

**Drug Master File
of
L-Ornithine-L-Aspartate**

Jing Jing Pharmaceutical Co., Ltd

2023.09.20



List

3.2.S Drug Substance	1
3.2.S.1 General Information	1
3.2.S.1.1 Nomenclature	2
3.2.S.1.2 Structure	2
3.2.S.1.3 General Properties.....	2
3.2.S.2 Manufacture	4
3.2.S.2.1 Manufacturer.....	5
3.2.S.2.2 Description of Manufacturing Process and Process Controls.....	5
3.2.S.2.3 Material control.....	8
3.2.S.2.4 Controls of Critical Steps and Intermediates	22
3.2.S.2.5 Process Validation and/or Evaluation	22
3.2.S.2.6 Manufacturing Process Development	24
3.2.S.3 Characterisation	25
3.2.S.3 Characterization	26
3.2.S.3.1 Description of structure and other characteristics.....	26
3.2.S.3.2 Impurity.....	31
3.2.S.3.2.1 Relative substance.....	31
3.2.S.3.2.2 Elemental Impurities	33
3.2.S.3.2.3 Specific discussion on potential genotoxic impurities	36
3.2.S.4 Control of Drug Substance.....	37
3.2.S.4.1 Specification.....	38
3.2.S.4.2 Analytical Procedures	38
3.2.S.4.3 Validation of Analytical Procedures	45
3.2.S.4.4 Batch Analysis	47
3.2.S.4.5 Justification of Specifications	48
3.2.S.5 Reference Standards of Materials	49
3.2.S.5.1 Reference Standards of Materials	50
3.2.S.5.2 List of standard substance	51
3.2.S.6 Container Closure System.....	52
3.2.S.6 Container Closure System.....	53
3.2.S.7 Stability	56
3.2.S.7.1 Stability Summary and Conclusions	57
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment.....	58
3.2.S.7.3 Stability data	59
APPENDIX	65



3.2.S Drug Substance

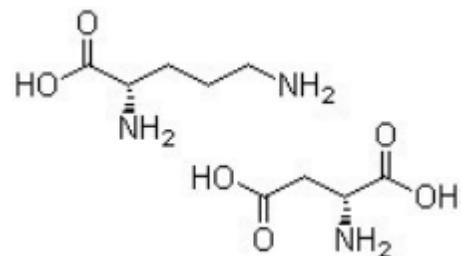
3.2.S.1 General Information

3.2.S.1.1 Nomenclature

- International nonproprietary name (INN): L-ornithine-L-aspartate
- Compendium name (DAB, Deutsches Arzneibuch): Ornithinapartat
- Chemical name: L-ornithine-L-aspartate
- Company code: L-ornithine-L-aspartate (LOA)
- IUPAC: (2S)-2-aminobutanedioic acid;(2S)-2,5-diaminopentanoic acid
- Chemical Abstracts Service (CAS) registry number: 3230-94-2

3.2.S.1.2 Structure

- Molecular structure



- Molecular Formula: $\text{C}_9\text{H}_{19}\text{N}_3\text{O}_6$

- Molecular Weight :265.26

3.2.S.1.3 General Properties

- Biological Activity: Hepatocyte recovery
- Appearance: White crystalline powder or colorless crystal
- Molecular formula: $\text{C}_9\text{H}_{19}\text{N}_3\text{O}_6$
- Formula weight: 265.26
- Solubility:
 - Freely soluble in water
 - Practically insoluble in ethanol, ether and methanol.
- Melting Point: 203.0 to 208.0 deg-C
- Specific rotation: +26.5 to +29.0 deg (C=1, 6mol/L HCl)

- pH: (25mg/mL in water)
- pKa value: 2.40 / 8.68 / 9.98 (Acid pKa1/ Base pKa2/ Base pKa 3)
- logP value: 0.14
- Hygroscopicity: non-hygroscopic



3.2.S.2 Manufacture



3.2.S.2.1 Manufacturer

1) Company Address

■ Company Name: Jing Jing Pharmaceutical Co., Ltd.

■ Manufacturing site:

No.88, Jingyi Road, Dacaozhuang Industrial Zone, Ningjin country, Xingtai city, Hebei Province, China

■ Tel: 86-311-83078913

■ Fax: 86-311-83078913

■ Drug production license:

Permit Number: 冀20170042

Valid until: 2022.12.24

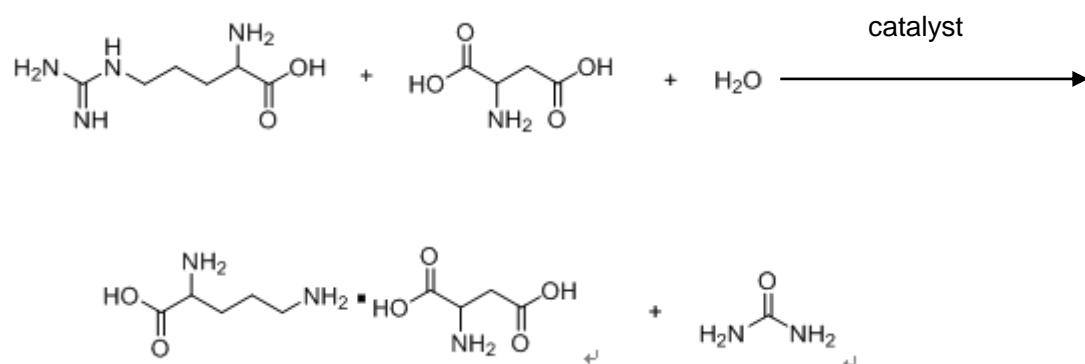
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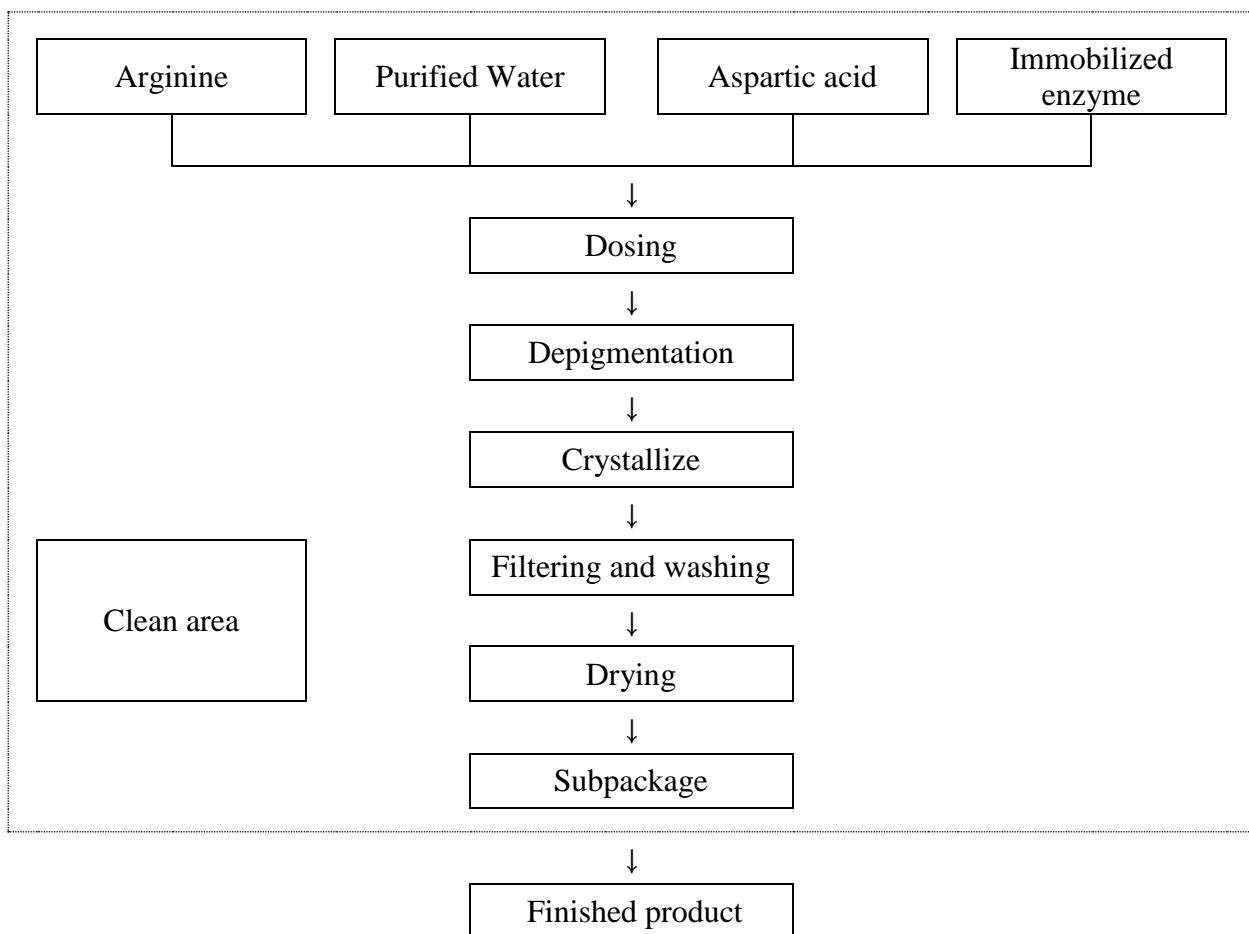
Production Scope: Sterile APIs, APIs

