Brief Introduction of Chinese Pharmacopoeia 2015 Vol. IV

Chinese Pharmacopoeia Commission
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Sino-Euro Pharmacopoeia Seminar

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Contents

- Background
- Overall Situation
- Major Changes
- Future Development

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Work requirements for compilation of 2015 ChP VoL. IV

-Key works

- Appendix integration

Separate notices, general rules, guidelines and exipients 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

2016/10/18

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Compilation of 2015 ChP Vol. IV

-improvement of drug standard

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

Type	2009	2010	2011	2013	2014	2015	Total
Methodology	4	/	12	55	18	11	100
Pharmaceutical excipients	50	25	25	240	174	13	537
Package material	50	/	/	33	14	10	107

About 151 Million RMB were used for the reseach on methodology, pharmaceutical exipients and drug packaging from 2009 to 2015

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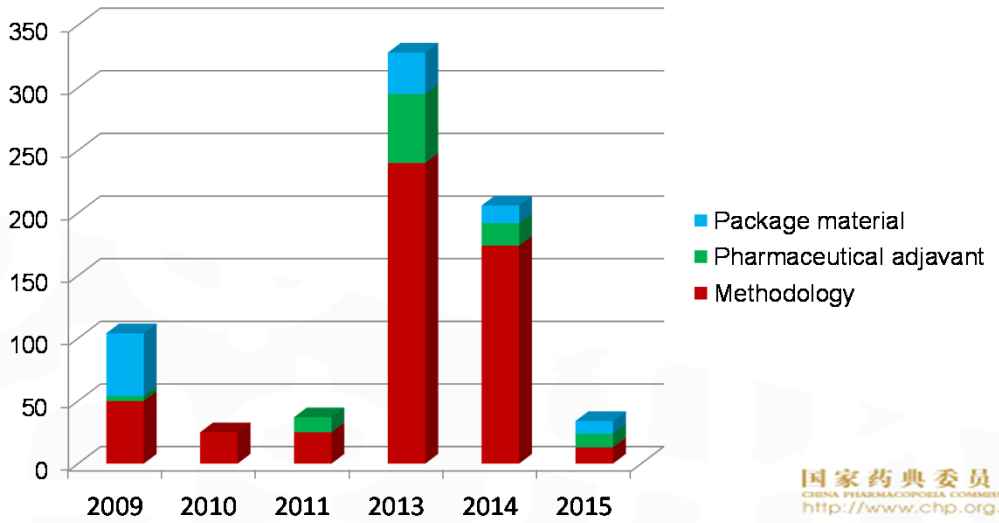
Compilation of 2015 ChP Vol.IV

-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
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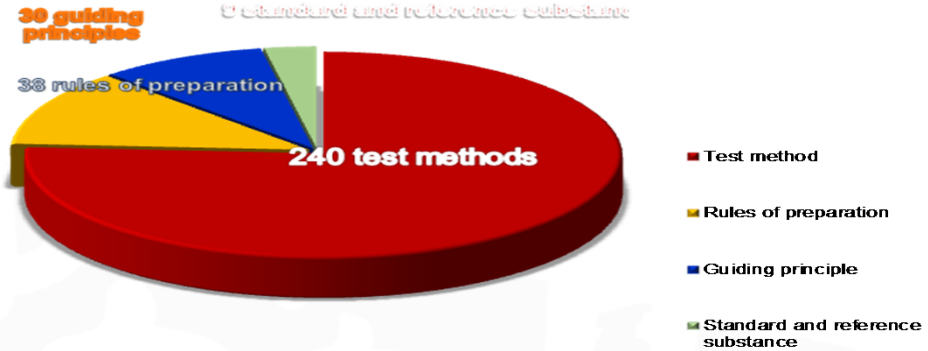
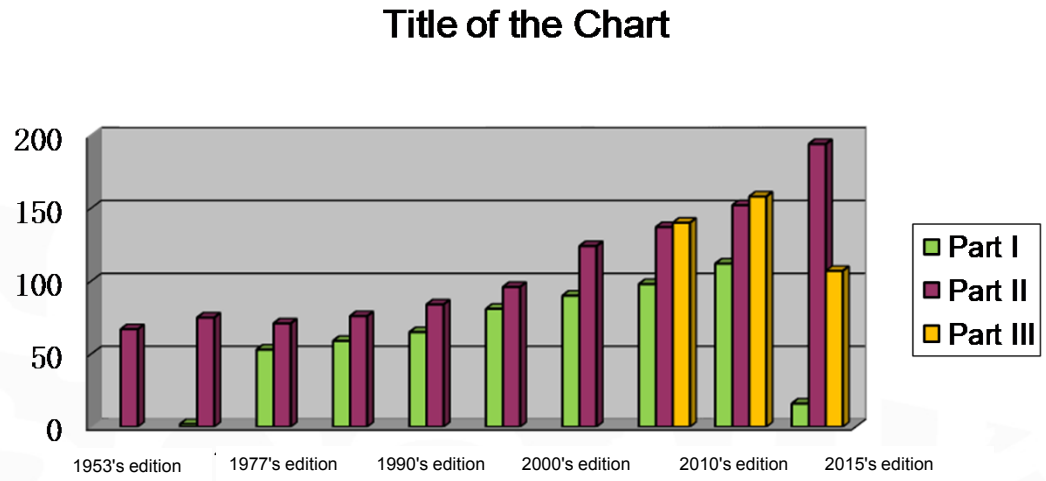
Compilation and revision of ChP 2015 Vol.IV

317 general rules have been included into Chinese Pharmacopoeia 2015 four parts



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

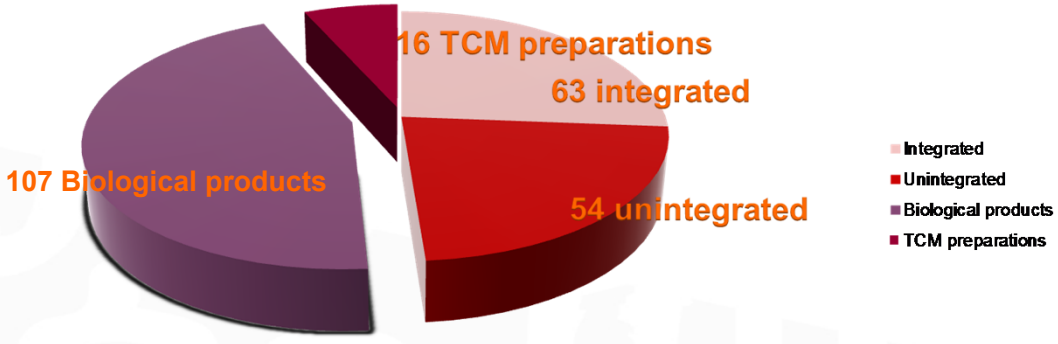
- ✓ Appendix integration (Part I, Part II, Part III)
- ✓ Focus on improvement based on standardization and unification
- ✓ Standardization and unification of the same methods in appendixes of all previous parts
- ✓ Settlement of non-uniform requirements for the same methods among all parts

Development and Revisions of ChP 2015 Vol.IV

Item	ChP 2010			ChP 2015	Addition
	Vol. I	Vol. II	Vol. III	Vol. IV	
Rules of preparation	26	21	12	38	1
Test method	68	102	132	117 (similarities) 16 (TCM preparations) 107 (biological products)	28
General requirements*/ Overview	2	1	9/1	14/4	2/ 3
Guidelines	7	15	2	30	15
Pharmaceutical Exicipients	/	132+2★	/	270	137（2 excluded）

