Brief Introduction of Chinese Pharmacopoeia 2015 Vol. IV

Chinese Pharmacopoeia Commission
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Sino-Euro Pharmacopoeia Seminar
October 17, 2016 Strasbourg, France

Contents

• Background
• Overall Situation
• Major Changes
• Future Development
Work requirements for compilation of 2015 ChP Vol. IV

- Key works

- Appendix integration
  Separate notices, general rules, guidelines and excipients into one part respectively and thus form the Chinese Pharmacopoeia vol. IV.
  General rules include:
  - Test methods
  - Common chapters (for preparations and various kinds of products)
  - Guidelines

- Improved test method
  - Standardization, reliability, advancement, practicability and operatibility

- Test technique reserve

- Leading role of Chinese Pharmacopoeia
  - Guiding function in production technique and test technology
  - Leading function in quality control requirement

Compilation of 2015 ChP Vol. IV

- improvement of drug standard

747 research projects on methodology, pharmaceutical excipients and drug packaging have been set up from 2009 to 2015

<table>
<thead>
<tr>
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About 151 Million RMB were used for the research on methodology, pharmaceutical excipients and drug packaging from 2009 to 2015.
Compilation of 2015 ChP Vol.IV
-Improvement of drug standard

Framework of ChP 2015 vol. IV

- Preface
- List of the 10th Chinese Pharmacopoeia Commission
- History of Chinese Pharmacopeia
- List of variety and general rule changes
- Notices
- Name contents (stroke index remained; text for variety is proposed to be ordered by Pinyin)
- General rules (appendixes of former ChP)
  - Guide graph
  - General requirements of preparation
  - General method/test method
  - Guidelines
- Schedules
  - Atomic chart
  - International unit conversion table
  - New and old appendixes/rule code table
- Excipients Monographs
- Chinese index
Main Contents

- ChP Vol.IV

- Background
- Overall Situation
- Major Changes
- Future Development

Compilation and revision of ChP 2015 Vol.IV

317 general rules have been included into Chinese Pharmacopoeia 2016 four parts

- 240 test methods
- 38 rules of preparation
- 38 guiding principles
- Test method
- Rules of preparation
- Guiding principle
- Standard and reference substance

Addition and revision account for 56.3% of the total
Appendixes of ChP in all previous versions

Requirements for Compilation of ChP 2015 Vol. IV
- Appendix integration

- Appendix integration (Part I, Part II, Part III)
- Focus on improvement based on standardization and unification
- Standardization and unification of the same methods in appendixes of all previous parts
- Settlement of non-uniform requirements for the same methods among all parts
### Development and Revisions of ChP 2015 Vol.IV

<table>
<thead>
<tr>
<th>Item</th>
<th>ChP 2010</th>
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<tr>
<td>Rules of preparation</td>
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<td>21</td>
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### Compilations and revisions of ChP 2015 Vol.IV

Development and revisions of test method and general chapters

- 16 TCM preparations
- 63 integrated
- 107 Biological products
- 54 un integrated
Main Contents

- ChP Vol.IV

• Background
• General
• Major Changes
• Future Development

By means of comprehensive development and revisions of ChP general rules, general chapters and general requirements of ChP have been more improved and the requirements for drugs quality control have been further promoted integrally.
Provisions of general rules

- General rules are an important component of ChP and are used to overall stipulate the inspection methods and limits of drug standards.
  - Appendix/General Chapters
  - Official drug inspection and test methods

Provisions of explanatory notes:
- Explanatory notes, general rules and overviews of Chinese Pharmacopoeia are important components of ChP.
- Have equivalent force to other national drug standards besides ChP.
- "Unless otherwise specified" used in the general rules means that any incompliance with the relevant provisions of appendixes should be noted in the text additionally and be implemented.

Additions and revisions of explanatory notes, general rules and overview of ChP 2015 Vol.IV

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<th>Type</th>
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<td>General rules of common requirements</td>
<td>1. General Rules of Drug and Herbal Detection</td>
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<td>2. General Rules of Medical Adjuvant</td>
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<td>Overviews of biological products</td>
<td>1. Regulations on Quality Control for Raw Materials and Adjuvants of Biological Products</td>
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<td>2. Human Vaccines Overview</td>
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<td></td>
<td>3. Overview of Human Recombinant DNA Protein Products</td>
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<td>4. Overview of Human Recombinant Monoclonal Antibody</td>
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<td></td>
<td>5. Management of Bacterial and Viral Strains for Production and Detection of Biological Products</td>
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<tr>
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<td>6. Biological Products Batching Code</td>
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<td>7. Biological Products Packaging Code</td>
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<td></td>
<td>8. Code for Preparation and Detection of Animal Cell Matrix for Biological Products</td>
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<td>9. Management of Bacterial and Viral Strains for Production and Detection of Biological Products</td>
<td>Revised</td>
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</table>
Additions and revisions of explanatory notes, general rules and general remarks of ChP 2015 Vol.IV