Appendix 1: Drug Manufacturing License, GMP certificate

3.2.S.2.2 Description of Manufacturing Process and Process Controls

1) Synthetic Scheme



2) Manufacturing process flow diagram

3) Sequential Procedural Narrative of the Manufacturing Process

Add purified water, arginine, aspartic acid, and immobilized enzyme into the reaction kettle, and start stirring. The temperature and pH are controlled in the whole process, and the transformation is carried out. The transformation time does not exceed 8 hours, and the transformation is completed. Add activated carbon to decolorize, Filter into the crystallization post, add a certain amount of solvent to crystallize. After the crystallization is completed, the wet powder of L-ornithine-L-aspartate is obtained by centrifugation, dried, and sampled for weight loss on drying. After passing the test, the finished product is packaged.



3.2.S.2.3 Material control

1) List of raw materials used in production process

Name	Application	Approved suppliers
Arginine	Raw material	CJ (Shenyang) Biotechnology Co., Ltd. Ajinomoto Co., Ltd. (Dealer: Shanghai Jinwang Pharmaceutical Technology Co., Ltd.) Jingjing Pharmaceutical Co., Ltd. Xingtai Food Additives Branch Hebei Amino Amino Acid Technology Co., Ltd.
Aspartate	Raw material	Changzhou YaBang Chemical Co., Ltd. Anhui Xuelang Biotech Co., Ltd.
Immobilized enzyme	catalyst	Hunan Fulaige Biotechnology Co., Ltd.
Purified water	solvent	Jingjing Pharmaceutical Co., Ltd.
Activated carbon	adsorbent	Shanghai Activated Carbon Co., Ltd. Nanping Yuanli Activated Carbon Co., Ltd.

2) Quality standards and testing methods of raw materials

2.1) Arginine

2.1.1) Quality standards of arginine

Item	Internal control standard
Properties	White crystal or crystalline powder
Specific rotation(°)	+26.9 ~ +27.9
Identification	The infrared absorption spectrum of the sample should be in consistent with the control one (spectrum set 1075).
pH	10.5 ~ 12.0
Chloride (%)	≤ 0.02
Sulfate (%)	≤ 0.02
Residue on ignition (%)	≤ 0.3
Loss on drying (%)	≤ 0.5
Arsenic salt (ppm)	≤ 1

Iron salt (ppm)	≤ 10
Heavy metal (ppm)	≤ 10
Transmittance (%)	≥ 98.0
Other Amino Acids (%)	≤ 0.4
Assay (%)	≥ 98.5
Purity (%)	≥ 98.0

1.1.2) Testing methods of arginine

1. Properties

Spread the arginine sample on clean A4 paper and observe it by eyes. The sample should be white, odorless, crystal or crystalline powder.

2. Specific rotation

Weigh two samples of 4.0g with a scale accurate to one ten-thousandth gram; place one of the sample in a 50ml volumetric flask, to which 6mol/L hydrochloric acid is added to dissolve the sample and make up to the volume; keep the flask in water bath for 20min at a temperature of 20°C, and conduct the measure according to “Standard Operating Procedures for WZZ-2B Digital Automatic Polarimeters” and a blank test is performed

Calculation formula:

$$\frac{(\alpha - \alpha_0) \times 100}{l \times m \times (1 - X) \times 100 / 50} \quad [a]^{D_{20}} =$$

Where:

α —measured optical rotation of the sample under test

α_0 —blank optical rotation

m—sample mass, g

l—length of the optical tube, dm

X—loss on drying of the sample, %

Judging criteria: $+26.9^\circ \sim +27.9^\circ$

3. Identification

3.1 Take appropriate amount of the product and arginine, to which 0.1mol/l hydrochloric acid is added respectively; dilute the solutions to make them containing about 10mg of hydrochloric acid per 1ml. The solutions should serve as the test solution and the reference solution. According to the chromatographic test under other amino acid terms, the position and color of the main spot of the test solution should be the same as that of the control solution.

3.2 According to General Rule 0402 (from the 4th volume of Chinese Pharmacopoeia (2015 edition), the potassium bromide pellet method should be adopted to perform the test. The infrared absorption spectrum of the sample should be in consistent with the control one (spectrum set 1075).

4. pH

Weigh 2.5g of the sample, and add 25ml of water to dissolve it; then measure the solution according to the “PB-10 Standard Operating Procedures of Precision pH Meter”. Judging criteria: 10.5 ~ 12.0

5. Chloride

Sample tube: Weigh 0.3g of sample and place it in 50ml Nessler colorimetric tube; add water into the tube to make the solution up to 25ml; and add 10ml of dilute nitric acid into it; then add more water to the solution to make it up to 40ml; Shake it up, and add 1.0 ml of silver nitrate test solution into it, then dilute it with water to make 50 ml, and shake well.

Standard tube: absorb 6.0ml of standard sodium chloride solution, and place it in 50ml natron colorimetric tube; add water to dissolve it into 25ml; then add 10ml of dilute nitric acid and water to make it into 40ml, shake it well; add 1.0ml of silver nitrate test solution, and dilute it with water to make it into 50ml, then shake it well.

Place the two tubes in the dark for 5 min, then, under the clarifier, place them on a black background and look down from above the colorimetric tube to compare the resulting turbidity. The turbidity of the sample tube must be lower than that of the standard tube.

Judging criteria: $\leq 0.02\%$

6. Sulfate

Sample tube: Weigh 1.0g of sample, and place it in 50ml Nessler colorimetric tube; add water into the tube to make it up to 40ml and dissolve the sample with ultrasonic waves. add 2ml of dilute nitric acid into it, then shake it well; add 5ml of 25% cesium chloride into the solution

and shake it well; add purified water into the solution to make it up to 50ml and shake it well. Leave it for 10 minutes and shake it well.