Compilations and revisions of ChP 2015 Vol.IV

Development and revisions of test method and general chapters



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Main Contents

- ChP Vol.IV

- Background
- General
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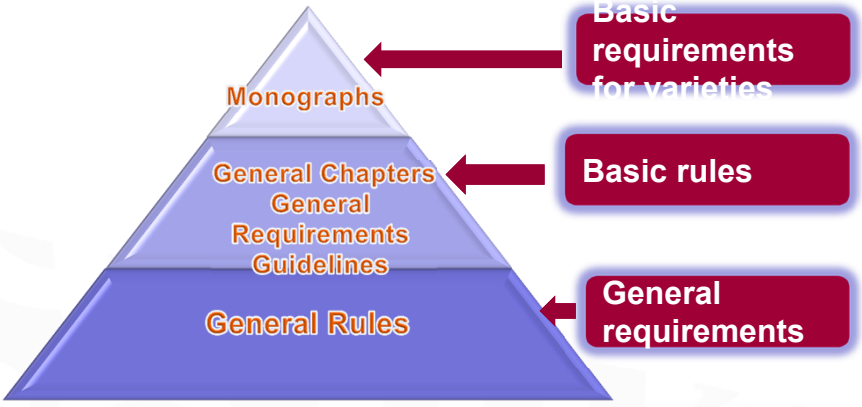
Major characteristics of ChP 2015 Vol.IV- 1

- improving overall level of ChP standards



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

Type	Name	Added/revised
Explanatory notes	Explanatory Notes of Part I, II, III and IV of ChP	Revised
General rules of common requirements	1. General Rules of Drug and Herbal Detection	Revised
	2. General Rules of Medical Adjuvant	Revised
	3. General Rules of National Standard Substances	Added
Overviews of biological products	1. Regulations on Quality Control for Raw Materials and Adjuvants of Biological Products	Added
	2. Human Vaccines Overview	Added
	3. Overview of Human Recombinant DNA Protein Products	Added
	4. Overview of Human Recombinant Monoclonal Antibody	Added
	5. Management of Bacterial and Viral Strains for Production and Detection of Biological Products	Revised
	6. Biological Products Batching Code	Revised
	7. Biological Products Packaging Code	Revised
	8. Code for Preparation and Detection of Animal Cell Matrix for Biological Products	Revised
	9. Management of Bacterial and Viral Strains for Production and Detection of Biological Products	Revised

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 Pharmaceutic Preparations	Revised
	Guiding Principle for Slow, Controlled and Delayed Release of Preparations	Revised
	Guiding Principle for Particle Preparations	Revised
	Guiding Principle for Verification 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 Quantative 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

Code series	Type	Quantity
0100 series	General chapter for preparations	38
0200 series	Other general chapters	6
0300 series	General identification test	1
0400 series	Spectroscopy	11
0500 series	Chromatography	11
0600 series	Physical constant measurement method	12
0700 series	Other measurement methods	10
0800 series	Limit test method	18
0900 series	Test method of physical properties	15
1000 series	Molecular biological technique	
1100 series	Biological test method	13
1200 series	Bioactivity measurement method	20
2000 series	Relevant TCM test methods	16
3000 series	Relevant test method for biological products	108
8000 series	Preparations and standard substances	8
9000 series	Guidelines	30

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

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Major characteristics of ChP 2015 Vol. IV- 4

- Improve test methods

General rule	Test method 1	Test method 2	Test method 3	Test method 4	Test method 5
Clarity test method	Visual method	Instrument method*			
Melting point determination method	Measurement of breakable solid drugs (method A: heating of heat transfer liquid ; method B: heating of rapidly electric heating air*)	Measurement of unbreakable solid drugs (such as fat, fatty acid, paraffin and wool)	Measurement of vaseline or other equivalent substances		
Determination of residue of sulfur dioxide	Titrimetry	Gas chromatography*	Ion chromatography*		
Aflatoxin test method	HPLC	High performance liquid - tandem mass spectrometry*			
Pesticide residues measurement	Gas chromatography	Gas chromatography - tandem mass spectrometry* Liquid chromatography -tandem mass spectrometry*			
Measurement of form and valence state of mercury and arsenic elements	Atomic absorption spectrometry	High performance liquid - inductively coupled plasma mass spectrometry*			
X-ray diffraction method	Single-crystal X-ray diffraction method	Powder x-ray diffraction method*			
Measurement of dissolution and release rate	Basket method	Slurry method	Small glass method	Slurry dish method*	Rotating cylinder method*
Measurement of aerodynamics characteristics of inhaled fine particles	Bipolar striker	Anderson-level striker*	New impacting method*		
Adhesion measurement	Initial adhesion determination	Measurement of permanent adhesion	Measurement of peel strength	Measurement of adhesive force*	
Formaldehyde concent measurement	Magenta method	Acetylacetone method*			

Major characteristics of ChP 2015 Vol.IV- 4

- Strengthen test technical reserves

Item	Applied techniques	Advantages compared with original methods
Drug evaluation technique and method for gene chips	Gene chip technique	Newly-added test technique
Molecular identification of TMC DNA barcode	DNA sequencing	Higher sensitivity and better specificity
Pigment measurement	1. Thin-layer chromatography 2. High-performance liquid chromatography 3. High-performance liquid chromatography - mass spectrometry	Newly-added test technique Higher sensitivity and better specificity
Bacteria and viral measurement for TCM herbs	High-performance liquid chromatography - mass spectrometry	Better sensitivity, stability and specificity; stronger anti-interference performance
Aluminum, chromium, iron and barium measurement for TCM herbs	Inductively coupled plasma mass spectrometry	Better sensitivity and stability; higher test efficiency
Measurement of form and valence state of mercury and arsenic elements	High performance liquid - inductively coupled plasma mass spectrometry[1)]	Better sensitivity and stability; higher test efficiency
Pesticide residues measurement	Gas chromatography - tandem mass spectrometry* Liquid chromatography -tandem mass spectrometry	Better sensitivity, stability and specificity; higher test efficiency

Major characteristics of ChP 2015 Vol.IV- 4

- Advanced test technical application

Test item	ChP 2010[1][2]	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) (11 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)

Major characteristics of ChP 2015 Vol.IV- 4

Safety control	Effectiveness control	Quality control
Measurement of forms and valence states of mercury and arsenic elements	Measurement of dissolution and release rates (slurry dish method, rotating cylinder method)	Inhaled preparations
Adhesion measurement (adhesive force measurement)	Inductively coupled plasma mass spectroscopy	Measurement of aerodynamics characteristics of fine particles in inhaled preparations (Anderson striker, new-type striker)
Inhibitory effectiveness test method★	Supercritical fluid chromatography	Guiding principles for verification of quantitative analysis method for biological samples
Hydroxylamine residue measurement	Critical point chromatography	Guiding principles for microorganism identification
Test technical requirements for viral nucleic acid of human plasma for blood products production	Raman chromatography★	Guiding principles for microorganism monitoring and control in drug clean lab
Sulfur dioxide residue measurement (gas chromatography, ion chromatography)	McAb molecular size variant measurement (CE-SDS method)	Guiding principles for isolated system identification for sterility test
Pesticide residue measurement (gas chromatography - tandem mass spectrometry, liquid chromatography - tandem mass spectrometry)	Bioactivity measurement of mouse nerve growth factors	Guiding principles for functional indexes research of medical adjuvant
Aflatoxin measurement (high-performance liquid chromatography - tandem mass spectrometry)	Nimotuzumab bioactivity measurement	Guiding principles for common requirements for drug packages
Powder X-ray diffraction method	Bioactivity measurement of recombinant human interleukin 11	Guiding principles for medical glass materials and containers
Clarity test method (instrument method)	Histamines test method	Guiding principles for preparation of national drug standard substances
Guiding principle for establishment of limit of hazardous residual substance in TCM herbs	Bioassay of heparin	Guiding principles for national drug standard substances
Guiding principle for pigment test method	Interferon bioactivity measurement	National standard substance category for biological products
Guiding principle for aluminum, chrome, iron and barium measurement	Titration method of bitrationBotulinum neurotoxin (parallel line method)	
General rules for national drug standard substances	Free formaldehyde measurement (method II)	
National standard substance category for biological products	Guiding principle for drug crystal type research and quality control	
	Guiding principle for drug evaluation technique and method based on chips	
	Guiding principle for DNA barcode molecular identification in TCM herbs	