Guiding principles

- Guiding Principle for Human Bioavailability and Bioequivalence Test of Pharmaceutical Preparations Revised
- Guiding Principle for Slow, Controlled and Delayed Release of Preparations Revised
- Guiding Principle for Particle Preparations Revised
- Guiding Principle for Identification of Drug Quality Standard Analysis Method Revised
- Guiding Principle for Drug Impurity Analysis Revised
- Guiding Principle for Alternative Method for Microorganism Examination in Drugs Revised
- Guiding Principle for Detection of Microorganism Limit of Nonsterile Products Revised
- Guiding Principle for Quality Management of Drug and Microbiological Lab Revised
- Guiding Principle for Application of Injection Safety Inspection Revised
- Guiding Principles for Quantitative Analysis Method for Biological Samples Added
- Guiding Principles for Crystal Form Research and Quality Control of Drugs Added
- Guiding Principles for Drug Evaluation Technology and Method Based on Gene Chip Added
- Guiding Principles for Molecular Identification Method for DNA Barcode of Chinese Medical Herbs Added
- Guiding Principles for Microorganism Identification Added
- Guiding Principles for Microorganism Monitoring and Control in Drug Cleaning Laboratory Added
- Guiding Principles for Isolated System Verification for Sterility Test Added
- Guiding Principles for Establishment of Limit of Amount of Residual Hazardous Substances in Chinese Medical Herbs Added
- Color Test Guiding Principles Added
- Guiding Principles for Determination of Aluminum, Chrome, Iron and Barium in Chinese Medical Herbs Added
- Guiding Principles for Determination of Eumycin in Chinese Medical Herbs Added
- Guiding Principles for Research of Functional Indicators of Pharmaceutical Adjuvant Added
- Guiding Principles for Common Requirements for Drug Package Added
- Guiding Principles for Pharmaceutical Glass Materials and Containers Added
- Guiding Principles for Preparation of National Drug Standard Substances Added

Major characteristics of ChP 2015 Vol.IV- 3

- Reorganize code of general chapters

<table>
<thead>
<tr>
<th>Code series</th>
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<td>0100 series</td>
<td>General chapter for preparations</td>
<td>38</td>
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<td>0200 series</td>
<td>Other general chapters</td>
<td>6</td>
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<tr>
<td>0300 series</td>
<td>General identification test</td>
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<td>0400 series</td>
<td>Spectroscopy</td>
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<td>0500 series</td>
<td>Chromatography</td>
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<td>0600 series</td>
<td>Physical constant measurement method</td>
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<td>Limit test method</td>
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<td>0900 series</td>
<td>Test method of physical properties</td>
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<td>1000 series</td>
<td>Molecular biological technique</td>
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<td>1100 series</td>
<td>Biological test method</td>
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<td>1200 series</td>
<td>Bioactivity measurement method</td>
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<td>2000 series</td>
<td>Relevant TCM test methods</td>
<td>16</td>
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<td>3000 series</td>
<td>Relevant test method for biological products</td>
<td>108</td>
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<td>8000 series</td>
<td>Preparations and standard substances</td>
<td>8</td>
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<tr>
<td>9000 series</td>
<td>Guidelines</td>
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</table>
Major characteristics of ChP 2015 Vol.IV - 4

- Strengthen test techniques

"International TCM-orientation" and "synchronous chemical drugs and biological products with international standards" can be realized by means of improving test methods and establishing new test methods.

Major characteristics of ChP 2015 Vol.IV - 4

- Strengthen test techniques

- Refer to international standards such as American, European and English Pharmacopoeias
- Improve the specificity, sensitivity and stability of test techniques
- Lay a foundation for further establishing strict quality standards and improving drug safety and effectiveness
## Major characteristics of ChP 2015 Vol. IV- 4
### - Improve test methods

<table>
<thead>
<tr>
<th>General rule</th>
<th>Test method 1</th>
<th>Test method 2</th>
<th>Test method 3</th>
<th>Test method 4</th>
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<tr>
<td>Clarity test method</td>
<td>Visual method</td>
<td>Instrument method*</td>
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<td>Melting point determination method</td>
<td>Measurement of breakable solid drug (method A: heating of heat transfer liquid ; method B: heating of rapidly electric heating air*)</td>
<td>Measurement of unbreakable solid drugs (such as fat, fatty acid, paraffin and wool)</td>
<td>Measurement of waxine or other equivalent substances</td>
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<td>Determination of residue of sulfur dioxide</td>
<td>Titrimetry</td>
<td>Gas chromatography*</td>
<td></td>
<td></td>
<td>Ion chromatography*</td>
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<tr>
<td>Ash test method</td>
<td>HPLC</td>
<td>High-performance liquid - tandem mass spectrometry*</td>
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<tr>
<td>Pesticide residues measurement</td>
<td>Gas chromatography</td>
<td>Gas chromatography - tandem mass spectrometry*</td>
<td>Liquid chromatography - tandem mass spectrometry*</td>
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<tr>
<td>Measurement of form and valence state of mercury and arsenic elements</td>
<td>Atomic absorption spectrometry</td>
<td>High performance liquid - inductively coupled plasma mass spectrometry*</td>
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<tr>
<td>X-ray diffraction method</td>
<td>Single-crystal X-ray diffraction method</td>
<td>Powder x-ray diffraction method*</td>
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<td></td>
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<tr>
<td>Measurement of dissolution and release rate</td>
<td>Basket method</td>
<td>Slurry method</td>
<td>Small glass method</td>
<td>Slurry dish method*</td>
<td>Rolling cylinder method*</td>
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<tr>
<td>Measurement of aerodynamic characteristics of inhaled fine particles</td>
<td>Bipolar striker</td>
<td>Anderson-level atril*</td>
<td>New impacting method*</td>
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<td>Adhesion measurement</td>
<td>Initial adhesion determination</td>
<td>Measurement of permanent adhesion</td>
<td>Measurement of peel strength</td>
<td>Measurement of adhesive force*</td>
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<td>Formaldehyde concentration measurement</td>
<td>Magneta method</td>
<td>Acetate acetone method*</td>
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## Major characteristics of ChP 2015 Vol.IV- 4
### - Strengthen test technical reserves

