国家药典委员会
CHINESE PHARMACOPOEIA COMMISSION

Overview of New Admissions and Revisions in Chinese Pharmacopoeia 2015 (Volume II)

Xiaohong ZHANG
Deputy Director of Chemical Drug Standards Division,
Chinese Pharmacopeia Commission
Beijing, China

2016-10-18
Strasbourg, France.

Agenda

1. Standards of ChP 2015 (Vol. II) Setting Process
2. Major highlights of ChP 2015 (Vol. II)
3. Issues needing further attention

ChP Since 1950

1. Standards of ChP 2015 (Vol. II) Setting Process

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

ChP Since 1950

ChPC: Standards Setting Expert Committees (EC)

TCMs	*Chemicals*		*Biologics*	*Medical Information*
Ingredients & Pre-Pared Slices	Chemical Drugs Monographs 1	Antibiotics	Biotech Products	Modern Medical
TCM Products	Chemical Drugs Monographs 2	Biochemical Drugs	Virus Products	TCM Medical
Oil, Fats and Extractives	Chemical Drugs Monographs 3	Radio-active Drugs	Bacterial Products	
Ethno-Medicines	Nomenclature		Plasma Products	

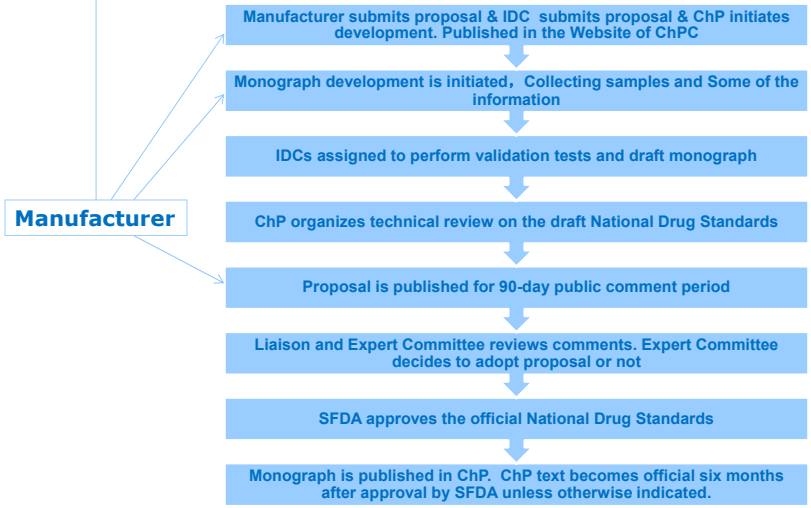
Comprehensive: General Chapters & Cross-Cutting

Physical & Chemical Analysis	Dosage Forms	Microbiology
Bioassay	Excipients	Reference Standards

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

http://www.chp.org.cn

Standards of ChP 2015 (Vol. II) Setting Process



2. Major highlights of ChP 2015 (Vol. II)

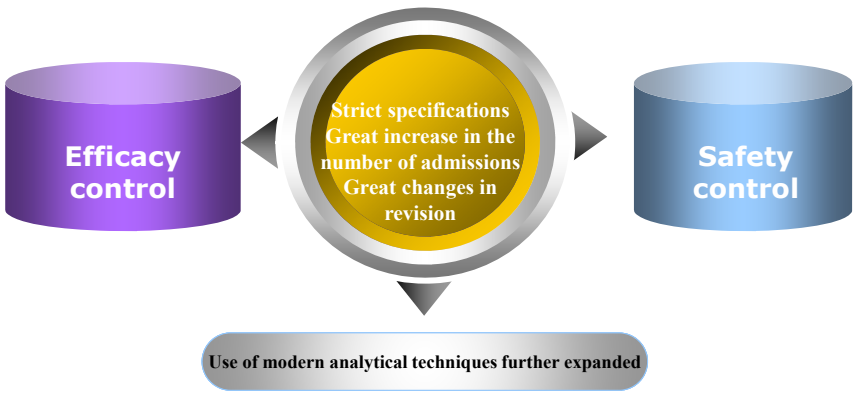
Comparison with other pharmacopoeias in chemical drug varieties included

Editions	APIs	DPs	Total	The proportion of APIs
USP 34	1315	2303	3618	36.3%
BP 2014	1870	1816	3686	50.7%
JP 16	852	489	1341	63.5%
ChP 2015 Chemicals Drugs	933	1670	2603	35.8%