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

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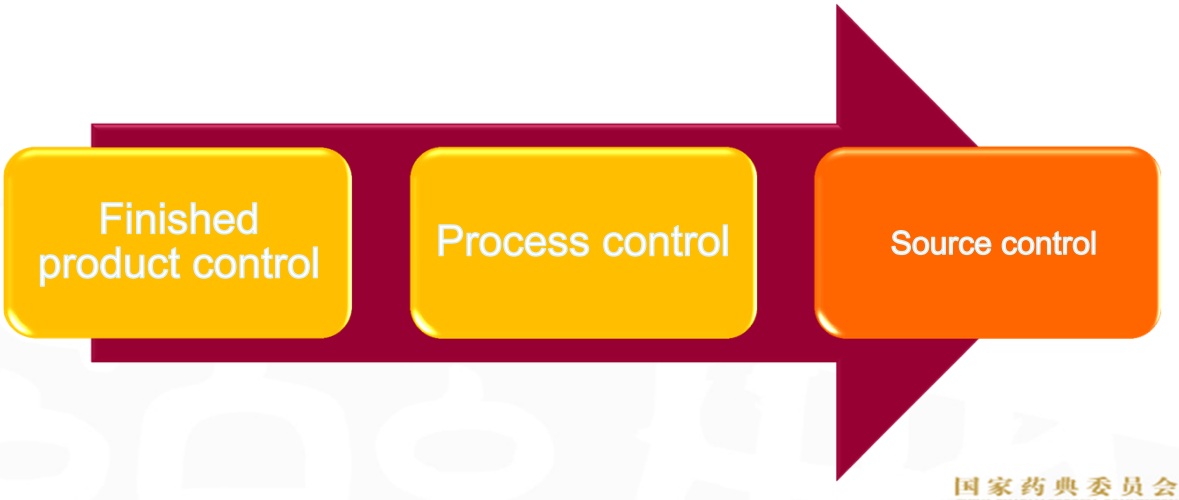
Main characteristics of ChP 2015 Vol.IV - 5

- Strengthen whole process control



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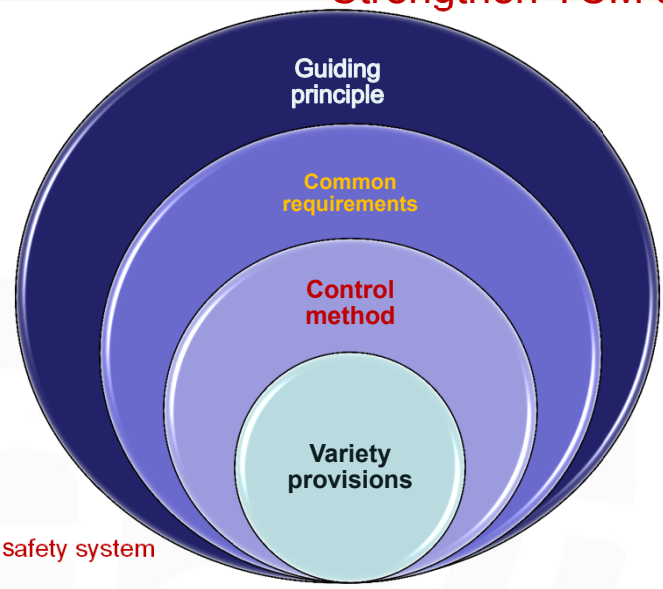
Main characteristics of ChP 2015 Vol.IV - 5

- Strengthen TCM safety control



Establishment of TCM safety system

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

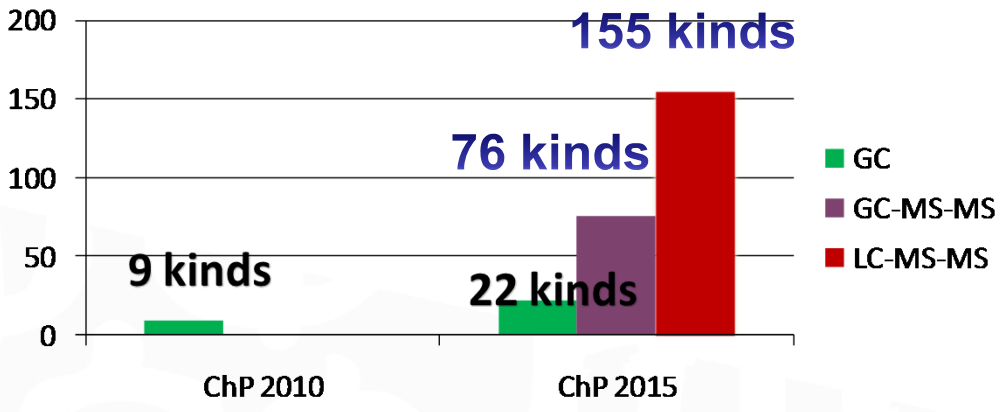
Control requirements for TCM commonality in ChP 2015

- 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



TCM safety control of ChP 2015

- Measurement of lead, cadmium, arsenic, mercury and copper

ChP2010	ChP2015
Atomic absorption spectrometry	Atomic absorption spectrometry
	Inductively coupled plasma - mass spectrometry (ICP-MS)

TCM safety control of ChP 2015

- Measurement of form and valence state of elements

- 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

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TCM safety control of ChP 2015

- Sulfur dioxide measurement

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

TCM safety control of ChP 2015

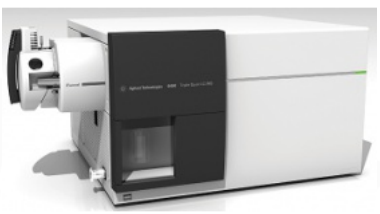
- Fungaltoxin measurement

ChP2010

4 kinds

ChP2015

11 kinds in 7 types



TCM safety control of ChP 2015

- Pigment measurement method

Method system	Method	Kinds for test
Qualitative	(1) Thin-layer chromatographic qualitative method (2) Liquid chromatographic qualitative method (3) Liquid chromatography - tandem mass spectrometry	27
Quantitative	(1) Liquid chromatographic quantitative method (2) Liquid chromatography - tandem mass spectrometry	25

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TCM safety control of ChP 2015

- DNA barcode identification method in TCM herbs

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

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)

PCR program

Degeneration at 94 ℃ for 5 min
Degeneration at 94 ℃ for 30 sec
Annealing at 56 ℃ for 30 sec
Expansion at 72 ℃ for 45 sec
Expansion at 72 ℃got for 10 min
} 40 circles — **ITS2**

Degeneration at 94 ℃ for 5 min
Degeneration at 94 ℃ for 1 min
Annealing at 55 ℃ for 1 min
Expansion at 72 ℃ for 1.5 min
Expansion at 72 ℃ for 7 min
} 30 circles — ***psbA-trnH***

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.

