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

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Agenda

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

1. Manufacturer submits proposal & IDC submits proposal & ChP initiates development. Published in the Website of ChPC.

2. Monograph development is initiated, Collecting samples and Some of the information.

3. IDCs assigned to perform validation tests and draft monograph.

4. ChP organizes technical review on the draft National Drug Standards.

5. Proposal is published for 90-day public comment period.

6. Liaison and Expert Committee reviews comments. Expert Committee decides to adopt proposal or not.

7. SFDA approves the official National Drug Standards.

8. Monograph is published in ChP. ChP text becomes official six months after approval by SFDA unless otherwise indicated.

2. Major highlights of ChP 2015 (Vol. II)
Comparison with other pharmacopoeias in chemical drug varieties included

<table>
<thead>
<tr>
<th>Editions</th>
<th>APIs</th>
<th>DPs</th>
<th>Total</th>
<th>The proportion of APIs</th>
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</thead>
<tbody>
<tr>
<td>USP 34</td>
<td>1315</td>
<td>2303</td>
<td>3618</td>
<td>36.3%</td>
</tr>
<tr>
<td>BP 2014</td>
<td>1870</td>
<td>1816</td>
<td>3686</td>
<td>50.7%</td>
</tr>
<tr>
<td>JP 16</td>
<td>852</td>
<td>489</td>
<td>1341</td>
<td>63.5%</td>
</tr>
<tr>
<td>ChP 2015</td>
<td>933</td>
<td>1670</td>
<td>2603</td>
<td>35.8%</td>
</tr>
</tbody>
</table>

Major highlights of ChP 2015 (Vol. II)

- Efficacy control
- Safety control
- Strict specifications
- Great increase in the number of admissions
- Great changes in revision
- Use of modern analytical techniques further expanded
Summary of admissions in the latest three editions of Chinese Pharmacopoeia (Volume II)

<table>
<thead>
<tr>
<th>Version</th>
<th>Admissions</th>
<th>New admissions</th>
<th>Revisions</th>
<th>Exclusions from previous edition</th>
</tr>
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<tbody>
<tr>
<td>2005 edition</td>
<td>1967</td>
<td>327</td>
<td>522</td>
<td>2</td>
</tr>
<tr>
<td>2010 edition</td>
<td>2139</td>
<td>330</td>
<td>1500</td>
<td>29</td>
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<tr>
<td>2015 edition</td>
<td>2603</td>
<td>492</td>
<td>415</td>
<td>28</td>
</tr>
</tbody>
</table>

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

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

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.
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 exit 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.

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.
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

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

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

Technical principles

- Assay and determination of ingredients
- Crystal form
- Identification
- Dissolution and release
- Content uniformity
- Other efficacy items

Efficacy

Use of modern analytical techniques

- HPLC and UPLC
- IR and XRD
- GC
- TLC
- IC
- Other analytical techniques

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

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

Quality control of polymorphic drugs in pharmacopoeias of four countries

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug Name</th>
<th>USP</th>
<th>BP</th>
<th>JP</th>
<th>ChP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbamazepine</td>
<td>XRD</td>
<td></td>
<td>IR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Antiflamine</td>
<td>XRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Erythromycin ethylsuccinate</td>
<td>XRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Orbifloxacin</td>
<td>XRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pantoprazole sodium</td>
<td>IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Lofepramine hydrochloride</td>
<td>IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Phenylpropanolamine hydrochloride, norephedrine hydrochloride</td>
<td>IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Indometacin</td>
<td>XRD</td>
<td>IR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Mebendazole</td>
<td>IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Chloramphenicol Palmitate</td>
<td>IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Chloramphenicol Palmitate Oral Suspension</td>
<td>IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Chloramphenicol Palmitate Tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Chloramphenicol Palmitate Granules</td>
<td></td>
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</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Year</th>
<th>Conforming batches</th>
<th>Non-conforming batches</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>190, 93.2%</td>
<td>16, 8.8%</td>
</tr>
<tr>
<td>2010</td>
<td>165, 98.2%</td>
<td>5, 1.8%</td>
</tr>
</tbody>
</table>
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 → ≥ 180 IU/mg
**Heparin sodium  (ChP2015 vs. EP8.3)**

