products from Purification after Incomplete Acid Hydrolysis, Alkaline Hydrolysis, or Enzymatic Degradation of Collagens in Health Animal Skin (pig or ox, etc.) or Bone (pig and ox), which are mainly derived from fresh bovine bone, pig skin, and bovine skin, and minorly derived from pig bone, etc.
  - The supplier for raw materials has a quarantine conformance certificate issued by a respective authority, and keeps relevant records, so that they are of traceable sources; bovine-derived materials are derived from animals in a district without prevalence of BSE.

- **EP 9.0**
  - Gelatin is derived from solidified or nonsolidified natural or dissolvable proteins derived from hydrolysis of animal skin or bone collagens
  - For animal bone:
    - Skull and spinal bone are removed for collection of bovine bone as raw material, of any age, any country source
    - Vertebra are removed, derived from oxen aged more than 30 months
    - Bovine femur for production of medical capsules for gastrointestinal administration is obtained from a district without BSE or at controllable risk

Relevant requirements in the ChP

- **Chinese Pharmacopoeia edition 2015 vol.II and vol.IV**
  - **Tissue Extract**
    - For drugs derived from extraction of animal tissues, the species of the animal used is clearly defined;
    - The organ used is derived from healthy animals through quarantine inspection.
    - The organ of bovine origin is derived from healthy cattle in a bovine spongiform encephalopathy-free area.
    - For drugs derived from extraction of human urine, human urine is obtained from healthy persons.
    - Viral inactivation process requirements and quality management requirements are clearly defined for the above drugs.

- **Biological Products**
  - For bacterial and viral strains used directly for production, human- and animal-derived cells, as well as DNA recombinant engineering bacteria and cells, the source is approved by the drug administration authorities of the State Council and complies with the relevant management requirements of our country.
Relevant requirements in the Chinese Pharmacopoeia

- **Chinese Pharmacopoeia, edition 2015 VOL III**
  
  **Animals for Production and Verification**
  
  - Animal cells for preparation of injectable live vaccines are derived from animals without any specific pathogens (SPF grade); animal cells for preparation of oral vaccines and inactivated vaccines are derived from animals of clean grade or higher. All animals comply with the relevant requirements for microbiological and parasitological tests (General Rules 3602 and 3603).
  
  - Bovine serum for cell cultivation is derived from healthy cattle in an area without bovine spongiform encephalopathy (BSE), with quality complying with the relevant requirements of the current edition of the Chinese Pharmacopoeia.
  
  - As demonstrated, trypsin for cell digestion is free of any exogenous or endogenous viral contamination.
  
  - Unless otherwise specified, eggs for preparation of chick embryo or chick embryo cells are derived from chicken flocks without specific pathogens.
  
  - Horses for production comply with the requirements of the "Quarantine and Vaccination Procedures for Horses for Production of Immune Serum"
  
  - Unless otherwise specified, animals with clean grade higher are used as animals for verification; mice are obtained from closed colony animals.
  
  - SPF grade animals are used, where bacterial or viral strains have to be passed by animals.

<table>
<thead>
<tr>
<th>Grade of Excipient</th>
<th>Marketing authorization certificate (such as registration or filing documents for drugs or excipients for production)</th>
<th>MP certificate of the supplier for drug production</th>
<th>Registration or filing certificates for excipients</th>
<th>Factory inspection report of the supplier</th>
<th>National sale certificate</th>
<th>Spot-check inspection in accordance with the national standard or the internal control quality standards of manufacturing enterprises for biological products</th>
<th>Tests for critical items (such as identification, microbial limit, bacterial endotoxin, and undue toxicity, etc.)</th>
<th>Further processing and purification</th>
<th>Evidence of source</th>
<th>Comply with the safety requirements for relevant animal-borne diseases (including TSE) in the country of origin and in China</th>
<th>Audit of Suppliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>—</td>
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<td>—</td>
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</tr>
<tr>
<td>Grade 2</td>
<td>√</td>
<td>—</td>
<td>√</td>
<td>—</td>
<td>—</td>
<td>Spot-check inspection (batches)</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Grade 3</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade 4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Test if animal-derived</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Test if animal-derived</td>
<td>—</td>
</tr>
</tbody>
</table>

Quality Control Procedures for Raw & Auxiliary Materials and Excipients for Production of Biological Products
International Relevant guidelines in the Europe and the United States