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TCM safety control of ChP 2015

- DNA barcode identification method for TCM herbs

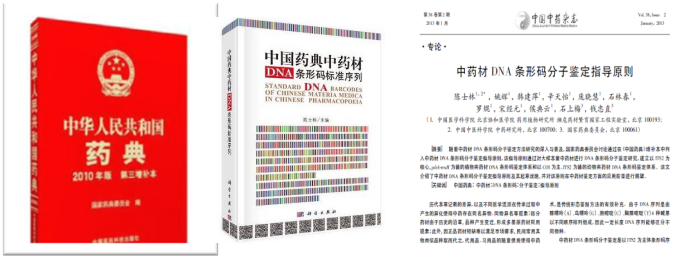
DNA barcode standard sequence for TCM herbs in ChP

DNA barcode standard sequences of more than 500 crude drugs

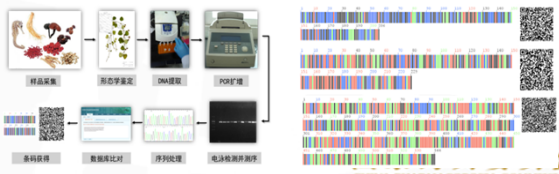
➢**Source of four samples**

Original species, medical material samples
Reference crude herbs, reviewed samples

Standard process for DNA extraction and sequence amplification



- Treatment of test samples
- DNA extraction
- Acquirement of barcode sequence
- Data treatment and analysis



➢**ITS2 and *psbA-trnH* sequence characteristic standard barcode**

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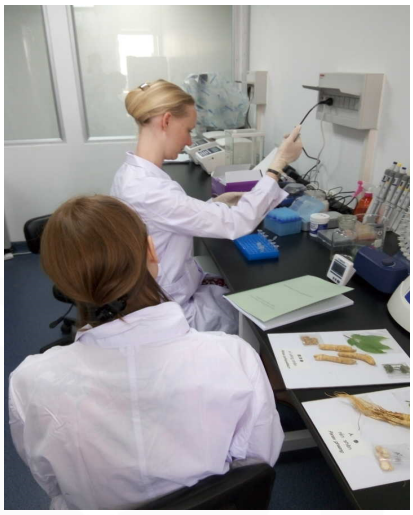
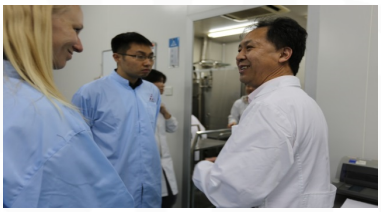
Safety control of TCM in pharmacopeia with Edition 2015
-TCM DNA barcode identification method

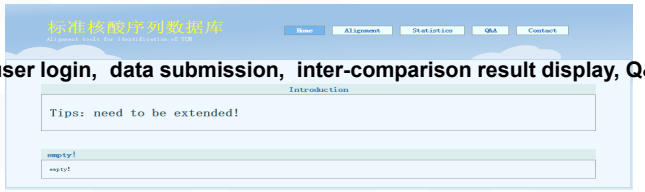

Longitudinal frame

Horizontal grid	Nucleic acid amplification techniques	Restriction enzyme fragment polymorphism	DNA sequencing technology	Multipoint sequence analysis technology	Molecular hybridization technique	...
	TCM	Identification and classification of provenance ingredients in medicinal animals and plants	Establishment of genetic resources center and identification of high-quality varieties	Research. classification and determination of substitute goods for TCM resources		
	Biochemical drug Biological product	Detection and identification of ingredients of animal origin in biochemical drugs	Sources and identification of bacterial and viral species in vaccine products	Gene and protein structure analysis of recombined products	Control of exogenous factors in biological products	Establishment of protein spectrum library for antibody-based products
	Microorganism	Acceptance, identification and confirmation of standard strain used for microorganism examination in drugs	Identification and confirmation of isolates in product quality control	Screening and identification of DNA molecular markers for typical contaminant microorganisms	Genomic identification for strains used for microbial drugs	
	...					

National standard nucleotide sequence data-**website**

Website login interface

Website homepage interface



Platform functions: user login, data submission, inter-comparison result display, Q&A etc.

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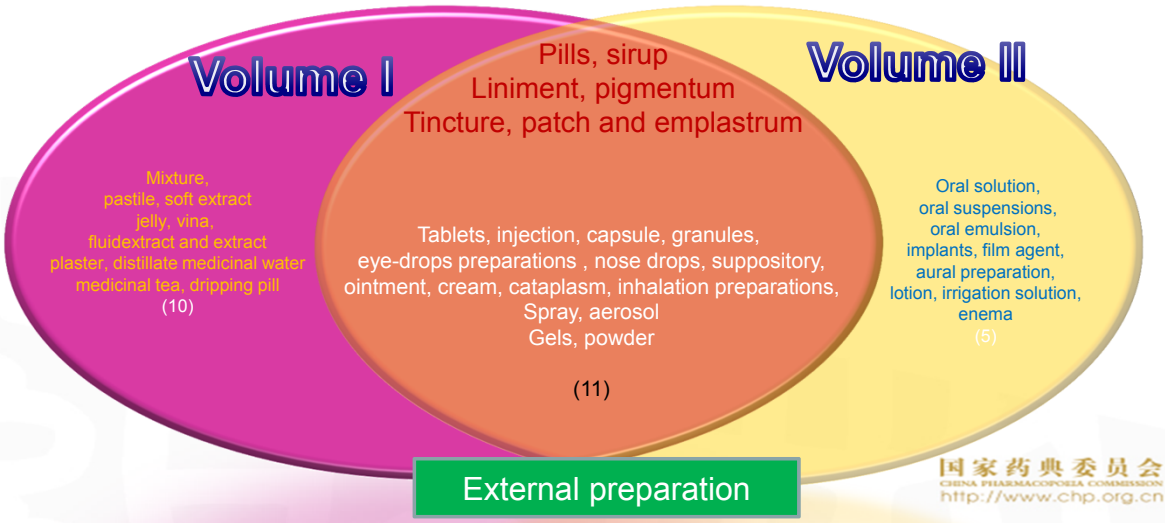
Safety control of TCM in pharmacopeia with Edition 2015

-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



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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.

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Features of four volumes in pharmacopeia with Edition 2015-6

- The similarity requirements of general rules on preparations

- 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.

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Features of four volumes in pharmacopeia with Edition 2015-6