7

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Major highlights of ChP 2015 (Vol. II)



8

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Summary of admissions in the latest three editions of Chinese Pharmacopoeia (Volume II)

Version	Admissions	New admissions	Revisions	Exclusions from previous edition
2005 edition	1967	327	522	2
2010 edition	2139	330	1500	29
2015 edition	**2603**	**492**	**415**	**28**

9

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

List of drugs admitted in ChP2010 (Volume II) but not in ChP2015 (Volume II)

No.	Drug Name	No.	Drug Name	No.	Drug Name
1	Buflomedil hydrochloride	11	Cortisone Acetate Eye Ointment	21	Azithromycin DispersibleTablets
2	Buflomedil Hydrochloride Tablets	12	Adenosine Disodium Triphosphate Injection	22	Roxithromycin Dispersible Tablets
3	Buflomedil Hydrochloride Injection	13	Adenosine Disodium Triphosphate for Injection	23	Potassium Dehydroandrographolide Succinate
4	Buflomedil Hydrochloride Capsules	14	Calcium Gluconate and Sodium Chloride Injection	24	Potassium Dehydroandrographolide Succinate for Injection
5	Buflomedil Hydrochloride for Injection	15	Carboplatin for Injection	25	Ligustrazine Phosphate Injection
6	Almitrine Bismesylate and Raubasine Tablets	16	Pefloxacin Mesylate for Injection	26	Ligustrazine Phosphate and Sodium Chloride Injection
7	Ketoconazole Tablets	17	Calcium Folinate for Injection	27	Sodium Cromoglicate Aerosol
8	Ketoconazole Capsules	18	Pamidronate Disodium for Injection	28	Isoprenaline Hydrochloride Aerosol
9	Analgin	19	Ciprofloxacin Lactate and Sodium Chloride Injection		
10	Analgin Tablets	20	Rifampicin for Eye Use		

10

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Chinese Pharmacopoeia 2015 (Volume II). General Notices

VI. Requirements in monographs are established for products complying with Good Manufacturing Practices (GMP). Any drug violating GMP or any drug manufactured with addition of substances without permission will be considered inconsistent with related requirements even if it complies with ChP or the added substances or related impurities are not detected as per ChP.

Chinese Pharmacopoeia 2015 (Volume II). General Notices

IX. Depending on the drug identity and dosage form, the following items may be listed in the following order in a monograph: (1) drug names (including Chinese name, Chinese phonetics and English name); (2) structural formula of organic compound; (3) molecular formula and molecular weight; (4) origin or chemical name of organic compound; (5) content or potency; (6) formula; (7) formulation; (8) description; (9) identification; (10) tests; (11) assay; (12) category; (13) strength; (14) storage; (15) preparations; (16) impurity profile**; etc.**

Names and structural formulae of known impurities in drug substances and drug products are usually listed in monographs of drug substances and directly cited in monographs of corresponding drug products. Impurities originating from interactions of active ingredients in compound preparations are generally listed in monographs of corresponding products.

Chinese Pharmacopoeia 2015 (Volume II). General Notices

XVII. Tests address test methods and limits reflecting drug safety and efficacy, preparation process requirements including uniformity and purity, etc.; the specified impurity tests are established for impurities that are possibly contained in drugs or generated in production according to established processes and normal storage and need to be controlled (e.g. residual solvents, related substances, etc.); **admission of new items or revision of related items should be considered when the manufacturing process is changed.**

Organic solvents introduced in the manufacturing process should be effectively removed in subsequent manufacturing procedures. For drugs with "residual solvents" specified in monographs, organic solvents introduced in the manufacturing processes must be analyzed as required; for other organic solvents not specified in the monographs or products without "residual solvents" specified in the monographs, if organic solvents are introduced in the manufacturing processes or residual organic solvents exits in products, "determination of residual solvents" should be carried out according to General Rules and limit requirements of related solvents should be satisfied.

When related substances are analyzed by chromatography, peaks (or spots) of solvents, excipients or inactive parts of drug substances should be excluded from impurity peaks (or spots). When necessary, suitable methods may be used for confirmation of the above non-impurity peaks (or spots).