<table>
<thead>
<tr>
<th>Item</th>
<th>Application method</th>
<th>Advantage compared with original methods</th>
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<tr>
<td>Drug evaluation technique and method for gene chips</td>
<td>Gene chip technique</td>
<td>Newly-added test technique</td>
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<tr>
<td>Molecular identification of TMC DNA barcode</td>
<td>DNA sequencing</td>
<td>Higher sensitivity and better specificity</td>
</tr>
<tr>
<td>Bacteria and viral measurement for TCM herbs</td>
<td>High-performance liquid chromatography - mass spectrometry</td>
<td>Better sensitivity, stability and specificity; stronger anti-interference performance</td>
</tr>
<tr>
<td>Aluminum, chromium, iron and barium measurement for TCM herbs</td>
<td>Inductively coupled plasma mass spectrometry</td>
<td>Better sensitivity and stability; higher test efficiency</td>
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<tr>
<td>Measurement of form and valence state of mercury and arsenic elements</td>
<td>High performance liquid - inductively coupled plasma mass spectrometry*</td>
<td>Better sensitivity and stability; higher test efficiency</td>
</tr>
<tr>
<td>Pesticide residues measurement</td>
<td>Gas chromatography - tandem mass spectrometry* Liquid chromatography - tandem mass spectrometry</td>
<td>Better sensitivity, stability and specificity; higher test efficiency</td>
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</tbody>
</table>
**Test item** | **ChP 2010[1]** | **ChP 2015[4]**
--- | --- | ---
Pesticide residues measurement | Gas chromatography (9 kinds) | Gas chromatography (16 kinds) Gas chromatography - tandem mass spectrometry (76 kinds) Liquid chromatography - tandem mass spectrometry (153 kinds)
Aflatoxin measurement | High-performance liquid chromatography | High-performance liquid chromatography - tandem mass spectrometry (newly-added)
Bacteria and viral measurement for TCM herbs | None | High-performance liquid chromatography - tandem mass spectrometry (newly-added) (91 kinds of fungal toxins in 7 types)
Aluminum, chromium, iron and barium measurement for TCM herbs | Atomic absorption spectrometry | Inductively coupled plasma mass spectrometry (newly-added)
Raman spectroscopy | Guiding principle (polarization spectrum technology) | Common method (polarization spectrum technology)
X-ray diffraction method | Single-crystal X-ray diffraction method | Powder X-ray diffraction method (newly-added)
Main changes of ChP 2015 Vol.IV - 5

Guide study & research & development
- Verification of quantitative analysis method for biological samples
- Slow, controlled and delayed release preparations
- Drug crystal type research and quality control
- Drug evaluation technique based on gene chips

Strengthen safety control
- Limit of hazardous residues in TCM herbs
- Pigment test
- Measurement of aluminum, chrome, iron and barium in TCM herbs
- Fungaltoxin measurement in TCM herbs

Strengthen test environment requirements
- Microorganism monitoring and control for drug clean lab
- Verification of isolated system for sterility test

Test technical diversity
- Molecular identification of DNA barcode in TCM herbs
- Microorganism identification

Improve contents of standard system
- Functional index research for drug packages
- Common requirements for drug packages
- Medical glass materials and containers
- Preparation of national drug standard substances

Main characteristics of ChP 2015 Vol.IV - 5
- Strengthen whole process control
Main characteristics of ChP 2015 Vol.IV - 5
- Strengthen TCM safety control

Control requirements for TCM commonality in ChP 2015
- General rules for medical materials and herbs

Test item
- Water
- Ash
- Impurity
- Toxic ingredient
- Heavy metal and hazardous element
- Sulfur dioxide residue
- Pesticide residue
- Aflatoxin
Control requirements for TCM commonality in ChP 2015
- Focuses of safety control

1. Pesticide residue measurement
2. Measurement of heavy metal and hazardous elements
3. Fungaltoxin measurement
4. Pigment residue measurement
5. Sulfur dioxide residue measurement

TCM safety control of ChP 2015
- Pesticide residue measurement

![Bar chart showing pesticide residue measurement in ChP 2010 and ChP 2015.](chart.png)
- 155 kinds
- 76 kinds
- 9 kinds
- 22 kinds
TCM safety control of ChP 2015
- Measurement of lead, cadmium, arsenic, mercury and copper