-Newly increased dosage forms in general rules on preparations

Orally disintegrating tablet

Inhalation preparation

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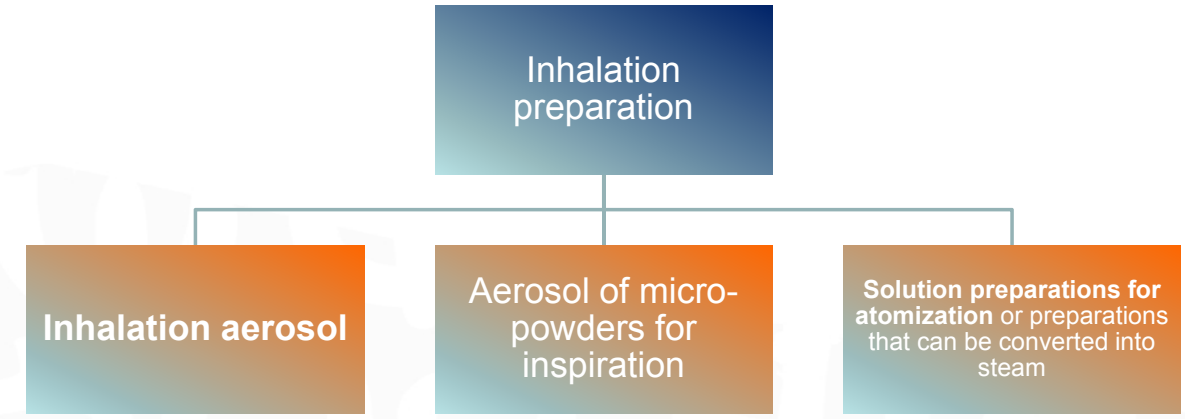
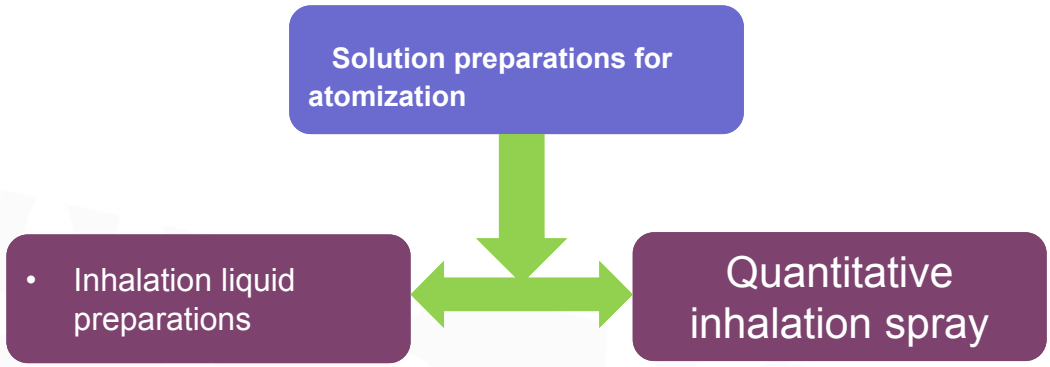
General rules on preparations of four volumes in pharmacopeia with Edition 2015

-Inhalation preparation (general rule 0111)



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

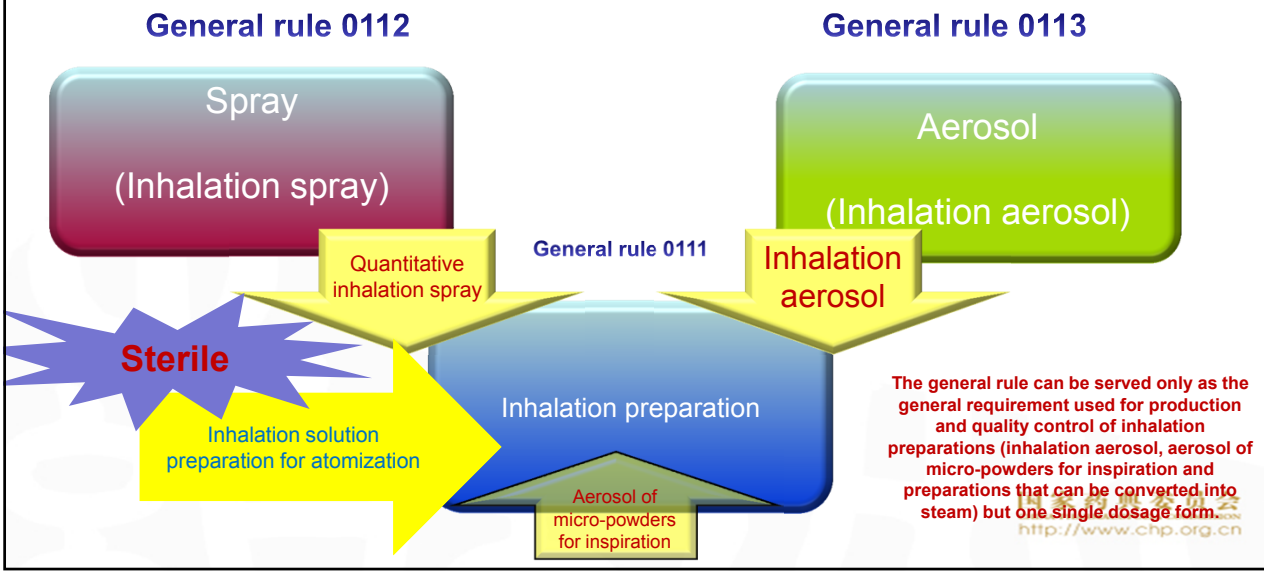
-Inhalation preparation (general rule 0111)



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 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-

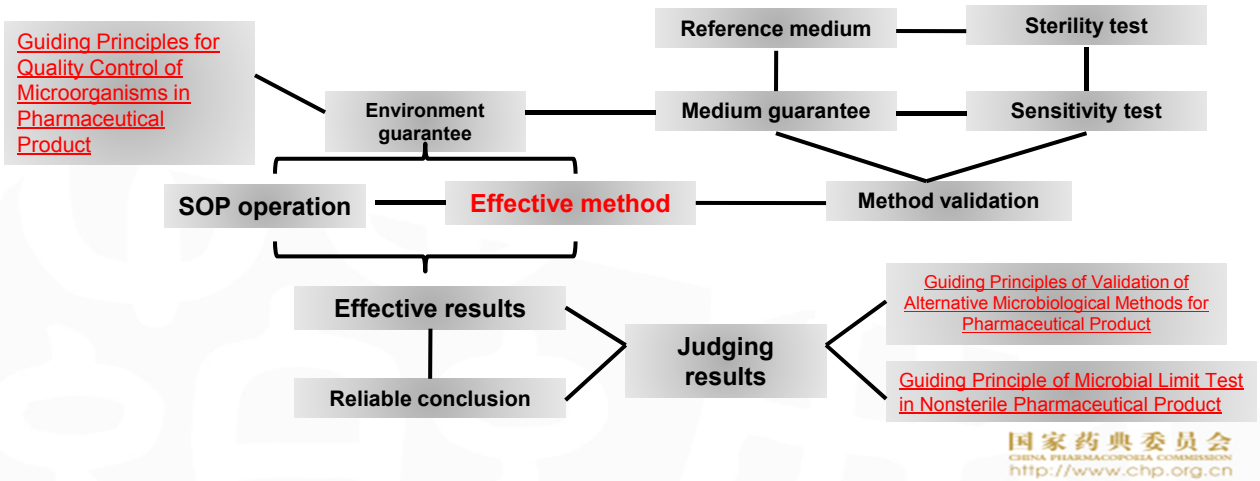
- Microbial detection requirement and international harmonization

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

Microbial detection of four volumes in pharmacopeia with Edition 2015

-Internationally harmonious

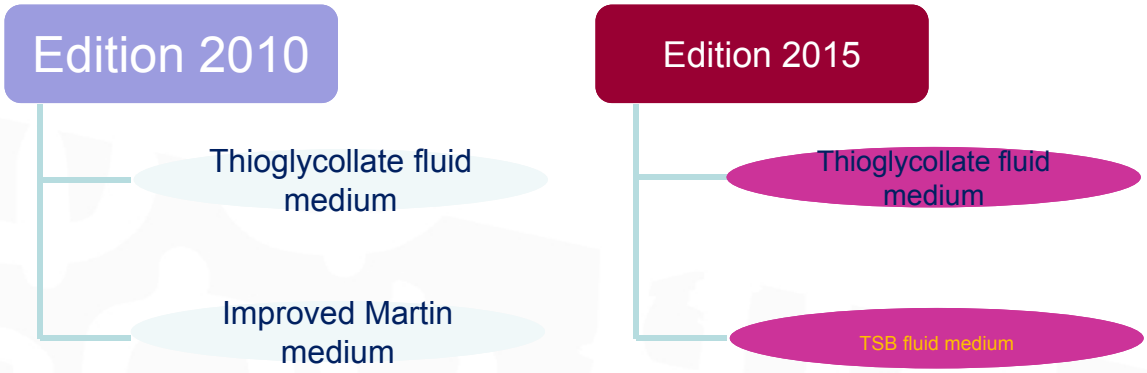
Intensified control for key points in test operation for bacteriological examination of pharmaceutical products