For injections and ophthalmic preparations containing antimicrobial agents in the formulae, suitable test methods should be established for controlling contents of the antimicrobial agents. **For products with antimicrobial agent tests specified in monographs, tests for antimicrobial agents used in the products must be carried out as required, and corresponding limit requirements should be satisfied.**

Drug substances directly dispensed as sterile powder for injection should be tested following requirements for injections and comply with related requirements.

All preparations, unless otherwise specified, should comply with related general requirements.

13

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Chinese Pharmacopoeia 2015 (Volume II). General Notices

XXIII. All drugs admitted in monographs of this edition of pharmacopoeia should be tested according to the specified methods. In tests using the methods specified in this edition of pharmacopoeia, suitability of the methods should be verified. If other methods are used, comparative studies should be conducted against the specified methods; methods may be selected depending on the study results. However, methods specified in this edition of pharmacopoeia will prevail in arbitration.

14

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Technical principles

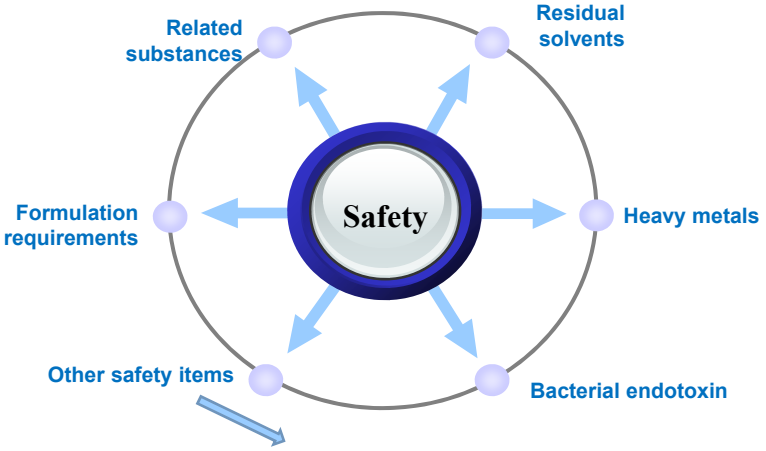
- General principles
  - ✓ Open, fair, just
  - ✓ Scientific, suitable, standard
  - ✓ References: EP, BP, USP, JP
  - ✓ Scientificity first, respect of originator drugs consideration of other drugs

Strict logical chain
Full evidence

- Technical regulations
  - ✓ Standardize generic names of drugs
  - ✓ Admit and revise safety and efficacy items
  - ✓ Appropriately introduce modern analytical techniques

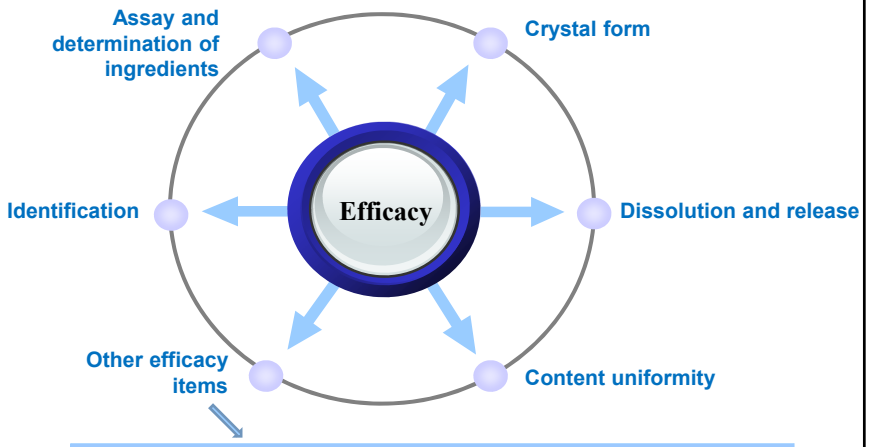
Standardization
Specification improvement
Clearance

Technical principles



Safety-related items including description, color and clarity, osmolarity, particle size, microbial limits, sterility, antimicrobial agents, inorganic ions, etc.