Standard tube: Pipette 2.0m of standard potassium sulfate solution into seven 50ml Nessler colorimetric tubes respectively; add water into the tubes to make them to 40ml; add 2ml of dilute hydrochloric acid into the tubes and shake them well; then add 5ml of 25% of cerium chloride into them respectively and shake them well; add purified water into the solutions to make them to 50ml; shake them well; stand it for 10 minutes, then repeat the shake.

Under the clarifier, place the sample tube and the standard tube against the same black background; observed from the top of the colorimetric tube to perform the colorimetric analysis. the milky white turbidity produced by the sample tube should not be deeper than the standard tube.

Judging criteria: $\leq 0.02\%$

7. Residue on ignition

Precisely weigh 1.0g of the sample into a constant-weight crucible, add 1ml of sulfuric acid to wet the sample, burn it on an electric furnace until the sulfuric acid vapor is completely removed, then move to a high-temperature furnace and burn at 700°C to completely ashed to constant weight.

Judging criteria: $\leq 0.3\%$.

8. Loss on drying

Weigh accurately 1.0g of sample into the constant-weight weighing bottle, and place it openly in the blast drying oven.

When the temperature rises to 105°C , start timing and dry it for 3h; then cover the weighing bottle, move it to a desiccator, and let it cool to the room temperature. Weigh the weighing bottle containing the sample precisely until a constant weight is achieved.

Calculation formula:

$$X = \frac{m - (m_1 - m_0)}{m} \times 100\%$$

Where :

m_0 -mass of the empty weighing bottle at a constant weight, g;

m -sample mass, g;

m_1 -mass of the weighing bottle and sample at a constant weight, g;

9. Arsenic salt

- (1) Sample bottle: Take 2.0g of sample, add 23ml of water to dissolve, and then add 5ml of hydrochloric acid.
- (2) Standard bottle: Precisely measure 2.0ml of standard arsenic solution, add 5ml of hydrochloric acid and 21ml of water.
- (3) Add 5 ml of potassium iodide test solution and 5 drops of acidic stannous chloride test solution to the two bottles respectively. After standing at room temperature for 10 minutes, add 2g of zinc particles. Immediately seal the installed airway C (with 60 mg of lead acetate cotton) on the bottle A, place the bottle A in a water bath at 25-40 °C, react for 45 minutes, and take out the mercury bromide test paper. Spots in sample vials should not be deeper than those in standard vials.
- standard one. Judging criteria: ≤ 1ppm

10. Iron salt

Sample tube: Weigh 1.0g of sample, and place it in 50ml Nessler colorimetric tube; add water into the tube to make the solution up to 25ml; add 4 ml of dilute hydrochloric acid and 50 mg of ammonium persulfate into it, then dilute with water to make 35 ml; then add 3 ml of 30% ammonium thiocyanate solution, and add water to make 50 ml, then shake it well.

Standard tube: absorb 1.0ml of standard iron solution, and place it in 50ml natron colorimetric tube and add water to make it to 25ml; then add 4ml of dilute hydrochloric acid and 50mg of ammonium persulfate and water to make it into 35ml; then add 3ml of 30% ammonium thiocyanate solution and water to make it into 50ml, then shake it well.

Place the two tubes against a white background immediately and look down from above the colorimetric tube to compare the resulting color. The color of sample tube must not be deeper than that of the standard tube.

Judging criteria: ≤ 10ppm

11. Heavy metals

Standard tube A: Take 2.0ml of standard lead solution into 25ml Nessler colorimetric tube, and add 2ml of acetate buffer (pH=3.5) into it; dilute with water to 25ml, and shake it up.

Sample tube B: Take 2.0g of sample into a 25ml Nessler colorimetric tube, and add 23ml of water to dissolve it; then add 2ml of acetate buffer (pH=3.5) and water to make it to 25ml, then shake it well.

Control tube C: Take 2.0g of the sample into a 25ml Nessler colorimetric tube, and add water to dissolve it; then add 2ml of standard lead solution and 2ml of acetate buffer (pH=3.5) into it, and dilute with water to make 25ml, then shake it up.

Add 2ml of thioacetamide test solution to tube A, B and C respectively and shake them well. Leave the tubes for 2min, then place them against a white background. Observe from the top of the colorimetric tube and compare the colors displayed by tube A, B and C. The color of B shall not be deeper than that of A. The color of the C should be lighter than that of the A.

Judging criteria: $\leq 10\text{ppm}$

12. Transmittance

Weigh 2.5g of the sample into a 25ml volumetric flask; dissolve it with water and dilute to the mark. Measure the light transmittance according to spectrophotometry by 1cm cuvette at 430 nm.

Judging criteria: $\geq 98.0\%$

Allowable deviation: Absolute difference of parallel samples $\leq 0.3\%$

13. Assay

Weigh accurately 0.08g of sample, and add 3ml of anhydrous formic acid to dissolve it; then add 50ml of glacial acetic acid, and titrate it with 0.1mol/L perchloric acid volumetric solution according to the Standard Operating Procedure of Metrohm 877 Titrino Plus, and correct the titration results with a blank test. Each 1 ml of perchloric acid titration solution (0.1mol/L) is equivalent to 8.710 mg of arginine.

Calculation formula:

$$Y = \frac{C \times (V - V_0) \times 8.710}{0.1 \times m \times (1 - X) \times 1000} \times 100\%$$

Where:

C-concentration of perchloric acid titration solution, mol / L;

V-volume of the perchloric acid titration solution consumed by the sample, ml;

V₀- volume of the perchloric acid titration solution consumed by the blank, ml;

m- mass of the sample taken, g;

X-Loss on drying of the sample, % Judging criteria: based on dry product, content $\geq 98.5\%$

14. Purity (HPLC)

Liquid chromatography conditions



Chromatographic column: C18 column, 250×4.6mm 5μm

Mobile phase: 0.25mol/L sodium dihydrogen phosphate buffer (adjust with phosphoric acid pH3.40±0.02): water = 1:3

Detection wavelength: 205nm

Flow rate: 0.8ml/min Column temperature: 30°C

Sample solution: weigh accurately 25mg of sample after drying and place it into 25ml measuring flask, and dilute it to a constant volume with mobile phase, then shake it well.

Take 20 μl of the test solution and inject it into the liquid chromatograph, and record the chromatogram.

Judging criteria: ≥ 98.0%

Appendix 2: Arginine raw material inspection report

2.2) Aspartate

2.2.1) Quality Standard

Item	Internal control standard
Properties	White or off-white crystalline powder
Specific rotation (°)	+24.0 ~ +26.0
Identification	Consistent with standard infrared patterns
Acidity	2.5 ~ 3.5
Light transmittance (%)	≥ 98.0
Chloride (%)	≤ 0.02
Sulfate (%)	≤ 0.02
Ammonium salt (%)	≤ 0.04
Loss on drying (%)	≤ 0.2
Residue on ignition (%)	≤ 0.1
Iron salt (%)	≤ 0.001
Heavy metal (%)	≤ 0.001
Arsenic salt (%)	≤ 0.0001
Content (%)	99.0 ~ 100.5

2.2.2) Inspection method

1. Properties

Spread the aspartic acid sample on clean A4 paper and observe it by eyes. The sample Should be white or off-white crystalline powder

2. Specific rotation

Weigh two samples of 4.0g with a scale accurate to one ten-thousandth gram; place one of the sample in a 50ml volumetric flask,to which 6mol/L hydrochloric acid is added to dissolve the sample and make up to the volume; keep the flask in water bath for 20min at a temperature of $20\pm0.5^{\circ}\text{C}$, and conduct the measure according to "Standard Operating Procedures for SGWzz-2 Thermostatic Automatic Polarimeters"and a blank test is performed.