Microbial detection of four volumes in pharmacopeia with Edition 2015

- Sterility test

☐ Revised medium for test



Microbial detection of four volumes in pharmacopeia with Edition 2015

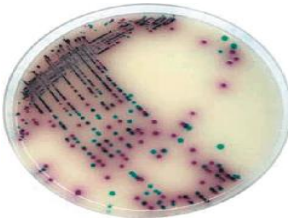
-Internationally harmonious

Pharmacopeia of Edition 2010	Pharmacopeia of Edition 2015
1. Thioglycollate fluid medium 30～ 35 ℃; 20～25℃ (Volume III) 2. Improved Martin medium To culture at 23 ～ 28 ℃ 3. Selective medium 4. 0.5% glucose bouillon culture-medium 5. Nutrient bouillon culture-medium 6. Nutrient agar medium 7. Improved Martin agar medium	1. Thioglycollate fluid medium To culture at 30～ 35 ℃ and 20～25℃ 2. TSB medium To culture at 20 ～ 25℃ 3. Neutralization or inactivation medium 4. 0.5% glucose bouillon culture-medium 5. Trypticase Soy Agar Medium (TSA) 6. Sabouraud Dextrose Broth medium 7. Sabouraud's dextrose agar medium

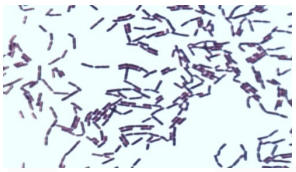
Microbial detection of four volumes in pharmacopeia with Edition 2015

- 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”



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Features of four volumes in pharmacopeia with Edition 2015

- Perfect standard substance formulation

Comparison products, comparison medicinal materials and comparison extracts 504

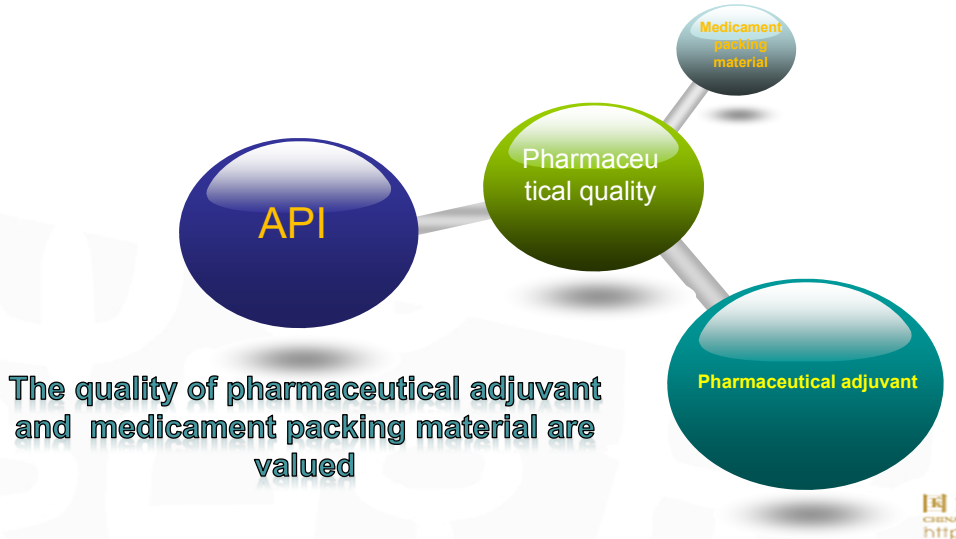
Standard substance of TCM 32

Reference substance of pharmaceutical chemicals 832

Standard substance of biological products 62

Features of four volumes in pharmacopeia 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 pharmacopeia 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

Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

-Effect of adjuvant

- ➢ Influence of drug effect
- ➢ Safety influence of preparations
- ➢ Preparation stability
- ➢ Consistency among lot numbers of preparations

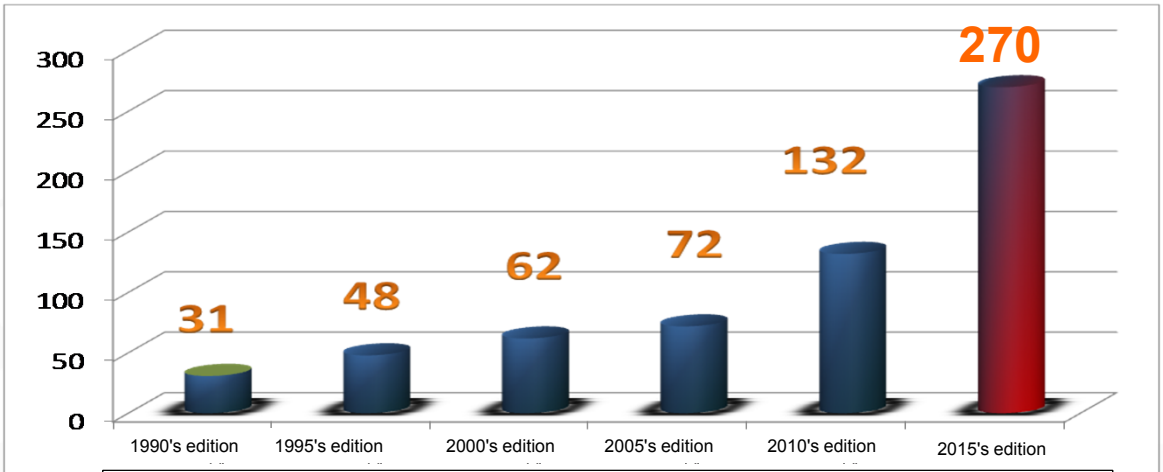
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

-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

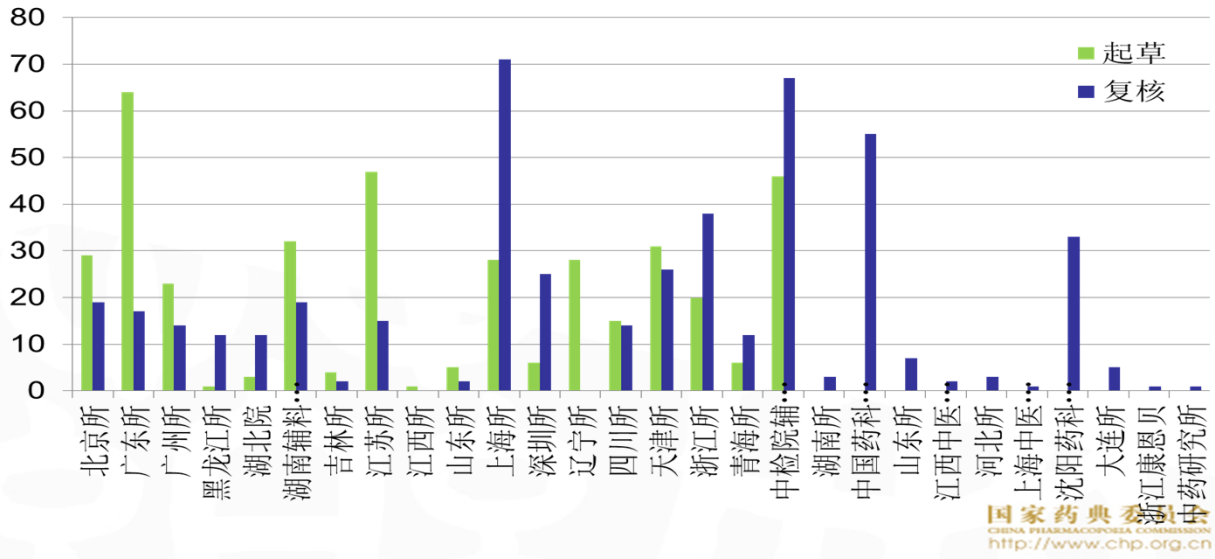
-Variety records are substantially promoted