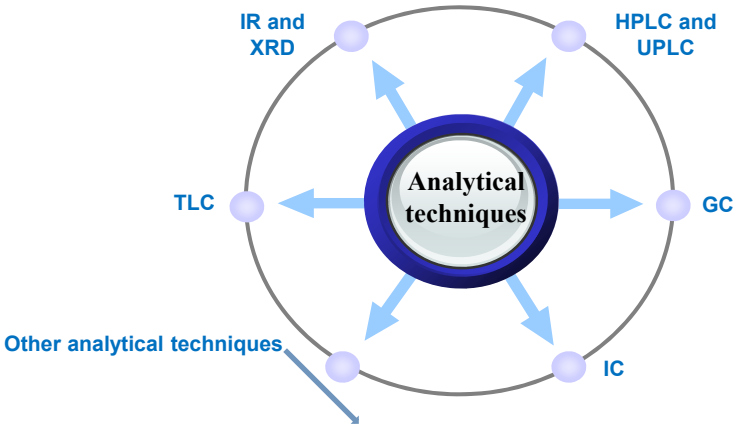
Technical principles



Efficacy items related to manufacturing pharmacy characteristics including description, acid resistance, dilatation, adsorption, fine particle dose, uniformity of delivered dose, etc.; methods of the same items for different preparations are unified.

17

Use of modern analytical techniques



Different HPLC detectors, GLC, CE, NMR, MS, XRD, volumetric analysis, etc.

18

Crystal form

- Melting point → Indometacin
- Thermal analysis
- Infrared spectrometry → Chloramphenicol Palmitate (type B); Mebendazole（A≤10%）
- X-ray diffraction → Aripiprazole, nateglinide

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Quality control of polymorphic drugs in pharmacopoeias of four countries

No.	Drug Name	USP	BP	JP	ChP
1	Carbamazepine	XRD	IR		
2	Amifostine	XRD			
3	Erythromycin ethylsuccinate	XRD			
4	Orbifloxacin	XRD			
5	Pantoprazole sodium		IR		
6	Lofepramine hydrochloride		IR		
7	Phenylpropanolamine hydrochloride, norephedrine hydrochloride		IR		
8	Indometacin	XRD	IR		
9	Mebendazole				IR
10	Chloramphenicol Palmitate				IR
11	Chloramphenicol Palmitate Oral Suspension				IR
12	Chloramphenicol Palmitate Tablets				
13	Chloramphenicol Palmitate Granules				

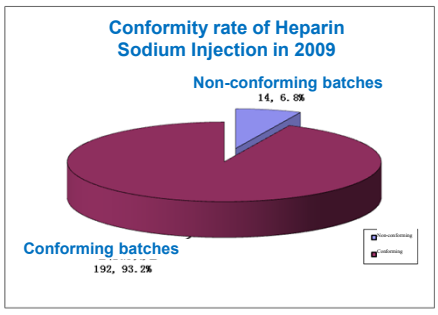
国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

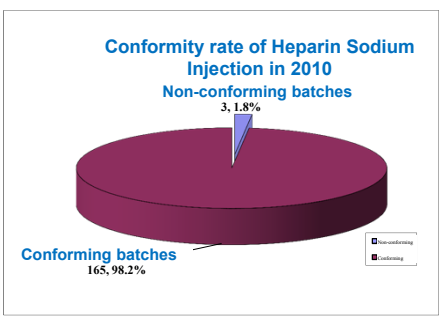
Examples

- X-ray powder diffraction (identification and impurity tests of smectite and its preparations; nateglinide, aripiprazole)
- New electrochemical detectors (assay of etimicin sulfate, HPLC, integral pulsed amperometric electrochemical detector
- Ion chromatography (alendronate sodium, phosphate and phosphate tests, assay)

National evaluative sampling inspection of Heparin Sodium Injection

- **Time: 2009, 2010**
- **Sampling:**
- 2009: 206 batches of Heparin Sodium Injection were sampled from 7 manufacturers in 31 provinces
- 2010: 168 batches of Heparin Sodium Injection were sampled from 7 manufacturers in 30 provinces





International collaborative studies in heparin products

- 2006: participated in international collaborative standardization of reference substances for determination of molecular weights of low molecular heparin EPCRS2 and EPCRS3 and WHO (05/112)
- 2009: participated in the 6th international collaborative standardization of heparin reference substances
- 2012: participated in the 3rd international collaborative standardization of reference substances of low molecular heparin
- 2012: participated in collaborative standardization of molecular weight reference substance of USP heparin
- 2012: participated in collaborative studies on methods for determination of protein and nucleic acid impurities in USP heparin