Calculation formula:

$$[\alpha]_{D}^{20} = \frac{(\alpha - \alpha_0) \times 100}{l \times m \times (1 - X) \times 100 / 50}$$

Where: α —measured optical rotation of the sample under test

α_0 —blank optical rotation

m—sample mass, g

l— length of the optical tube, dm

X—loss on drying of the sample, %

Judging criteria: +24.00 ~ +26.00

3.Identify

Take an appropriate amount of this product and tablet with potassium bromide. Check the "Standard Operating Procedure of Infrared Spectrophotometer" according to law, and the infrared absorption spectrum of the sample is consistent with the spectrum set 913.

4. Acidity

Weigh 0.1g of the sample, and add 20ml of freshly boiled and purified water (within 4h) into it; stir it with a glass rod, then conduct measure according to "Standard Operating Procedure of PB-10 Precision pH Meter".

Judging criteria: 2.5 ~ 3.5

5. Light transmittance



Weigh 2.5g of the sample into a 25ml volumetric flask; dissolve it with 1 mol/L hydrochloric acid and dilute it to the mark. Measure the light transmittance according to spectrophotometry by 1cm cuvette at 430 nm. Judging criteria: $\geq 98.0\%$

6. Chloride

Sample tube: Weigh 0.3g of sample, and place it in 50ml Nessler colorimetric tube; add water into the tube to make the solution up to 25ml; and add 10ml of dilute nitric acid into it; then add more water to the solution to make it up to 40ml; Shake it up, and add 1.0 ml of silver nitrate test solution into it, then dilute it with water to make 50 ml, and shake well.

Standard tube: absorb 6.0ml of standard sodium chloride solution, and place it in 50ml natron colorimetric tube; add water to dissolve it into 25ml; then add 10ml of dilute nitric acid and water to make it into 40ml, shake it well; add 1.0ml of silver nitrate test solution, and dilute it with water to make it into 50ml, then shake it well.

Place the two tubes in the dark for 5 min, then, under the clarifier, place them on a black background and look down from above the colorimetric tube to compare the resulting turbidity.

The turbidity of the sample tube must be lower than that of the standard tube.

Judging criteria: $\leq 0.02\%$

7. Sulfate

Sample tube: Weigh 1.0g of sample, and place it in 50ml Nessler colorimetric tube; add 4ml of dilute hydrochloric acid to it and shake it well. Should the solution be not clear, filter it with 0.22 μ m water membrane, and add water to make it 40ml; then add 5ml of 25% barium chloride and shake it well; then add purified water into the solution to make it up to 50ml and shake it well. Leave it for 10 minutes and shake it well.

Standard tube: Take 2.0ml of standard potassium sulfate solution into 50ml Nessler colorimetric tube, and dilute with water to 40ml, then add 5ml of 25% barium chloride solution and shake it well. Then add purified water to make it to 50ml and shake it well. Repeat the shake after 10minutes' of standing.

Under the clarifier, place the sample tube and the standard tube against the same black background; observe from the top of the colorimetric tube to perform the colorimetric analysis. It is normal when the solution is cloudy and muddy; it is abnormal when the solution is silver white and a redetermination is needed. The color of the sample tube shouldn't be deeper than that of the standard one.

Judging criteria: $\leq 0.02\%$



8. Ammonium salt

- (1) Sample tube: Weigh 0.10g of sample, add 200ml of ammonia-free distilled water, and add 1g of magnesium oxide. Heating and distillation, the distillate was introduced into a 50ml Nessler colorimetric tube with 1 drop of dilute hydrochloric acid and 5ml of ammonia-free distilled water. The distillation was stopped when the distillate reached 40 ml. Add 5 drops of sodium hydroxide test solution, add ammonia-free distilled water to 50ml and shake well.
- (2) Standard tube: add 4.0ml of standard ammonium chloride solution, 200ml of ammonia-free distilled water, and 1g of magnesium oxide. Heating and distillation, the distillate was introduced into a 50ml Nessler colorimetric tube with 1 drop of dilute hydrochloric acid and 5ml of ammonia-free distilled water. When the distillate reaches 40ml, stop the distillation, add 5 drops of sodium hydroxide test solution, add ammonia-free distilled water to 50ml and shake well.
- (3) Add 2ml of alkaline mercury potassium iodide test solution to each of the sample tube and the standard tube, shake well, let stand for 15 minutes, put it on a white background, observe from top to bottom, compare the color, and it should not be darker.

Judging criteria: $\leq 0.04\%$

9. Loss on drying

Weigh accurately 1.0g of sample and place it in a weighing bottle at a constant weight; keep the bottle open and put it in a blast drying oven; When the temperature rises to 105°C, start timing and dry it for 3h; then cover the weighing bottle, move it to a desiccator, and let it cool to the room temperature. Weigh the weighing bottle containing the sample precisely until a constant weight is achieved.

Calculation formula:

$$X = \frac{m - (m_1 - m_0)}{m} \times 100\%$$

Where :

m0-mass of the empty weighing bottle at a constant weight, g;

m-sample mass, g;

m1-mass of the weighing bottle and sample at a constant weight, g;

Judging criteria: $\leq 0.2\%$

10. Residue on ignition



Weigh precisely 1.0g of sample, and place it in a constant-weight crucible; place the crucible on the resistance furnace in a fume hood; slowly burn the crucible containing the sample (to avoid the sudden explosion or burning of the sample because of heat) until the sample is completely carbonized and no longer smoking. Allow it to cool to the room temperature. Add 1 ml of sulfuric acid to make the carbide completely wet and continue to heat it on the electric furnace until the removal of sulfuric acid vapor and the complete disappearance of the white smoke. Place the crucible in a box-type resistance furnace and ignite it at a temperature of 550 °C until the full ashing of the sample. Stop the heating when the sample achieve a constant weight. Remove the crucible from the box, and cool it in the air for 1 ~ 2min, then place it in a suitable desiccator to cool it to room temperature, then accurately weigh the crucible.

Calculation formula:

$$X = \frac{m_1 - m_0}{m} \times 100\%$$

Where :

m-mass of the sample before ignition, g;

m0- mass of the crucible before ignition, g;

m1-mass of the crucible and residue after ignition, g;

Judging criteria: ≤ 0.1%

11.Heavy metals

(1) Tube A: Take the residue left under the residue on ignition of this product, add 0.5ml of nitric acid, evaporate to dryness, and let it cool. Add 2 ml of hydrochloric acid, evaporate to dryness on a water bath, and add 15 ml of water. Add ammonia test solution dropwise until it is neutral to the phenolphthalein indicator solution, add 2ml of acetate buffer (pH=3.5), dissolve with slight heat, transfer it to a Nessler colorimetric tube, add water to dilute to 25ml, and shake well.

(2) Tube B: Take the reagent for preparing the test solution. After evaporating to dryness in a porcelain dish, add 2ml of acetate buffer (pH=3.5) and 15ml of water. After dissolving with slight heat, transfer it into a Nessler colorimetric tube, add 1ml of standard lead solution, and then dilute it with an appropriate amount of water to make 25ml, and shake well.

(3) Add 2ml of thioacetamide test solution to tubes A and B respectively, shake well, and let stand for 2 minutes. Put it on the same white paper and see through it from top to bottom. The color displayed in tube A should not be darker compared to tube B.