**ChP2010**
- Atomic absorption spectrometry

**ChP2015**
- Atomic absorption spectrometry
- Inductively coupled plasma - mass spectrometry (ICP-MS)

- Establish the arsenic valence analysis method in realgar:
- Establish the mercury valence analysis method incinnabar:
- Analysis of hexavalent chromium in TCM herbs (Chloriti Lapis, lumbricus):

Establishment of HPLC-ICP-MS method for arsenic, mercury and chromium valence states helps to correctly evaluate the forms and toxicity of arsenic, mercury and chromium in TCM herbs.
TCM safety control of ChP 2015

- Sulfur dioxide measurement

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Titrimetry</td>
<td>Simple, low-cost, easily popular</td>
<td>• Tendency of false positive;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unapparent terminal judgment for some TCM herbs;</td>
</tr>
<tr>
<td>Pharmacopoeia method</td>
<td></td>
<td>• Low precision of distillation due to effect of operating factors</td>
</tr>
<tr>
<td>Ion chromatography</td>
<td>• Stronger specificity;</td>
<td>• Pretreatment by means of distillation method, with distillation operation</td>
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<tr>
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<td>• Higher sensitivity;</td>
<td>defects inevitably</td>
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<tr>
<td></td>
<td>• Better stability.</td>
<td>• Expensive ion chromatography leads to a high cost</td>
</tr>
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<td>• Matrix interference sometimes.</td>
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<tr>
<td>Gas chromatography</td>
<td>• Strong specificity</td>
<td>Gastight needle type headspace sampling device is needed (such as CTC which</td>
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<td>• High sensitivity</td>
<td>is a new-type sample injector adopted internationally and increasingly</td>
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<td></td>
<td>• Good precision</td>
<td>extensively).</td>
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<tr>
<td></td>
<td>• High accuracy</td>
<td></td>
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<tr>
<td></td>
<td>• High degree of automation</td>
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</table>

TCM safety control of ChP 2015

- Fungaltoxin measurement

**ChP2010**

- 4 kinds

**ChP2015**

- 11 kinds in 7 types
### Method System

<table>
<thead>
<tr>
<th>Method System</th>
<th>Method</th>
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<tr>
<td>Qualitative</td>
<td>(1) Thin-layer chromatographic qualitative method</td>
</tr>
<tr>
<td></td>
<td>(2) Liquid chromatographic qualitative method</td>
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<tr>
<td></td>
<td>(3) Liquid chromatography - tandem mass spectrometry</td>
</tr>
<tr>
<td>Quantitative</td>
<td>(1) Liquid chromatographic quantitative method</td>
</tr>
<tr>
<td></td>
<td>(2) Liquid chromatography - tandem mass spectrometry</td>
</tr>
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</table>

**Method System: Qualitative**

- Thin-layer chromatographic qualitative method
- Liquid chromatographic qualitative method
- Liquid chromatography - tandem mass spectrometry

**Method System: Quantitative**

- Liquid chromatographic quantitative method
- Liquid chromatography - tandem mass spectrometry

### Basic Principles
- Comply with the characteristics of simpleness and accuracy of pharmacognostic identification with definite identification standards
- Realize identification by means of common DNA barcode in each variety of TCM herb
- As for common barcode for vegetable drugs, select ITS2 sequence as the main sequence and *psbA-trnH* as auxiliary sequence
- As for common barcode for animal drugs, use COI as the main sequence and ITS2 as the auxiliary sequence

### PCR Program

- Degeneration at 94 °C for 5 min
- Degeneration at 94 °C for 1 min
- Annealing at 56 °C for 30 sec
- Expansion at 72 °C for 45 sec
- Expansion at 72 °C for 10 min

#### ITS2

- Degeneration at 94 °C for 5 min
- Degeneration at 94 °C for 1 min
- Annealing at 56 °C for 1 min
- Expansion at 72 °C for 1.5 min
- Expansion at 72 °C for 7 min

#### psbA-trnH

- Degeneration at 94 °C for 5 min
- Degeneration at 94 °C for 1 min
- Annealing at 56 °C for 30 sec
- Expansion at 72 °C for 45 sec
- Expansion at 72 °C for 10 min

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**DNA Extraction Method**

- Kit method (applicable to drugs for animal, vegetables and fungi)
- Improved CTAB method (applicable to DNA extraction of drugs for vegetables and fungi)
TCM safety control of ChP 2015
- DNA barcode identification method for TCM herbs

Research on influence factors
- DNA extraction test conditions
- PCR condition and product purification
- Guarantee of accuracy of test method

Research on method applicability
- Measurement of more than 10 batches of drugs
- Determination of intraspecific sequence variation size
- Guarantee of the applicability of the method

Comparison validation of original plant species
- Original plants determined by taxonomists as the subject
- Obtain the barcode data by means of the method
- Compare with the barcodes of relevant medical materials
- Prevent endophytic fungal contamination and ensure accuracy of results

Accuracy investigation
- Repeatability: among at least three batches of test products, evaluate the results after test for each batch for three times or for one batch for six times; the test results should be uniform basically
- Intermediate precision: to investigate the effect of change of internal conditions of the lab (such as different personnel, instruments, working days and test date) on the test results; the changes personnel of a lab at least should be investigated
- Reproducibility: the test results can be reproduced in more than three labs.