Heparin Sodium(2015 edition)

New items

- **Molecular weight and molecular weight distribution**
- **The ratio of anti-factor Xa activity and anti-factor IIa activity**

Revised items

- **Definition, pigs or oxen → pigs**
- **Protein, absorption at 280nm≤0.10 → Lowry,≤0.5%**
- **Related substance**

---- Degradation of samples using nitrite

---- Optimized chromatographic conditions

---- Revised limits: dermatan sulfate ≤5.0% → ≤2.0%, Other impurities may not be detected

- **Assay: coagulation methods →Anti-FIIa, ≥170→≥180IU/mg**

Heparin sodium （ChP2015 vs. EP8.3）

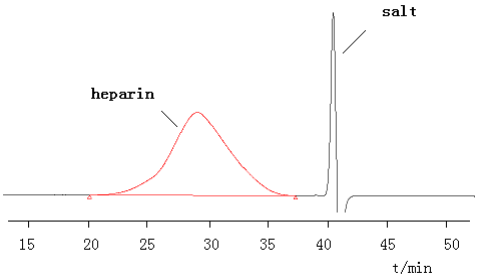
Item	CHP2015	EP8.3
Identification	Intestinal mucosae of pigs	Intestinal mucosae of pigs
Specific optical rotation	≥+50°	/
Identification	1. anti-FXa/anti-FIIa :0.9～1.1 2. the principal peak in the chromatogram obtained with test solution is similar with the reference solution 3. sodium	1. Complies with the repuirments described under assay 2. anti-FXa/anti-FIIa: 0.9～1.1 3. NMR 4. the principal peak in the chromatogram obtained with test solution is similar with the reference solution 5. sodium
Nucleotidic impurities	absorption at 260nm≤0.10	absorption at 260nm≤0.15
Protein	Lowry, ≤0.5%	Lowry, ≤0.5%
Related substance	DS≤2.0%, Others may not detected	DS≤2.0%，Others may not detected
Residual solvents	MeOH≤0.3%,EtOH≤0.5%,Acetone≤0.5%	/
Sodium	10.5%～13.5%	10.5%～13.5%
Molecular weight and molecular weight distribution	Mw:15000 ～ 19000 ， M_{24000}≤20% ， M_{8000}～M_{16000}/M_{16000}～M_{24000}≥1.0。	/
Assay	Anti-FIIa，≥180IU/mg	Anti-FIIa，≥180IU/mg

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Heparin-Molecular weight and molecular weight distribution

ChP Since 1950

- **Method**： HPSEC，Refractive index，Broad standard
- **Acceptance criteria**：The system suitability sample is within 500 Da of the labeled value. Mw:15000～19000，M_{24000}≤20%，M_{8000}～M_{16000}/M_{16000}～M_{24000}≥1.0。



Chromatogram of heparin molecular weight calibrant （140819-201501）

Broad Standard Table for heparin molecular weight calibrant （140819-201501）

Point	M	% below M
1	6000	<3.3%
2	8000	<10.3%
3	10000	<20.1%
4	12000	<31.9%
5	14000	<44.4%
6	16000	<56.6%
7	18000	<67.2%
8	20000	<75.5%
9	22000	<81.6%
10	24000	<86.1%
11	26000	<89.2%
12	28000	<91.6%
13	32000	<94.6%
14	36000	<96.4%
15	40000	<97.6%

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

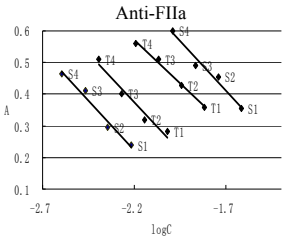
Heparin-Assay

- **Method**：The coagulation method was replaced by chromogenic substrate method. The method is more specific.
- **Acceptance criteria**：≥170IU/mg→≥180IU/mg

1、ATⅢ+HP→[ATⅢ-HP]