Judging criteria: $\leq 0.001\%$

12. Arsenic salt

Sample bottle: Take 2.0g of sample to arsenic-containing Bottle A , and add 5ml of hydrochloric acid and 23ml of water to dissolve it; then add 5ml of potassium iodide test solution and 5 drops of acid stannous chloride test solution into it , then leave it at room temperature for 10min; add 2g of zinc particles into it , then densely plug the well-prepared airway tube C (containing 60 mg of lead acetate cotton) to Bottle A; place the bottle in a 25~40 °C water bath for 45 minutes; then take the mercury bromide test paper out.

Standard bottle: Take 2.0ml of standard arsenic solution arsenic to Bottle A, then add 5ml of hydrochloric acid and 21ml of water to dissolve it; then add 5ml of potassium iodide test solution and 5 drops of acidic stannous chloride test solution into it, and leave it at room temperature for 10min; add 2g of zinc granules and densely plug the well-prepared airway tube C (containing 60 mg of lead acetate cotton) to Bottle A immediately. Place the bottle in a 25~40 °C water bath for 45 minutes, then take the mercury bromide test paper out.

The arsenic spots produced by the sample should not be deeper than those of the standard one.

Judging criteria: $\leq 0.0001\%$

13.Iron salt

Sample tube: Weigh 1.0g of sample, and place it in 50ml Nessler colorimetric tube; add water into the tube to make the solution up to 25ml; add 4 ml of dilute hydrochloric acid and 50 mg of ammonium persulfate into it, then dilute with water to make 35 ml; then add 3 ml of 30% ammonium thiocyanate solution, and add water to make 50 ml, then shake it well.

Standard tube: absorb 1.0ml of standard iron solution, and place it in 50ml natron colorimetric tube and add water to make it to 25ml; then add 4ml of dilute hydrochloric acid and 50mg of ammonium persulfate and water to make it into 35ml; then add 3ml of 30% ammonium thiocyanate solution and water to make it into 50ml, then shake it well.

Place the two tubes against a white background immediately and look down from above the colorimetric tube to compare the resulting color. The color of sample tube must not be deeper than that of the standard tube.

Judging criteria: $\leq 10\text{ppm}$

14. Content



Accurately weigh 80 mg of the sample, add 5 ml of anhydrous formic acid, and 30 ml of glacial acetic acid, and titrate with 0.1 mol/L perchloric acid according to the Standard Operating Procedure of Automatic Potentiometric Titrator, and correct the titration result with a blank test. Each 1ml of perchloric acid titration solution (0.1mol/L) is equivalent to 13.31mg of aspartic acid.

Calculation formula:

$$Y = \frac{C \times (V - V_0) \times 13.31}{0.1 \times m \times (1 - X) \times 1000} \times 100\%$$

Where:

C-concentration of perchloric acid titration solution, mol / L;

V-volume of the perchloric acid titration solution consumed by the sample, ml;

V0- volume of the perchloric acid titration solution consumed by the blank, ml;

m- mass of the sample taken, g;

X-Loss on drying of the sample, %

Judging criteria: based on dry product, content 99.0 ~ 100.5%

C Reagents, etc.

In addition, quality standards for excipients: activated carbon (for co-injection) and methanol have been established. See the table below for details

Appendix 3: Aspartic Acid raw material inspection report

2.3) Activated carbon Quality standard

Item	Internal control standard
Properties	This product is black powder; No odor, no taste, no sand
Identification	should present positive reaction
pH	should present neutral reaction
Chloride (%)	≤ 0.1
Sulfate (%)	≤ 0.05
Uncarbonized substances	Comply with the regulations
Sulfide	Comply with the regulations
Cyanide	Comply with the regulations

Solutes in ethanol (mg)	≤ 8
Fluorescent substance	Less than the absorbance of the control solution
Acid soluble substances (mg)	≤ 8
Loss on drying (%)	≤ 10.0
Residue on ignition (%)	≤ 3.0
Fe salt (%)	≤ 0.02
Zinc salt (%)	≤ 0.005
Heavy metal(ppm)	≤ 30
Adsorbent capacity	Comply with the regulations
Microbial limit(cfu/g)	The total number of aerobic bacteria is less than or equal to 1000 The total number of molds and yeasts is less than or equal to 100 E. coli shall not be detected Salmonella should not be detected10g
Bacterial endotoxin (EU/g)	< 2
Adsorption capacity of activated carbon to bacterial endotoxin (%)	> 99

Appendix 4: Activated carbon raw material inspection report

2.4) Purified water quality standard

Item	Pharmacopoeia of the People's Republic of China (2020 Edition)
Properties	This product is a colorless clear liquid; odorless
pH	Meets the requirements
Nitrate (%)	≤ 0.000006
Nitrite (%)	≤ 0.000002
Ammonia (%)	≤ 0.00003
Conductivity	Meets the requirements
Total organic carbon (mg/L)	≤ 0.50
Non-volatile matter (mg/100ml)	≤ 1

Heavy metal (%)	≤ 0.00001
Microbial limit(cfu/g)	≤ 100

3.2.S.2.4 Controls of Critical Steps and Intermediates

1) Process Control and Standards

No	Process	Parameter	Standard
1	convert	Temperature	-
2		pH	-
3	dry	Temperature	-

2) Intermediate quality standard

No	Name	Code	Test items	Standard
1	L-ornithine-L-aspartate Wet Powder	S55	loss on drying	$\leq 50\%$
2	L-ornithine-L-aspartate Dry Powder	G55	loss on drying	$\leq 7.0\%$

Test Method in Process

Weigh 10.0g of sample, measure it on a rapid moisture analyzer, dry it at 105°C for 10 minutes until the moisture no longer drops, the scale moves statically, and read the recorded data.

3.2.S.2.5 Process Validation and/or Evaluation

1) Purpose

Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of consistently producing a finished product of the required quality. The purpose is the documented demonstration that went into developing a process has led to a process that will consistently produce a given product.

The processes used for each step of L-Ornithine-L-Aspartate will consistently provide the process developing during a product's lifetime. Also the quality will provide the desired degree of assurance as defined in the batch production records. We conducted for three batches in order to demonstrate validity of a given process. The critical steps and parameters were determined at study stage.

2) Information of batch

Batch Number	Batch Size	Manufacture Date
C552202010	400.84kg	2022.02.08
C552202011	400.84 kg	2022.02.09
C552202012	400.84kg	2022.02.09

3) In-Process Control

No	Process name	Project
1	Convert	Temperature
2		pH
3	Separate wash	Dry weight loss
4	Dry	Temperature
		Dry weight loss

4) Yield

Item	Range	C552202010	C552202011	C552202012
Product(kg)	400~500 kg	400.84kg	400.84kg	400.84kg
Yield	80~100%	98.13%	98.60%	98.13%

5) Result of Process Validation

All three Production batches studied were in conformity with the specification (DAB). The Certificates of Analysis for the above-mentiones are provide in 3.2.S.4.4 batch analysis.