- **USA**  The U.S. Department of Agriculture (USDA) regulations for veterinary products as specified in the 9CFR 113 regulations (9CFR). (FDA)
- **FDA**  The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use Guidance for Industry
- **ICH**  VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS DERIVED FROM CELL LINES OF HUMAN OR ANIMAL ORIGIN Q5A(R1)
- **ICH**  Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

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Relevant Guidelines issued by EMEA

- **Adventitious Agents Safety Evaluation**
  - Viral Safety Development of a Guideline on Viral Safety Evaluation of Biotechnological Products to be used in Clinical Trials (CHMP/BWP/124447/04)
  - Guidance on the Use of Bovine Serum in the Manufacture of Human Biological Medicinal Products (CPMP/BWP/1793/02)
  - Quality of Biotechnological Products: Viral safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin (CPMP/ICH/295/95 ICH Topic Q5A)
  - Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses (CPMP/BWP/268/953AB8A)
Relevant Guidelines issued by EMEA

- **Transmissible Spongiform Encephalopathies (TSE) (Animal and Human)**
  - Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, Amendments to section 6.2 and 6.3. (EMEA/410/01 Rev. 2)
  - Position Paper on Re-establishment of Working Seeds and Working Cell Banks using TSE compliant materials (EMEA/22314/02)
  - Public Report on Risk and Regulatory Assessment of Lactose and other products prepared using Calf Rennet (EMEA/CPMP/BWP/498/01)
  - Joint CPMP/CVMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/CPMP/BWP/476/01)
  - Public Statement on the Evaluation of Bovine Spongiform Encephalopathies (BSE) - Risk via the Use of Materials of Bovine Origin in or during the Manufacture of Vaccines (EMEA/CPMP/BWP/476/01)
  - Explanatory Note: Gelatin for Use in Pharmaceuticals (EMEA/430600/00)
  - Position Statement on Polysorbate 80 (CPMP/BWP/1952/98)
  - Position Paper on Production of Tallow Derivatives for Use in Pharmaceuticals (CPMP/1163/97)

Relevant Requirements in the European Pharmacopoeia

**EP9.0**

Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

- **Applicable Scope:**
  - Serum and Serum Replacements
  - Recombinant Protein Products (growth hormone, cytokines, hormones, enzymes, and monoclonal antibody products)
  - Proteins extracted from biological materials (enzymes and polyclonal antibodies)

- **Including:**
  - Source
  - Manufacturing Process (removing and inactivation process of exogenous factors, process validation, exogenous factor examination)
  - Identification
  - Examination
Requirements for decreasing the risk of TSE transmission in EP

**EP 9.0: Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products**

- Transmissible Spongiform Encephalopathies (TSE)
- Bovine Spongiform Encephalopathy (BSE) in cattle,
- Scrapie in sheep and goats,
- Chronic wasting disease (CWD) in cervids (deer and elk),
- Transmissible mink encephalopathy (TME) in farmed mink,
- Feline spongiform encephalopathy in fields (specifically domestic cats and captive large cats), and
- Spongiform encephalopathy of exotic ungulates in zoos.

Key Considerations for High-risk Materials

- Collagen
- Gelatin
- Bovine Blood and Blood Derivatives
- Tallow derivatives
- Animal Charcoal
- Milk and Milk Derivatives
- Wool Derivatives
- Amino Acids
- Peptones
Pharmaceutical excipients standard system planning

Quality Control Key Points
Key points for control of animal-derived excipients

- **Starting materials control**
  - Animal species, population health status
  - Feeding facilities and environment, pathogen monitoring
  - Organ extraction, collection, storage and transportation
  - Screening before putting into production
  - Adventitious agents screening (the minimum units)
  - SOP for the pick up the organs of the animals
  - Collect, storage, transport the organs
  - Selected the organs before put into production
  - Strengthen auditing of suppliers

- **In-process Control**
  - Process Validation
  - Stability
  - Inter-batch consistency
  - Determine key points for quality control of the process
  - Establish relevant physical and chemical properties, to ensure effects of process treatment
  - Strengthen test of intermediates for contamination of adventitious agents; in-process control may be more effective than finished product control
  - Comply with the Good Manufacturing Practices (GMP) for drugs or excipients
  - Avoid contamination / across contamination of any adventitious agents during preparation
  - Prevent any potential risk for cross contamination between batches during production
Key points for control of animal-derived excipients

- Establish a reliable viral inactivation process
  - Establish an appropriate viral inactivation process, to maximize inactivation or removal of known or unknown adventitious agents
  - Validation for effective viral inactivation
  - Evaluation of viral inactivation effects
  - Impact of the viral inactivation process on ingredients