2、[ATⅢ-HP]+ excess FⅡa→[ATⅢ-HP-FXa/FⅡa]+ remaining FⅡa

3、 remaining FⅡa+ substrate →pNA, Abs 405nm



Anti-FIIa assay

25μl sample + 25μl ATIII

mixed 37℃, 2min

50μl FIIa

mixed 37℃, 2min

50μl S-2238

mixed 37℃, 2min

50μl 50%HAC

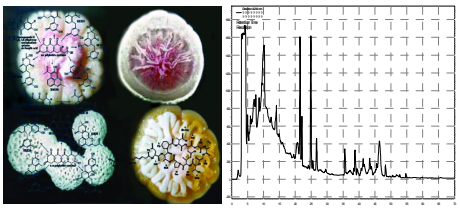
mixed

405nm,Abs

27

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

Changes of quality control philosophy of antibiotics in ChP



Before ChP2000

Biological analysis-centered drug quality control system

ChP2005

Mainly biological control, secondarily chemical analysis

ChP2015

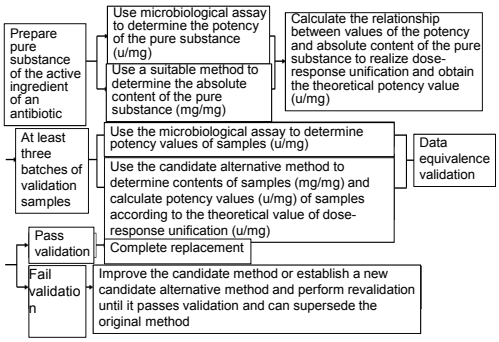
Mainly chemical analysis, secondarily biological analysis

28

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

1. Substantial progress has been made in unification of assay and purity analysis

Difficulty: how to trace potency values with specific metrological units to international units (SI).



Solution using chemical methods instead of potency method to determine contents of single-component antibiotics

①Theoretical potency of **amphotericin B** is 1048.63U/mg

② Theoretical potency of **gentamycin** is C1a=1286.98U/mg

C2=1095.74U/mg

C2a=1079.52U/mg

C1=739.61U/mg

Example: calculation of ingredient contents in gentamycin preprations:

$$\text{Content of ingredients C} = \left(\frac{A_{tC_{1a}}}{A_{sC_{1a}}} \times P_{sC_{1a}} \times 1286.98 + \frac{A_{tC_1}}{A_{sC_1}} \times P_{sC_1} \times 739.61 + \frac{A_{tC_{2a}}}{A_{sC_{2a}}} \times P_{sC_{2a}} \times 1079.52 + \frac{A_{tC_2}}{A_{sC_2}} \times P_{sC_2} \times 1095.74 \right)$$

Where: A_t is peak area of the test sample;

A_s is peak area of the reference substance;

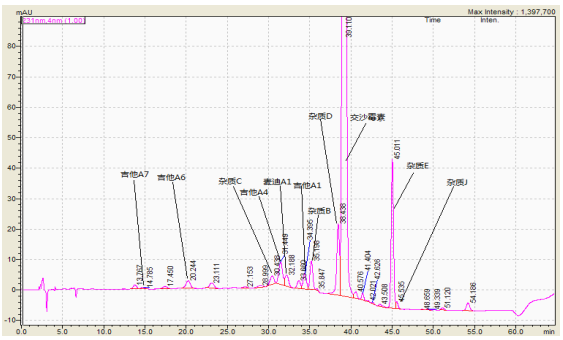
Ps is the absolute content of the reference substance;

C_{1a}, C_1, C_{2a} and C_2 denote gentamycin C ingredients;

1286.98, 739.61, 1079.52 and 1095.74 are theoretical potency values of gentamycin C_{1a}, C_1, C_{2a} and C_2.

2. Separate control of active ingredients and impurities in multi-component antibiotics to ensure product stability

Example: For josasmycin (a multi-component antibiotic with kitasamycin A3 as the major ingredient), it is specified that the total content of ingredients A (kitasamycin A1, A3, A4, A6 and A7 and midecamycin A1) is not less than 90.0%; the content of kitasamycin A3 is not less than 87%; the content of other related substances is not more than 8%.

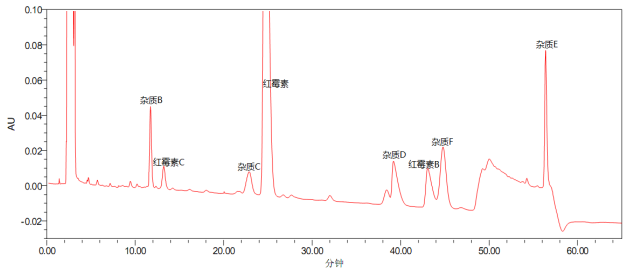


According to the EMA guideline, the control limit of impurities closely related to the structure of the parent compound is usually 0.50%, and the control limit of other impurities is usually 0.15%.