<table>
<thead>
<tr>
<th>Item</th>
<th>CHP2015</th>
<th>EP8.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Intestinal mucosae of pigs</td>
<td>Intestinal mucosae of pigs</td>
</tr>
<tr>
<td>Specific optical rotation</td>
<td>≥ +50°</td>
<td>/</td>
</tr>
</tbody>
</table>
| 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 requirements 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, M24000≤20%, M8000~M16000/M16000~M24000≥1.0 | / |
| Assay                       | Anti-FIIa: ≥180IU/mg | Anti-FIIa: ≥180IU/mg |

**Heparin-Molecular weight and molecular weight distribution**

- **Method**: HPSEC. Refractive index. Broad standard
- **Acceptance criteria**: The system suitability sample is within 500 Da of the labeled value. Mw:15000~19000, M24000≤20%, M8000~M16000/M16000~M24000≥1.0.

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

<table>
<thead>
<tr>
<th>Point</th>
<th>M</th>
<th>% below M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6000</td>
<td>&lt;3.3%</td>
</tr>
<tr>
<td>2</td>
<td>8000</td>
<td>&lt;10.3%</td>
</tr>
<tr>
<td>3</td>
<td>10000</td>
<td>&lt;20.3%</td>
</tr>
<tr>
<td>4</td>
<td>12000</td>
<td>&lt;31.0%</td>
</tr>
<tr>
<td>5</td>
<td>14000</td>
<td>&lt;44.4%</td>
</tr>
<tr>
<td>6</td>
<td>16000</td>
<td>&lt;58.2%</td>
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<tr>
<td>7</td>
<td>18000</td>
<td>&lt;77.5%</td>
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<tr>
<td>8</td>
<td>20000</td>
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</tr>
<tr>
<td>9</td>
<td>22000</td>
<td>&lt;81.4%</td>
</tr>
<tr>
<td>10</td>
<td>24000</td>
<td>&lt;84.5%</td>
</tr>
<tr>
<td>11</td>
<td>26000</td>
<td>&lt;89.2%</td>
</tr>
<tr>
<td>12</td>
<td>28000</td>
<td>&lt;91.0%</td>
</tr>
<tr>
<td>13</td>
<td>30000</td>
<td>&lt;94.4%</td>
</tr>
<tr>
<td>14</td>
<td>32000</td>
<td>&lt;96.4%</td>
</tr>
<tr>
<td>15</td>
<td>40000</td>
<td>&lt;97.3%</td>
</tr>
</tbody>
</table>
Heparin-Assay

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

1. $\text{AT III} + \text{HP} \rightarrow [\text{AT III} + \text{HP}]$
2. $[\text{AT III} + \text{HP}] + \text{excess FII a} \rightarrow [\text{AT III} + \text{HP} - \text{FIIa}] + \text{remaining FII a}$
3. remaining FII a + substrate →pNA, Abs 405nm

**Anti-FIIa assay**

25µl sample + 25µl ATIII
mixed

37°C, 2min

50µl FIIa
mixed
37°C, 2min

50µl S-2238
mixed
37°C, 2min

50µl 50%HAC
mixed

405nm, Abs

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
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**

① Theoretical 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 preparations:**

\[
\text{Content of ingredients } C = \left( \frac{A_t}{A_s} \times P_s \times 1286.98 + \frac{A_t}{A_{C1a}} \times P_{C1a} \times 379.61 + \frac{A_t}{A_{C1}} \times P_{C1} \times 1079.52 + \frac{A_t}{A_{C2a}} \times P_{C2a} \times 1095.74 \right)
\]

Where:
- \(A_t\) is peak area of the test sample;
- \(A_s\) is peak area of the reference substance;
- \(P_s\) 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 josamycin (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%.

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
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 “NMT 3.0%”
- 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

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 cephalaxin 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
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 ethyldene 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

b. Optimization of HPLC methods

<table>
<thead>
<tr>
<th>Chromatographic conditions</th>
<th>Number of impurities</th>
<th>Asymmetry factor of principal peak As</th>
<th>Analytical time Rt (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old method</td>
<td>28</td>
<td>4.39</td>
<td>82</td>
</tr>
<tr>
<td>New method</td>
<td>40</td>
<td>1.48</td>
<td>70</td>
</tr>
</tbody>
</table>

Comparison of HPLC analytical methods of penicillium before and after optimization
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)

3. Issues Further concern
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!