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

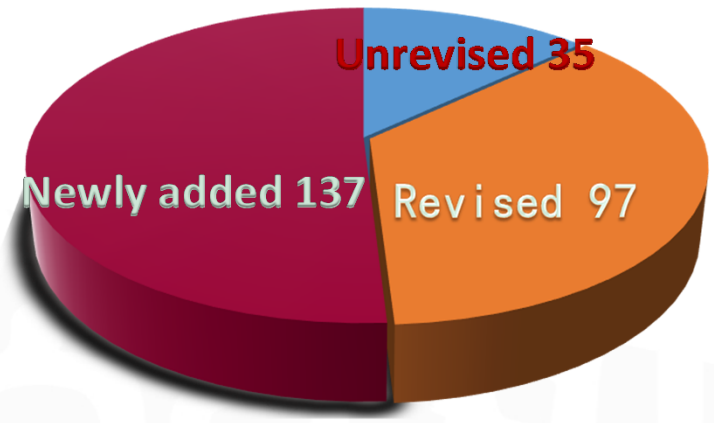
- Units participating in drafting adjuvant standards



Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

-Development and revision conditions of varieties

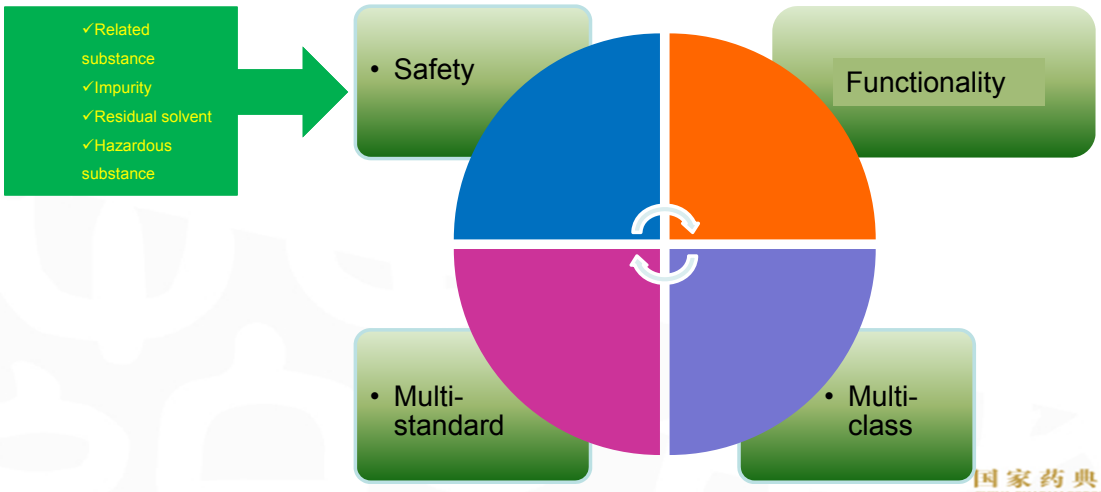
Totally 270 varieties of recorded adjuvant



With no records: thiomersalate, DEP

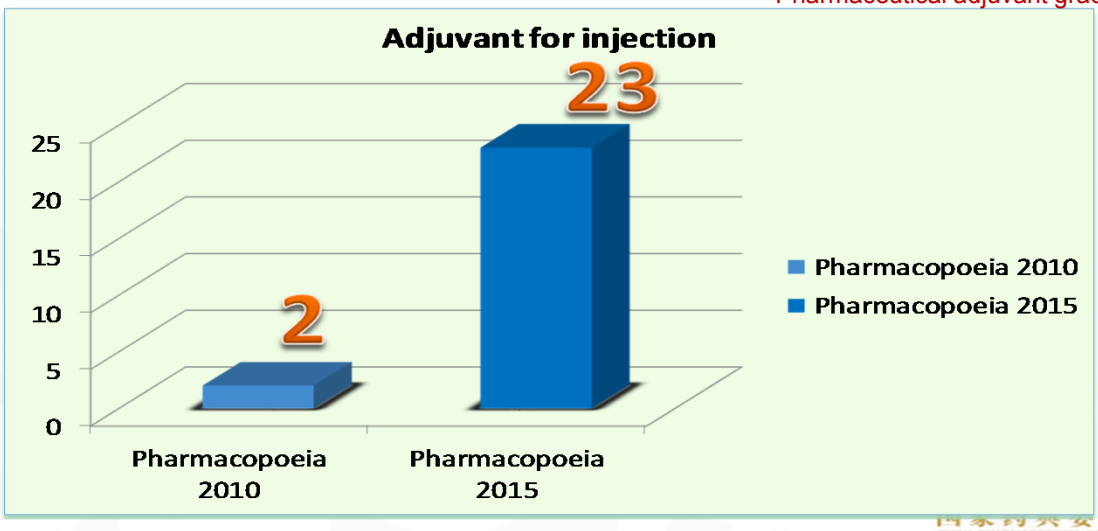
Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