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

3. With advantages of manufacturers brought into full play, specifications of part antibiotics manufactured by fermentation have significantly improved.

Example: revision of the specification of erythromycin:



HPLC system can separate more impurities in current EP and USP；Limit of erythromycin: ≥88.0%→ ≥93.0%

Limit of erythromycin B and C: ≤5.0% → ≤3.0%

6 specified impurities (A, B, C, D, E and F) are specified

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

4. The role of national evaluative sampling inspection is played to timely discover defects of home-made products

- Cefotaxime sodium (evaluative sampling inspection in 2010): water limit changed from “NMT 6.0%” to “NMT3.0%”
- Cefpodoxime proxetil oral preparations (evaluative sampling inspection in 2013): dissolution method revised according to USP (non-conformity rate was 37.0%)

Test items and limits approximate to foreign pharmacopoeias

33

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

5. Control of impurities is paid critical attention to

- ✓ Impurities not admitted in foreign pharmacopoeias have been discovered, and specific analytical methods have been established, e.g. cefalotin 3-position isomer, 2-naphthol in cephalexin and cefradine, etc.
- ✓ For part antibiotics such as cefpodoxime proxetil, spectinomycin hydrochloride, gentamycin sulfate, etc., not only impurities admitted in foreign pharmacopoeias but also specified impurities in home-made products have been specified; structures of impurities have been supplemented for antibiotics manufactured only in China (e.g. etimicin);
- ✓ Mistakes in foreign pharmacopoeias have been corrected, e.g. wrong identification of the peak position of cefalotin impurity A in EP/BP

In control of impurities in antibiotics, ChP2015 is basically in line with foreign pharmacopoeias

34

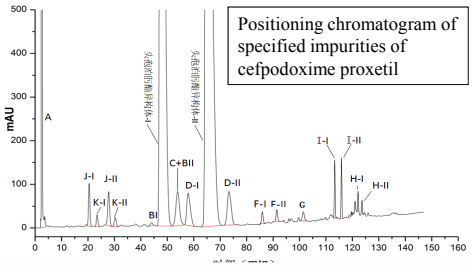
国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

6. Both practicality and progressiveness are considered for analytical methods

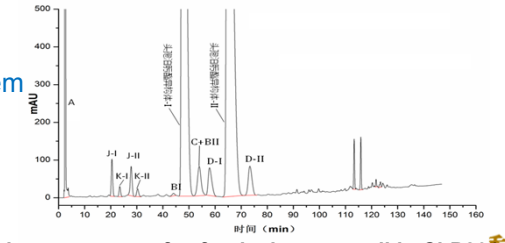
- ✓ Determination of 3-position isomer of cefalotin
  - HPLC using a column packed with phenylhexyl triple bond bonded ethylidene bridge hybridized particles (method I)
  - Capillary electrophoresis (method II)
- ✓ Determination of related substances in aminoglycosides including etimicin, spectinomycin and gentamycin
  - HPLC-ELSD method (method I)
  - Four-waveform electrochemical detector (method II)

7. Related standard chromatograms are attached to specifications

(A) Simulated standard chromatogram:



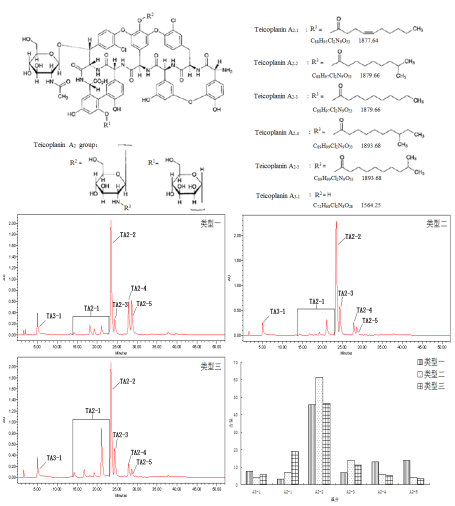
(B) Chromatogram of system suitability test：