Source of four samples
- Original species, medical material samples
- Reference crude herbs, reviewed samples

Standard process for DNA extraction and sequence amplification
- Treatment of test samples
- DNA extraction
- Acquisition of barcode sequence
- Data treatment and analysis

Comparison of ITS2 and psbA-trnH sequence characteristic standard barcode
<table>
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<tbody>
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<td>Biochemical drug</td>
<td>Biological product</td>
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<tr>
<td>TCM</td>
<td>Identification and classification of provenance ingredients in medicinal animals and plants</td>
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<tr>
<td>Restriction enzyme fragment polymorphism</td>
<td>Establishment of genetic resources center and identification of high-quality varieties</td>
</tr>
<tr>
<td>DNA sequencing technology</td>
<td>Research, classification and determination of substitute goods for TCM resources</td>
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<tr>
<td>Multipoint sequence analysis technology</td>
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<td>Molecular hybridization technique</td>
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<tbody>
<tr>
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<tr>
<td>Acceptance, identification and confirmation of standard strain used for microorganism examination in drugs</td>
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<tr>
<td>Identification and confirmation of isolates in product quality control</td>
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<td>Screening and identification of DNA molecular markers for typical contaminant microorganisms</td>
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<tr>
<td>Genomic identification for strains used for microbial drugs</td>
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</table>
Safety control of TCM in pharmacopeia with Edition 2015

- General requirements in safety control of TCM

- Guiding principles enacted for the maximum limited amount of harmful residues in traditional Chinese medicine

- Application guidance principles of injection safety inspection technique

- Inspection technique for related substances in traditional Chinese medicine injections

- Pharmaceutic adjuvant (used in injection)
Features of volumes in pharmacopeia with Edition 2015 Vol. IV-6

- Improving requirements of general chapter on preparations

Features of four volumes in pharmacopeia with Edition 2015-6

- The similarity requirements of general rules on preparations

The general rules on preparations are applicable to traditional Chinese medicine, chemical drugs, and biological products used for treatment (including blood products, immune sera, cell factors, monoclonal antibody, immunomodulator, microecologics etc.). Biological products for precaution shall be prepared as required under corresponding varieties in three volumes of Chinese Pharmacopoeia in this version.

Raw material medicines refer to active substances used for preparations, including traditional Chinese medicine, chemical drug and biological product raw material medicines.

Raw material medicines of TCM refer to vegetable oil and fat, extractive, effective constituent or effective part;

Raw material medicines of chemical drugs refer to chemosynthetic effective constituent, or sourced from natural-occurring substance or obtained with biotechnology (namely raw material medicines); raw material medicines of biological products refer to biological product stoste or prepared raw powder after drying biological product stoste.
In the general rules on preparations, all the dosage forms and sub-dosage forms do not apply to all the raw material medicines but shall depend on properties of raw material medicines, clinical dosage requirements, as well as safety, effectiveness and stability of drugs.

- Unless otherwise specified, biological products shall be stored and transported at 2-8C away from light.
- Bacteriostatic agent: when confirming formulation, inhibitory effectiveness shall accord with inhibitory effectiveness inspection technique.
- Dissolution rate, releasing rate, content uniformity (microbial limit) (tablets, granula, pill, and capsule)
- Conduct fusion inspections for TCM lozenge
- [microbial limit]

Tablets prepared with non-monomer ingredients sourced from animals, plants and mineral substance, tablets of biological products, as well as tablets used for parts such as mucosal or cutaneous inflammation or cavity (such as oral cavity paster, solution tablets for external use, vaginal tablets, vaginal effervescent tablets and so on) shall be examined according to microbial limit of non-sterile products: it is necessary to inspect according to microorganism counting technique (general rule 1105) and control bacteria detection method (general rule 1106) as well as microbial limit standard of non-sterile drugs (general rule 1107), which shall meet the stipulations.
Inhalation preparation

- Inhalation aerosol
- Aerosol of micro-powders for inspiration
- Solution preparations for atomization or preparations that can be converted into steam

General rules on preparations of four volumes in pharmacopeia with Edition 2015

Inhalation preparation (general rule 0111)

Solution preparations for atomization

- Quantitative inhalation spray
- Inhalation liquid preparations

Liquid preparations used for atomization refer to the solution to generate aerosol for inhalation through continuous or quantitative atomizers.
General rules on preparations of four volumes in pharmacopeia with Edition 2015

- Inhalation preparation (general rule 0111)

General rule 0112
Spray (Inhalation spray)

General rule 0113
Aerosol (Inhalation aerosol)

The general rule can be served only as the general requirement used for production and quality control of inhalation preparations (inhalation aerosol, aerosol of micro-powders for inspiration and preparations that can be converted into steam) but one single dosage form.