Test	Specification	C552202010 (PV1)	C552202011 (PV2)	C552202012 (PV3)
Appearance	White crystal or crystalline powder	Conform	Conform	Conform
A. Specific rotation	+26.5 ~ +29.0 °	+28.0	+28.3	+28.3

Identification	B. IR	Corresponding to STD	Conform	Conform	Conform
Purity	1) Clarity / Coloration	Transparent	Conform	Conform	Conform
	2) pH	6.0 ~ 7.0	6.3	6.3	6.3
	3) Related substance (TLC)	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Conform	Conform	Conform
	4) Chloride	≤ 300 ppm	< 300	< 300	< 300
	5) Sulfate	≤ 200 ppm	< 200	< 200	< 200
	6) Ammonium	≤ 400 ppm	< 400	< 400	< 400
	7) Iron	≤ 30 ppm	< 30	< 30	< 30
	8) Heavy metals	≤ 10 ppm	< 10	< 10	< 10
	9) Water	≤ 7.0 %	0.81	0.66	0.77
	10) Sulfated ash	≤ 0.2 %	0.02	0.03	0.01
Assay		98.0 ~ 102.0 %	98.6	98.9	99.0
Residual solvent (Methanol, In-house)		≤ 3,000 ppm	91	95	89

Appendix5: Process Verification (C552202010) Finished Product Inspection Report

Appendix6: Process Verification (C552202011) Finished Product Inspection Report

Appendix7: Process Verification (C552202012) Finished Product Inspection Report

3.2.S.2.6 Manufacturing Process Development

Not applicable

3.2.S.3 Characterization



3.2.S.3 Characterization

3.2.S.3.1 Description of structure and other characteristics

L-Ornithine L-Aspartate is a complex of basic amino acids (ornithine) and acidic (aspartic acid) amino acids. Ornithine has α amino and α carboxyl groups, with an amino group at the other end, and aspartate has α amino and α carboxyl groups, with a carboxyl group at the other end. The molecular ions of ornithine and aspartic acid have positive and negative charges respectively. Ornithine aspartic acid can be obtained by the reaction of ornithine and aspartic acid in the aqueous phase. The crystallization of L-Ornithine L-aspartate is soluble in water, and the amino and carboxyl groups are dissociated in the divalent ionic solution.

Confirm that the L-Ornithine L-Aspartate manufactured by our company meets the specification.
(Refer to 3.2.S.5 Reference standard)

1) The nuclear magnetism

1.1) Instrument: Germany Brooker

1.2) Specifications: AV II- 500 BKUKER

1.3) Equipment name: nuclear magnetic resonance instrument, made in Switzerland.

1.4) Solvent: D₂O

1.5) Method: take the appropriate amount of L-Ornithine L-Aspartate sample (Batch No. C552202010) and reference standard (Batch No. 07125-SLBW4848) at room temperature dissolve it in D₂O and analyzed by NMR at 298K.

1.6) Result

1.6.1) Hydrogen (H) spectrum analysis results of L-Ornithine L-Aspartate sample and reference standard

Chemical shift(δ)		Proton number	Multiplicity	Hydrogen identification
Sample (C552202010)	Standard product (07125-SLBW4848)			

1.716-1.743	1.694-1.709	2	m	H-2
1.787-1.805	1.769-1.783	2	m	H-3
2.622-2.809	2.615-2.783	2	m	H-8
3.011-3.041	2.989-3.019	2	t	H-1
3.745-3.769	3.727-3.751	1	t	H-4
3.858-3.883	3.838-3.862	1	dd	H-7

1.6.2) Carbon (C) spectrum analysis results of L-Ornithine L-Aspartate sample and reference standard

Chemical shift(δ)		Carbon type	Carbon identification
Sample (C552202010))	Standard product (07125-SLBW4848)		
22.12	22.13	Secondary carbon	C-2
26.79	26.81	Secondary carbon	C-3
35.93	35.93	Secondary carbon	C-1
38.24	38.27	Secondary carbon	C-8
51.56	51.62	Tertiary carbon	C-7
53.48	53.51	Tertiary carbon	C-4
173.53	173.51	Quaternary carbon	C-5
173.53	173.64	Quaternary carbon	C-6
176.92	176.96	Quaternary carbon	C-9

1.7) Hydrogen spectrum analysis $^1\text{H-NMR}$

In the hydrogen nuclear magnetic resonance spectrum ($^1\text{H-NMR}$), the hydrogen proton patterns of the sample and the standard are consistent. Both integral values show 10 hydrogen protons instead of 19, which is due to the rapid exchange of 9 active hydrogens (3 -OH and 3 -NH₂) with deuterium in the molecular formula. Therefore, these nine hydrogen proton peaks are not shown.

1.8) Carbon spectrum analysis $^{13}\text{C-NMR}$

In the hydrogen nuclear magnetic resonance spectrum ($^{13}\text{C-NMR}$), the carbon spectra of the sample and the standard are consistent. The total number of peaks in each group is 9. It is shown

that there are 9 carbons in the molecular structure, which is consistent with the molecular carbon number of L-ornithine-L-aspartate.

1.9) Conclusion

It can be seen from the H NMR spectrum that the carbon spectrum and H spectrum of the L-ornithine-L-aspartate sample are consistent with the standard substance, the carbon and hydrogen protons are consistent, and the two structures are completely consistent.

1.10) Nuclear magnetic spectrum

Appendix 8: Hydrogen spectrum analysis $^1\text{H-NMR}$

Appendix 9: Sample hydrogen spectrum $^1\text{H-NMR}$

Appendix 10: Standard carbon spectrum $^{13}\text{C-NMR}$

Appendix 11: Sample carbon spectrum $^{13}\text{C-NMR}$

2) Mass spectrum

2.1) Instrumentation: Thermofisher LTQ

2.2) Test data

Batch number	Mass-to-charge ratio(m/z)	Relative abundance	Remarks
Sample	264.90	100	---
Standard product	264.18	100	---

2.3) Analysis

The comparison between the sample and the standard sample was basically consistent.

2.4) Mass spectrogram

Appendix 12: Mass spectrum

3) Elemental analysis

3.1) Instrument: Model Vario EL III CHNSO, Germany

3.2) Results

Element		Actual test value (%)	Theoretical value (%)	Atomic weight
Standard	C	39.49%	40.71%	12.0107
	H	7.50%	7.22%	1.00794
	N	15.21%	15.84%	15.9999
sample	C	39.96%	40.71%	12.0107
	H	7.49%	7.22%	1.00794
	N	15.63%	15.84%	15.9999

3.3) Conclusion

The results of elemental analysis showed that the proportion of C, H and N in L-Ornithine L-aspartate sample was consistent with that of reference standard.

Appendix 13 Elemental Analysis Spectrum

4) X-ray diffraction

4.1) Instruments: Bruker D8 Advance, Germany

4.2) Sample preparation: Sample (Batch No. C552202010), Reference Standard (Batch No. 07125-SLBW4848) are directly compressed to tablet and tested on the machine.

4.3) Conclusion: the main diffraction peak location of the sample is the same with that of the reference standard, and the crystal form is comparable.