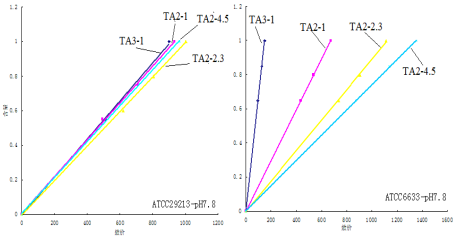


HPLC chromatogram of cefpodoxime proxetil in ChP2015

8. New techniques for quality control of drugs are developed, and new drug analysis methods are established

a. Selection of test strains for multi-component antibiotics





Test strains for assay of teicoplanin:

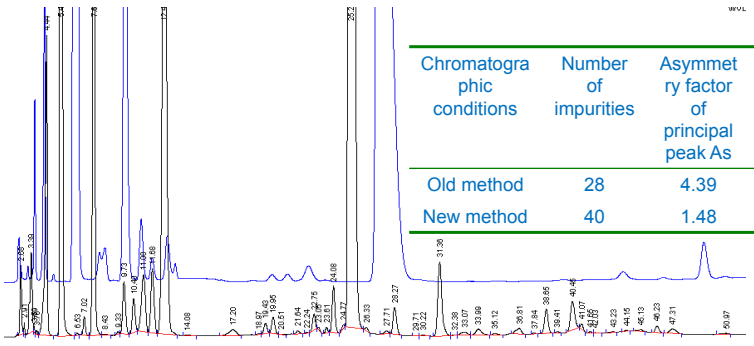
Bacillus subtilis ATCC6633

↓

Staphylococcus aureus ATCC29213

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

b. Optimization of HPLC methods



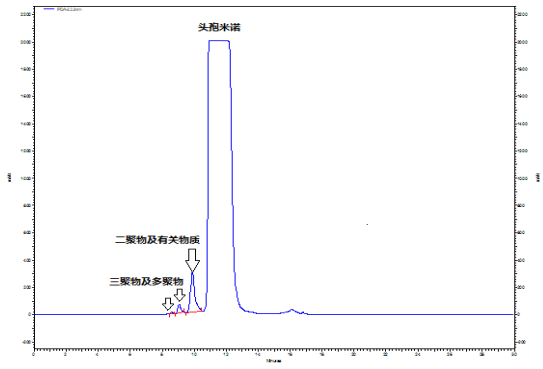
Chromatographic conditions	Number of impurities	Asymmetry factor of principal peak As	Analytical time Rt (min)
Old method	28	4.39	82
New method	40	1.48	70

Comparison of HPLC analytical methods of penicillium before and after optimization

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

ChP Since 1950

c. New method for analysis of β-lactam antibiotic polymer



Chromatograms before the principal peak of cefminox are both peaks of mixtures. In the figure, the impurity peak near the peak of cefminox contains dimer and other impurities, and other impurities can be detected by the method for related substance I, while polymers cannot be detected.

Analysis of cefminox sodium by high performance gel chromatography (method for related substance II)

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

ChP Since 1950

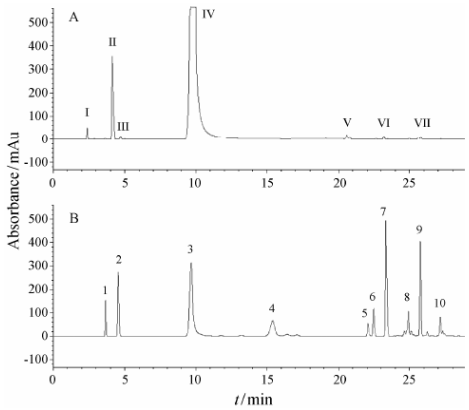
3. Issues Further concern

国家药典委员会 CHINESE PHARMACOPOEIA COMMISSION HTTP://WWW.CHP.ORG.CN

3. Issues Further concern

- Control of specialized impurities
- Control of impurities in compound preparations

Example: Amoxicillin and Clavulanate Potassium for Suspension



Mixed amoxicillin impurity reference substance is used for positioning impurities in Amoxicillin and Clavulanate Potassium for Suspension.

Acknowledgements

- Drug control institutes, scientific research institutes and colleges
- Expert Committees
- CPC members
- Manufacturers and industrial associations

http://www.chp.org.cn

E-mail of Chemical Drug Standard Division：
chp2015huayao@chp.org.cn

谢 谢！

Thanks for your attention!