Sterile
Inhalation solution preparation for atomization

General rules on preparations of four volumes in pharmacopeia with Edition 2015

- Eye-drops preparations (general rule 0105)

- Preservative
Multi-dose eye-drops preparations shall generally be added with proper bacteriostatic agent, select and use bacteriostatic agent with little safety risks as far as possible, and categories and labelled amount of bacteriostatic agent shall be marked on product labels. Unless otherwise specified, when confirming formula with preparations, inhibitory effectiveness of the formula shall accord with stipulations of inhibitory effectiveness inspection technique (general rule 1121).

- Sedimentation ratio
Ophthalmic suspension (except eye drops including raw power of medicinal slices) shall be inspected according to the following method and sedimentation ratio shall be no lower than 0.90.

- Sterile
Unless otherwise specified, the inspection according to the sterile inspection technique (general rule 1101) shall accord with stipulations.
### Features of four volumes in pharmacopeia with Edition 2015-

**Microbial detection requirement and international harmonization**

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Name of general rule</th>
<th>Supplement and revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1101</td>
<td>Sterile Inspection Technique</td>
<td>Revised</td>
</tr>
<tr>
<td>1105</td>
<td>Microbial Limit Test for Non-sterile Products: Microorganism Counting Technique</td>
<td>Revised</td>
</tr>
<tr>
<td>1106</td>
<td>Microbial Limit Test for Non-sterile Products: Control Bacteria Inspection Technique</td>
<td>Revised</td>
</tr>
<tr>
<td>1107</td>
<td>Microbial Limit Standard for Non-sterile Products</td>
<td>Revised</td>
</tr>
<tr>
<td>1121</td>
<td>Inhibitory Effectiveness Inspection Technique</td>
<td>Newly increased</td>
</tr>
<tr>
<td>1201</td>
<td>Antibiotic Microbial Detection Technique</td>
<td>Unrevised</td>
</tr>
<tr>
<td>1421</td>
<td>Sterilization</td>
<td>Unrevised</td>
</tr>
<tr>
<td>9201</td>
<td>Guiding Principles of Validation of Alternative Microbiological Methods for Pharmaceutical Product</td>
<td>Unrevised</td>
</tr>
<tr>
<td>9202</td>
<td>Guiding Principle of Microbial Limit Test in Nonsterile Pharmaceutical Product</td>
<td>Revised</td>
</tr>
<tr>
<td>9203</td>
<td>Guiding Principles for Quality Control of Microorganisms in Pharmaceutical Product</td>
<td>Revised</td>
</tr>
<tr>
<td>9204</td>
<td>Guiding Principles of Microbiological Assay</td>
<td>Newly increased</td>
</tr>
<tr>
<td>9205</td>
<td>Guiding Principles of Microbiological Monitoring and Control in Clean Pharmaceutical Product Laboratory</td>
<td>Newly increased</td>
</tr>
<tr>
<td>9206</td>
<td>Guiding Principles of Isolated System Verification Used for Sterility Test</td>
<td>Newly increased</td>
</tr>
</tbody>
</table>

### Microbial detection of four volumes in pharmacopeia with Edition 2015

**-Internationally harmonious**

Intensified control for key points in test operation for bacteriological examination of pharmaceutical products

- SOP operation
- Reference medium
- Environment guarantee
- Sterility test
- Medium guarantee
- Sensitivity test
- Method validation
- Effective method
- Guiding Principles of Validation of Alternative Microbiological Methods for Pharmaceutical Product
- Judging results
- Reliable conclusion
- Guiding Principle of Microbial Limit Test in Nonsterile Pharmaceutical Product

**Guiding Principles for Quality Control of Microorganisms in Pharmaceutical Product**

**Guiding Principles for Quality Control of Microorganisms in Pharmaceutical Product Environment**

**Guiding Principles of Isolated System Verification Used for Sterility Test**

**Guiding Principles of Microbiological Monitoring and Control in Clean Pharmaceutical Product Laboratory**

**Guiding Principles of Validation of Alternative Microbiological Methods for Pharmaceutical Product**

**Guiding Principles of Microbial Limit Test in Nonsterile Pharmaceutical Product**

[http://www.chp.org.cn]
Microbial detection of four volumes in pharmacopeia with Edition 2015

- Sterility test

Revised medium for test

**Edition 2010**
- Thioglycollate fluid medium
- Improved Martin medium

**Edition 2015**
- Thioglycollate fluid medium
- TSB fluid medium

1. **Thioglycollate fluid medium**
   - To culture at 30 ~ 35 °C; 20 ~ 25°C (Volume III)

2. **Improved Martin medium**
   - To culture at 23 ~ 28 °C

3. **Selectiv medium**

4. 0.5% glucose bouillon culture-medium

5. Nutrient bouillon culture-medium

6. Nutrient agar medium

7. Improved Martin agar medium

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. Thioglycollate fluid medium</td>
<td>1. Thioglycollate fluid medium</td>
</tr>
<tr>
<td>30~ 35 °C; 20~25°C (Volume III)</td>
<td>To culture at 30~ 35 °C and 20~25°C</td>
</tr>
<tr>
<td>2. Improved Martin medium</td>
<td>2. TSB medium</td>
</tr>
<tr>
<td>To culture at 23 ~ 28 °C</td>
<td>To culture at 20 ~ 25°C</td>
</tr>
<tr>
<td>3. Selective medium</td>
<td>3. Neutralization or inactivation medium</td>
</tr>
<tr>
<td>4. 0.5% glucose bouillon culture-medium</td>
<td>4. 0.5% glucose bouillon culture-medium</td>
</tr>
<tr>
<td>5. Nutrient bouillon culture-medium</td>
<td>5. Trypticase Soy Agar Medium (TSA)</td>
</tr>
<tr>
<td>7. Improved Martin agar medium</td>
<td>7. Sabouraud's dextrose agar medium</td>
</tr>
</tbody>
</table>