4.4) X-ray Diffraction Pattern

Appendix 14: X-ray diffraction patterns of Sample

Appendix 15: Standard X-ray diffraction patterns

5) Infrared

5.1) Instrument: FTMIC-IR-RAM Type: VERTEX 70 (Fourier transform microinfrared Raman HYPERION-VERTEX70-RAMII) , BRUCKNER

5.2) Test method: KBr tabletting

5.3) Test results

The infrared absorption spectrum of the L-ornithine-L-aspartate sample ((Batch No. C552202010)is consistent with the infrared absorption spectrum of the reference substance ((Batch No. 07125-SLBW4848)

5.4) Infrared spectrum

Appendix 16: Sample infrared spectrum

Appendix 17:Standard infrared spectrum

3.2.S.3.2 Impurity

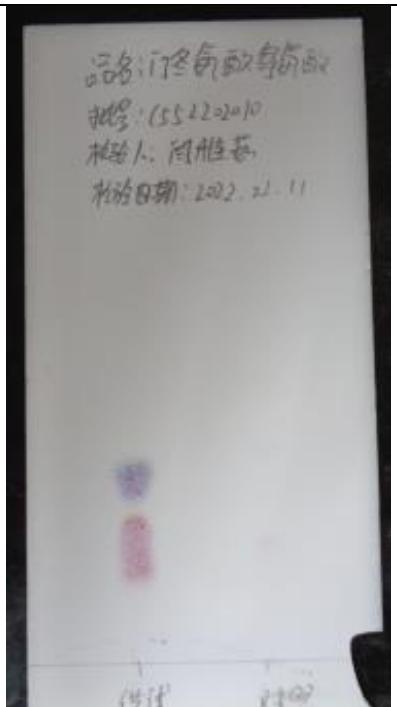
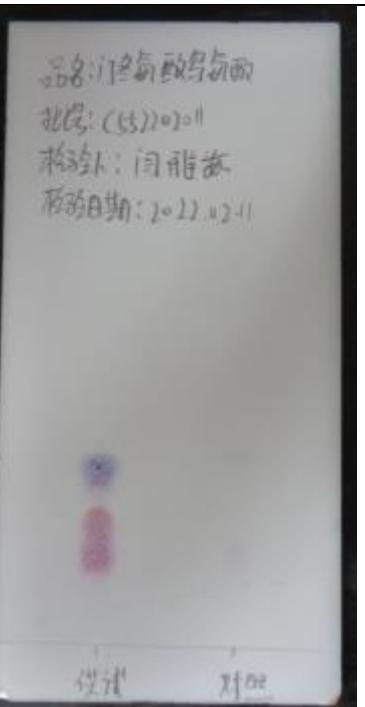
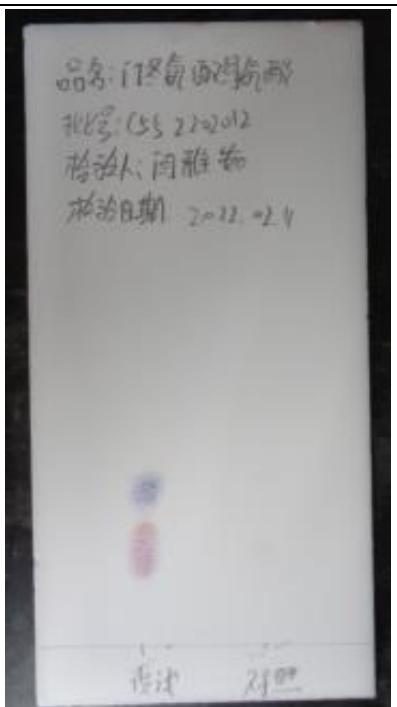
3.2.S.3.2.1 Relative substance

1) Test method (TLC)

Precisely weighed 2.5 g of this solution into a 100mL volumetric flask, add 100 mL of water and dissolve. Use this solution as the sample solution. Take exactly 2 mL of the sample solution and dilute it with 100 mL of water. Use this solution as the standard solution. Dissolve 5 μ L of the above sample solution and standard solution on a thin plate made of silica gel for thin layer chromatography according to European Pharmacopoeia Thin Layer Chromatography. Next, it is developed at about 10 cm using water: acetic acid (98%): 1-butanol = 25: 25: 50 as a developing solvent, and then dried at 110 °C for 15 minutes. When the ninhydrin solution is evenly sprayed and dried at 110 °C for 10 minutes.

2) Results

Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution

C552202010	C552202011	C552202012
		
sample solution	standard solution	sample solution
		standard solution
		sample solution
		standard solution

3) Review

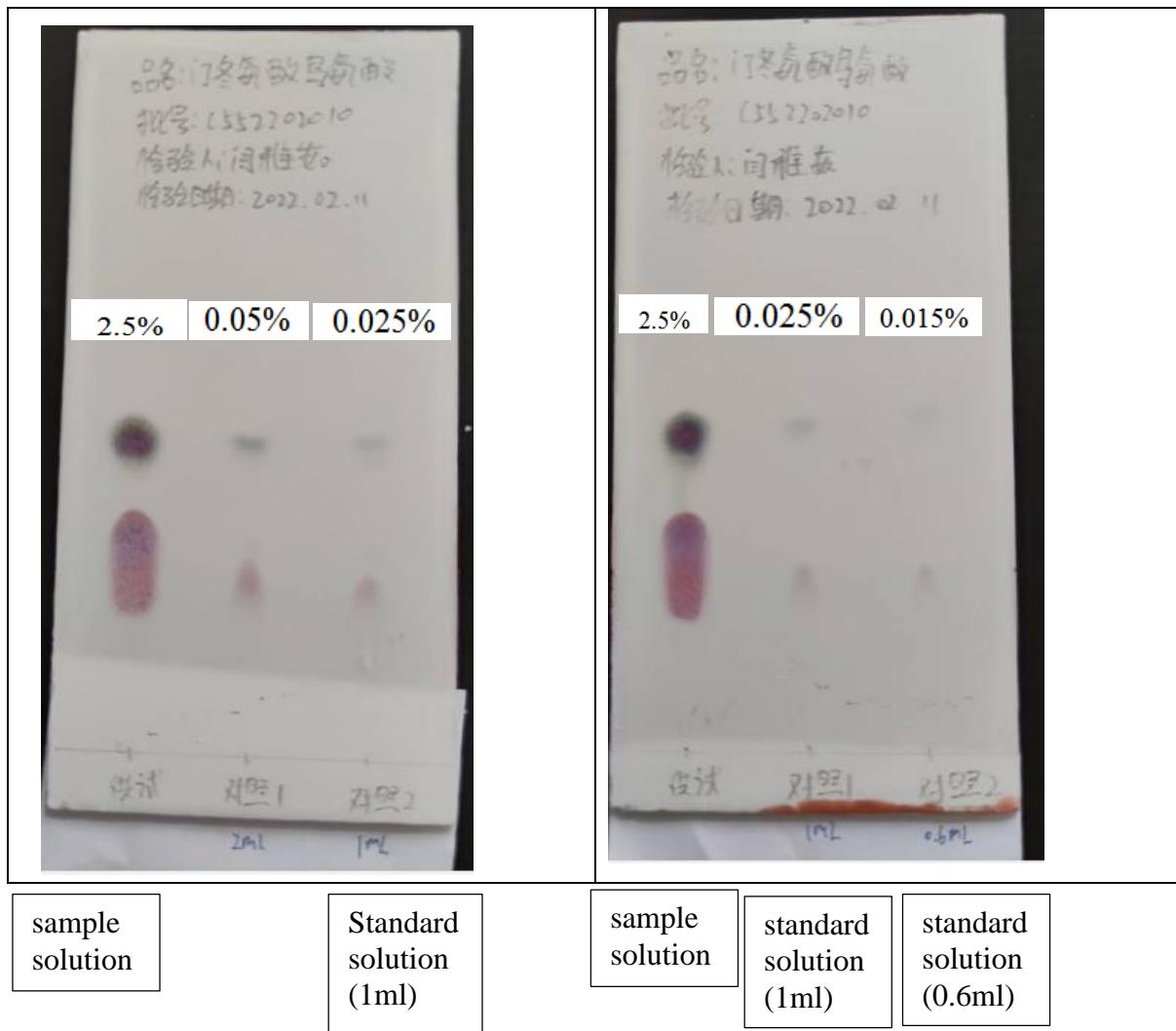
Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2g/day	0.05%	0.1% or 1.0mg Per day intake (whichever is lower)	0.15% or 1.0mg Per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[ICH Q3AR2, Attachment 1 Thresholds]

Based on the criteria of Attachment 1 Thresholds of ICH Guideline Q3 AR2, the Reporting threshold is 0.03% if Maximum Daily dose exceeds 2 g / day. Therefore, we compared and confirmed the standard Spot at concentrations of 0.05% and 0.03%.