Key points for control of animal-derived excipients

- Control of ingredients
  - Control of ingredients in the product
  - Control of impurities/residual substances
  - Test for at-risk substances, and establishment of the safety test limit
  - Control for residual reagents used during process
- Stability control of ingredients
  - Packaging
  - Storage and transportation
  - Establishment of the expiration date
  - Potential impact during use
Control of Adventitious Agents

1950’s, Avian leukemia due to contamination of chick embryo for production of yellow fever attenuated live vaccine;
SV40 virus-contaminated metanephros cells for production of oral poliomyelitis vaccine attenuated live vaccine
Blood products contaminated with HIV/HCV
Human growth factors containing CJV

1940’s, Stabilized human blood products contaminated with HBV

Adventitious Agent Contamination Events

• Cache Valley Virus (CVV) – fermentors from multiple manufacturers have been infected. CVV, although not typically recognized as a bovine virus, is a multispecies virus with bovine host range.
• The operators of a manufacturing enterprise for biotherapeutic products were infected with Cache valley viruses
• Calicivirus 2117 [vesivirus]-facility contamination forced a costly facility shutdown resulting in product shortage that deprived patients of product.
• Production facilities contaminated with calcicviruses
• Multiple contaminations of fermentors with reoviruses, another virus family with wide host range.
• Fermentation tank contaminated with reoviruses
• Porcine circovirus type 1 and type 2 nucleic acid contamination of live rotavirus vaccines
Events of pancreatin contaminated with exogenous factors

• PCF were detected in batches of the stock solution and the finished product
• The user population was under close observation
• Though PCF was detected in the products, there are no adequate clinical data suggesting that PCV, irrespective of PCV-1 or PCV-2, may result in human infections.

International Quality Control Requirements for Pancreatin

WHO, FDA, and EMA have strict provisions for quality management and quality control of pancreatin for drug production
Control of bovine-borne advantitious agents

- **Bovine Spongiform Encephalopathy (BSE)**

  BSE is a progressive neurological disorder of cattle; its symptoms are similar to a disease of sheep, called scrapie. BSE has been called “mad cow disease”. BSE and scrapie both result from infection with a very unusual infectious agent. As of July 2000, more than 176,000 cases of BSE were confirmed in Great Britain in more than 34,000 herds of cattle. The epidemic peaked in January 1993 at almost 1,000 new cases per week. The outbreak may have resulted from the feeding of scrapie-containing sheep meat-and-bone meal to cattle. There is strong evidence and general agreement that the outbreak was amplified by feeding meat-and-bone meal prepared from cattle to young calves.

(For questions and inquiries call: 1-800-835-4709 or 1-301-827-2000.)

Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jak

Test methods for exogenous viruses

- **Conventional method**
  - transmission electron microscopy
  - in vitro infectivity
  - biochemical assays
  - in vivo assays

- **Modern detection techniques**
  - PERT
  - polymerase chain reaction (PCR) tests
  - next generation sequencing (NGS)
  - microarrays
  - PCR paired with mass spectrometry
Evaluation of signals for detected adventitious agents

Viral inactivation/removal/process validation


- Selection of Methods for Viral Removal/Inactivation
- Evaluation of Common Methods for Viral Removal/Inactivation
- Validation of Special Methods for Viral Removal/Inactivation
- Validation for Viral Removal/Inactivation Performance by the Manufacturing Process
- Revalidation of Methods for Viral Removal/Inactivation
Viral Inactivation of Bovine Serum

**Method**

- Heat Inactivation
- γ-ray irradiation (temperature, time, container, position, and dose)
- Processing for 60 min at 37 °C (EDQM)
- Ultrasonic Irradiation

**Selection of indicator viruses**

<table>
<thead>
<tr>
<th>Viral Characteristics</th>
<th>Enteroviruses</th>
<th>Reoviruses</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine diarrhea viruses</td>
<td>Present</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Infectious bovine rhinotracheitis</td>
<td>Present</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bovine adenoviruses</td>
<td>None</td>
<td>Double-stranded DNA</td>
<td>Single-stranded DNA</td>
</tr>
<tr>
<td>Porcine paroviruses</td>
<td>None</td>
<td>Double-stranded DNA</td>
<td>Single-stranded DNA</td>
</tr>
</tbody>
</table>

**Summary**

- High risk for the excipients derived from animals
- Whole processing control is the base of the quality assurance
- Especially for the starting materials and processing control
- Processing validation
- Set up the well establishment Viral inactivated processing
- Adventitious agents testing method and the evaluation
- Storage situation for the excipients stability
Thank you for your attention!