- Internationally harmonious
Microbial detection of four volumes in pharmacopoeia with Edition 2015

- microbial assays

- <1105> Microbial limit test for non-sterile products: microorganism counting technique
- <1106> Microbial limit test for non-sterile products: test method for control bacteria
- <1107> Microbial limit test for non-sterile pharmaceutical products

- Revised test atmosphere and it shall accord with the requirements of microbial limit test
- Revised medium system and experiment process of microorganism counting, control bacteria examination and methodology validation
- No longer stipulate reexamination, but emphasize to comprehensively judge detection results through risk investigations and suitable technological means
- Microbial limit standard in non-sterile medicinal materials, auxiliary material, Chinese herb extracts and Chinese herbal pieces are revised and enlarged in “microbial limit standard”

Features of four volumes in pharmacopoeia with Edition 2015

- Perfect standard substance formulation

- Comparison products, comparison medicinal materials and comparison extracts 504
- Standard substance of TCM 32
- Reference substance of pharmaceutical chemicals 832
- Standard substance of biological products 62
Features of four volumes in pharmacopoeia with Edition 2015

- The standard level of stand pharmaceutical adjuvant has an integral elevation

The quality of pharmaceutical adjuvant and medicament packing material are valued

Pharmaceutical adjuvant of four volumes in pharmacopoeia with Edition 2015

- concept of pharmaceutical adjuvant

- ChP
  ✓ Adopted excipients and additives while producing drugs and blending prescriptions
  ✓ As inactive substances, pharmaceutical adjuvants has important functions such as solubilizing and controlled release besides serving as a carrier and promoting stability
  ✓ Chinese herbal medicinal ingredient influencing quality, safety and efficiency of preparations

- USP/IPEC
  ✓ Prepare pharmacological active ingredients as non-pharmacological active ingredients in pharmaceutical preparations
  ✓ All the ingredients besides active ingredients and all ingredients
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

- Levels of pharmaceutical adjuvant reflects levels of preparations

- In favor of machining of finished products
- Promote stability of pharmaceutical preparations
- Enhance bioavailability
- Enhance patients' compliance
- Help to indentify pharmaceutical preparations from appearance
- Improve pharmaceutical preparations from storage
- Improve drug safety and effectiveness

- Effect of adjuvant

- Influence of drug effect
- Safety influence of preparations
- Preparation stability
- Consistency among lot numbers of preparations
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

- Influence factor

- Source
  Selection, traceability and control of raw materials

- Preparation technology
  Process certification and process stability

- Manufacturing technique process control

- Production management standard of pharmaceutical adjuvant

- Quality control

- Control of impurities and pollutants (Control for exogenous factor of adjuvant sourced from animals)

- Packaging, storage, transport, and period of validity

Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

- Variety records are substantially promoted

Adjuvant started to be collected in Pharmacopeia with Edition 1977 with seldom varieties at that time including only several varieties such as paraffin, vaseline, kaolin, lactose, starch, and dextrin
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015
- Units participating in drafting adjuvant standards

Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015
- Development and revision conditions of varieties

Totally 270 varieties of recorded adjuvant

With no records: thiomersalate, DEP
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

- Controlled key points of pharmaceutical adjuvant

- Related substance
- Impurity
- Residual solvent
- Hazardous substance

- Safety
- Functionality
- Multi-standard
- Multi-class

Pharmaceutical adjuvant grading

Adjuvant for injection

Pharmacopoeia 2010
Pharmacopoeia 2015
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

- Functions and uses

55 uses including newly increased 21 uses

The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient

- Function & Application

ChP 2010
ChP 2015

ChP 34
USP38 101

ChP 55
The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient
- Excipient varieties recorded in each country’s pharmacopoeia

![Bar chart showing the number of pharmaceutical excipient varieties in different pharmacopoeias: ChP2015, USP38, EP8.5, and JP 16.]