-Controlled key points of pharmaceutical adjuvant



Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

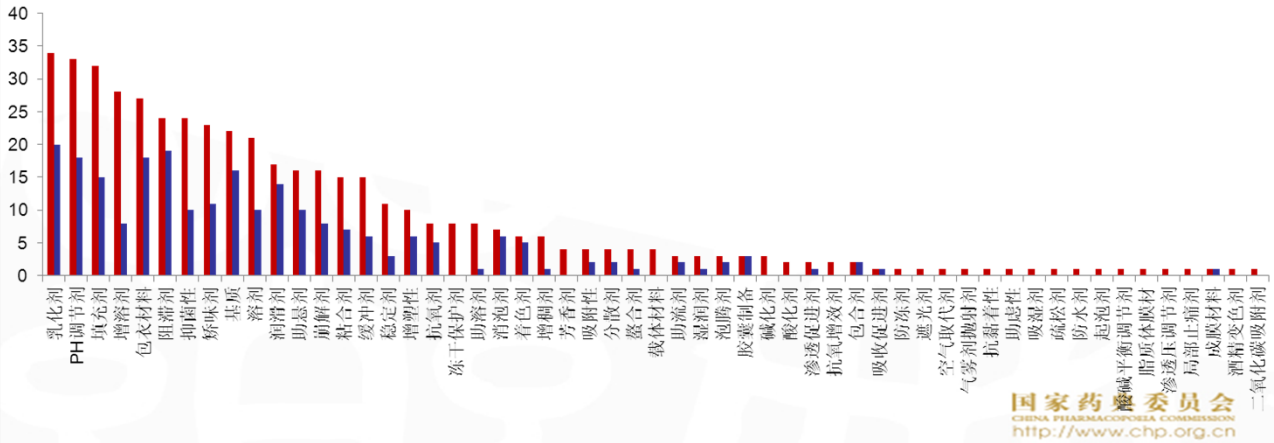
-Pharmaceutical adjuvant grading



Pharmaceutical adjuvant of four volumes in pharmacopeia with Edition 2015

-Functions and uses

55 uses including newly increased 21 uses



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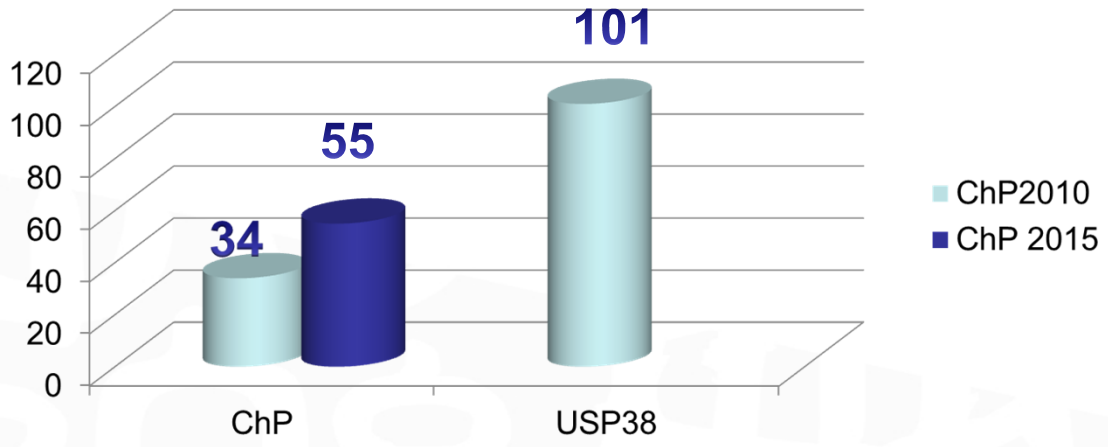
The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient

-Function & Application



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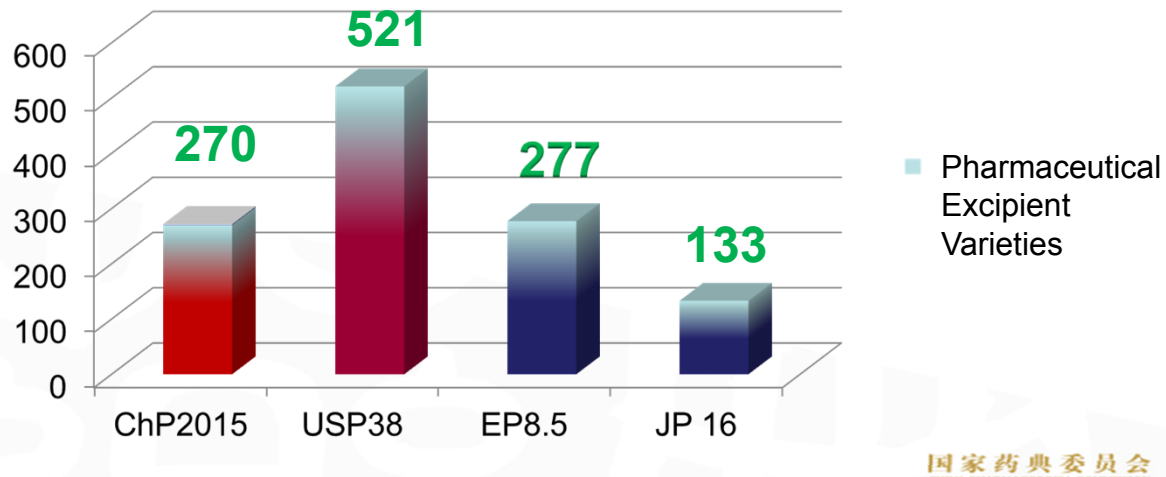
The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient

- Excipient varieties recorded in each country's pharmacopoeia

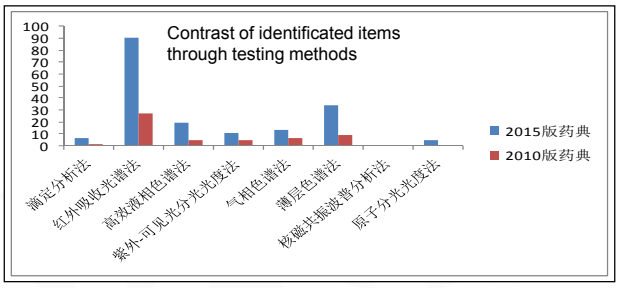


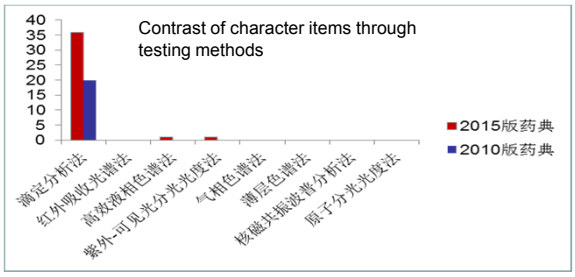
The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient

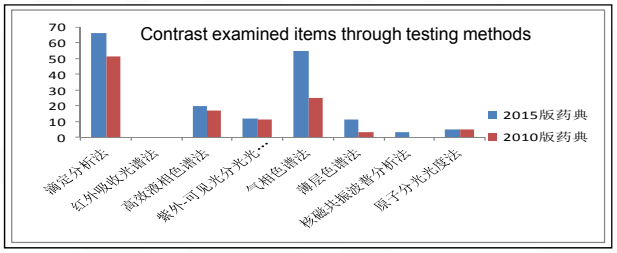
-Enhanced application of advanced testing technology

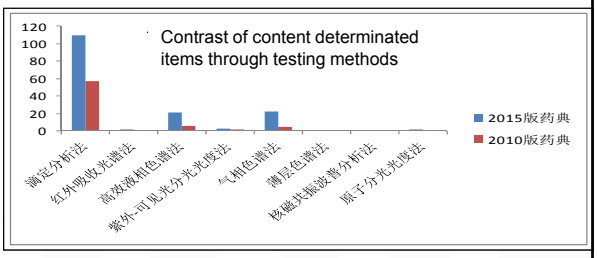
Method	Character		Identification		Examination		Content determination		Total	
	2015 Edition	2010 Edition	2015 Edition	2010 Edition	2015 Edition	2010 Edition	2015 Edition	2010 Edition	2015 Edition	2010 Edition
Titrimetric Analysis	36	20	6	1	66	51	109	57	217	129
IR	0	0	90	27	0	0	1	0	91	27
HPLC	1	0	19	5	20	17	21	6	61	28
UV- visible spectrophotometry	1	0	11	5	12	11	3	2	27	18
GC	0	0	13	6	63	25	22	5	98	36
TLC	0	0	34	9	11	3	0	0	45	12
NMR spectral method	0	0	0	0	3	0	0	0	3	0
AAS	0	0	5	0	5	5	1	0	11	5

The Vol.IV of the 2015 Edition Pharmacopoeia on Pharmaceutical Excipient
-- Enhanced application of advanced testing technology









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

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

- Enhance Functional Control

	Functional Performance
diluent	Granularity and granularity distribution, particle morphology, bulk density, tap density, true density, specific surface area, crystallinity, moisture, fluidity, solubility, compressibility, hygroscopicity
adhesives	Surface tension, granularity, granularity distribution, solubility, viscosity, bulk density and tap density , specific surface area, etc.
disintegrants	Particle size and the distribution, water absorption rate, expansion rate or expansion index, powder flowability, moisture, effervescence, etc.
lubricant	Granularity and granularity distribution, specific surface area, moisture, polymorphism, purity, melting point or melting range, powder flowability
Glidants and anticaking agent	Granularity and granularity distribution, surface area, powder flowability, absorptivity, etc.
Capsule	Moisture, breathability, disintegration, friability, tenacity, frost force strength, tightness
Coating	Solubility, film-formation, viscosity, substituent and degree of substitution, tensile strength, breathability, granularity
Solubilizer	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
Suppository matrixes	Melting point, solidification point, fat and fatty oil
Glidant	Granularity and granularity distribution, surface area, powder flowability, absorption, etc.
Ointment	Viscosity and melting range

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

  Scientificalness, 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

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.**

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Thank You !

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