- Enhanced application of advanced testing technology

<table>
<thead>
<tr>
<th>Method</th>
<th>Character Identification</th>
<th>Examination</th>
<th>Content determination</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titrimetric Analysis</td>
<td>36</td>
<td>20</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>IR</td>
<td>0</td>
<td>0</td>
<td>90</td>
<td>27</td>
</tr>
<tr>
<td>HPLC</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>UV-visible spectrophotometry</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>GC</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>TLC</td>
<td>0</td>
<td>0</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>NMR spectral method</td>
<td>0</td>
<td>0</td>
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<tr>
<td>AAS</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient
-- Enhanced application of advanced testing technology

- More Completed Excipient Standard System

- Pharmaceutical Excipient Guide Requirements
- Pharmaceutical Excipient Applicability

- Pharmaceutical Excipient General Rules
- Pharmaceutical Excipient Functional Research Evaluation Principles
- Biological Product Used Raw and Auxiliary Material General Rules

- 270 Excipient Standards

Contrast of identified items through testing methods
2015版药典
2010版药典

Contrast of character items through testing methods
2015版药典
2010版药典

Contrast examined items through testing methods
2015版药典
2010版药典

Contrast of content determinated items through testing methods
2015版药典
2010版药典
The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient

- Enhance Functional Control

<table>
<thead>
<tr>
<th>Functional Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolvents</td>
</tr>
<tr>
<td>Granularity and granularity distribution, particle morphology, bulk density, tap density, true density, specific surface area, crystallinity, moisture, fluidity, solubility, compressibility, hygroscopicity</td>
</tr>
<tr>
<td>dispersions</td>
</tr>
<tr>
<td>Surface tension, granularity, granularity distribution, solubility, viscosity, bulk density and tap density</td>
</tr>
<tr>
<td>Disintegrants</td>
</tr>
<tr>
<td>Particle size and distribution, water absorption rate, expansion rate or expansion index, powder flowability, moisture, effervescence, etc.</td>
</tr>
<tr>
<td>Lubricants and anti-caking agent</td>
</tr>
<tr>
<td>Granularity and granularity distribution, specific surface area, moisture, polymorphism, purity, melting point or melting range, powder flowability</td>
</tr>
<tr>
<td>Glidants and anticaking agent</td>
</tr>
<tr>
<td>Granularity and granularity distribution, surface area, powder flowability, absorptivity, etc.</td>
</tr>
<tr>
<td>Tablets</td>
</tr>
<tr>
<td>Moisture, breathability, disintegration, friability, tensility, frost force strength, tightness</td>
</tr>
<tr>
<td>Tablets</td>
</tr>
<tr>
<td>Solubility, film-formation, viscosity, substituent and degree of substitution, tensile strength, breathability, granularity</td>
</tr>
<tr>
<td>Syrups</td>
</tr>
<tr>
<td>HLB value (hydrophilic-lipophilic balance), viscosity, composition, identification, relative density, viscosity, pH, fat and fatty oil, thermoanalysis, granularity and granularity distribution, etc. critical micelle concentration, surface tension</td>
</tr>
<tr>
<td>Suppository matrixes</td>
</tr>
<tr>
<td>Melting point, solidification point, fat and fatty oil</td>
</tr>
<tr>
<td>Syrups</td>
</tr>
<tr>
<td>Granularity and granularity distribution, surface area, powder flowability, absorption, etc.</td>
</tr>
<tr>
<td>Syrups</td>
</tr>
<tr>
<td>Viscosity and melting range</td>
</tr>
</tbody>
</table>

Ensure the performance of the pharmaceutical excipients remaining the same during their period of validity

Main contents

- Chinese Pharmacopoeia Vol.IV

- Compilation background
- Overall Situation
- Main changes
- Future development
Development direction of Chinese Pharmacopoeia 2020 Edition
- Testing method

- Complete and standardize testing methods
  Scientificality, normativity, practicability, operability
- Enhance universal testing methods
  Generality, applicability and stability
- Closely keep up with the trend of pharmacopoeia standards
  Enhance application of advanced mature testing technology in control of drug security and effectiveness

Development direction of Chinese Pharmacopoeia 2020 Edition
- General rules on pharmaceutical manufacturing

* Add new, mature records of dosage form and sub-dosage form
* Guiding by ensuring clinical effectiveness and Security, combine functional requirements of pharmaceutical excipient with completing general rules on pharmaceutical manufacturing, to further complete the requirements on pharmaceutical manufacturing.
  - Mainly enhance stability and consistency between batches, reduce quality differences of same kind products produced by different companies.
**Development direction of Chinese Pharmacopoeia 2020 Edition**

- **Guiding principle**

* Keep completing existing guiding principles, to keep up with the international pace
* Fully use the experience on advanced concepts of international drug administration, and combine the real situation of domestic production, to keep enriching relevant technical guiding principles involving drug R&D, manufacturing, process control, analytical methods, testing methods and drug packaging, delivery, storage and stability.
* Gradually form comprehensive quality control of drug life cycle, continuously improve drug quality

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**Development direction of Chinese Pharmacopoeia 2020 Edition**

- **Pharmaceutical excipient and packing materials of drugs**

* Further enhance and complete standard system on pharmaceutical excipient and packing materials of drugs
* Add records about common standards of pharmaceutical excipient and packing materials of drugs, promote records about standards of mature new-type pharmaceutical excipient and packing materials of drugs, and promote upgrading of pharmaceutical excipient and packing materials of drugs
* Enhance formulation of pharmaceutical excipient universality requirements and technical guiding principles
* Further enhance control on impurities in pharmaceutical excipient
* Establish and complete functional evaluation method of pharmaceutical excipient and method on controlling compatible, toxic and hazardous substances
* The security control on pharmaceutical excipient and packing materials of drugs should be in accordance with international requirements.
Thank You!