The concentration of the sample spot may be displayed slightly darker. So additional checks were made as to whether there are other spots through serial dilution. As a result, no other spots were identified

Under other amino acids, for other amino acids, the sample solutions were taken and serially diluted to obtain standard solutions of different concentrations. The standard solution was tested, and additional checks were made as to whether there are other spots. As a result, no other spots were found.



4) Conclusion

Impact of reporting level according to ICH guidelines has not been confirmed. Our LOA complies with the German Pharmacopoeia (DAB).

3.2.S.3.2.2 Elemental Impurities

Based on ICH Q3D, a risk assessment for elemental impurities is performed on the API. and the assessment demonstrates the risk of elemental impurities of the API can be negligible. To facilitate your evaluation, we provide Risk Management summary (RMS), following it, a summary for screening impurity result is provided for reference.

Risk management summary (RMS)

Intended Route of Administration/Use of the Substance: Oral				
Element	Class	Intentionally added	Considered in Risk Assessment	Conclusion
Cd	1	No	Yes	Absent
Pb	1	No	Yes	Absent
As	1	No	Yes	Absent
Hg	1	No	Yes	Absent
Co	2A	No	Yes	Absent
V	2A	No	Yes	Absent
Ni	2A	No	Yes	Absent
Tl	2B	No	No	No risk identified
Au	2B	No	No	No risk identified
Pd	2B	No	No	No risk identified
Ir	2B	No	No	No risk identified
Os	2B	No	No	No risk identified
Rh	2B	No	No	No risk identified
Ru	2B	No	No	No risk identified
Se	2B	No	No	No risk identified
Ag	2B	No	No	No risk identified
Pt	2B	No	No	No risk identified
Li	3	No	No	No risk identified
Sb	3	No	No	No risk identified
Ba	3	No	No	No risk identified
Mo	3	No	No	No risk identified
Cu	3	No	Yes	Absent
Sn	3	No	No	No risk identified
Cr	3	No	Yes	Absent
Conclusion	The risk of elemental impurities of the API can be negligible.			

Note: "Absent" means each screening impurity in the API is less than 30 % of ICH Q3D option 1

limit.

Limits of the elemental impurities to be considered in the risk assessment

Element	Class	Oral PDE in ICH Q3D, ug/day	ICH Q3D option 1 limit, ug/g	Control threshold (30% of ICH Q3D option 1), ug/g
Cd	1	5	0.125	0.0375
Pb	1	5	0.125	0.0375
As	1	15	0.375	0.1125
Hg	1	30	0.75	0.225
Co	2A	50	1.25	0.375
V	2A	100	2.5	0.75
Ni	2A	200	5	1.5
Cu	3	3000	75	22.5
Cr	3	11000	275	82.5

The maximum daily dose of L-ornithine-L-aspartate is 40g, and the limit of each element is calculated.

Summary for screening impurity test result and test method

Test Items	Class	30% ICH Q3D option 1 limit, ppm	Batch No. and Test Results using ICP-MS method /ppm		
			C552202010	C552202011	C552202012
Cd	1	< 0.0375	Not detected	Not detected	Not detected
Pb	1	< 0.0375	Not detected	Not detected	Not detected
As	1	< 0.1125	0.0078	Not detected	Not detected
Hg	1	< 0.225	Not detected	Not detected	Not detected
Co	2A	< 0.375	0.00183	0.00147	0.00137
V	2A	< 0.75	0.0022	0.0038	0.00235
Ni	2A	< 1.5	Not detected	Not detected	Not detected
Cu	3	< 22.5	Not detected	Not detected	Not detected
Cr	3	< 82.5	0.0748	0.109	0.195

Conclusion: the level of screening impurity is far less than 30% ICH Q3D option I limit, so the risk of elemental impurities of the API can be negligible.

Appendix 18: L-ornithine-L-aspartate (C552202010) Elemental Analysis Test Report

Appendix19: L-ornithine-L-aspartate (C552202011) Elemental Analysis Test Report

Appendix 20: L-ornithine-L-aspartate (C552202012) Elemental Analysis Test Report

3.2.S.3.2.3 Specific discussion on potential genotoxic impurities

Impurities arising from the introduction of aspartate L-ornithine-L-aspartate raw materials and the production process are all quite different from genotoxic impurities and warning structures. Therefore, pur the finished arginine product has no risk of introduction of genotoxic impurities.

3.2.S.4 Control of Drug Substance



3.2.S.4.1 Specification

Test	Specification	Methods
Appearance	White crystal or crystalline powder	DAB
Identification	A. Optical Rotation, °	+26.5 ~ +29.0 °
	B. IR	corresponds to standard
	C. Ninhydrin reaction	Violet
	D. Mercuric acetate reaction	White Precipitation
	E. Molybdophosphoric acid reaction	Yellow Precipitation
Purity	1) Clarity / Coloration	Clear, Colourless
	2) pH	6.0 ~ 7.0
	3) Related substance (TLC)	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution
	4) Chloride	≤ 300 ppm
	5) Sulfate	≤ 200 ppm
	6) Ammonium	≤ 400 ppm
	7) Iron	≤ 30 ppm
	8) Heavy metals	≤ 10 ppm
	9) Water	≤ 7.0 %
	10) Sulfated ash	≤ 0.2 %
Assay	98.0 ~ 102.0 %	Ph. Eur. 2.2.20
Residual solvent(Methanol)	≤ 3,000 ppm	In-house

3.2.S.4.2 Analytical Procedures

1) Appearance: White crystal or crystalline powder

Take 1 g of sample in a watch glass placed on a white paper or a white paper.

Identification

2) Identification, B can be omitted when A, C, D, E was carried out and C,D,E can be omitted when A, B was carried out.

2.1) A. Specific rotation: +26.5 ~ +29.0 °

Dissolve 2.0 g of sample (as anhydrous) in 25 mL of 6 mol / L HCl solution and measure the D line of the sodium (589.3 nm) at 20 ±0.5°C and 100 mm length. (Ph. Eur. 2.2.7)

2.2) B. IR: The IR Spectrum of sample corresponds to L-ornithine-L-Aspartate standard.

Sample and Standard have the same absorption spectrum as Standard when measured according to the potassium bromide method (KBr) of the infrared spectral method. (Ph. Eur. 2.2.24)

2.3) C. Ninhydrin reaction: Violet

Add 0.5 mL of ninhydrin solution (2.5 mg / mL) to 2 mL of the solution (5 mg / mL) prepared by dissolving 0.1 g of the sample in 20 mL of water, heat in a water bath for 10 minutes, and check the reaction. (DAB)

2.4) D. Mercuric II acetate reaction: White Precipitation

To 0.5 mL of the solution (5 mg/mL) in which 0.1 g of the sample is dissolved in 20 mL of water, 0.5 mL of Mercuric II acetate solution (100 mg / mL) is added, and the reaction state is checked. (DAB)

2.5) E. Molybdophosphoric acid: Yellow Precipitation

Add 1 mL of a molybdophosphoric acid solution (50 mg/mL) to 2 mL of the solution (5 mg / mL) obtained by dissolving 0.1 g of the sample in 20 mL of water and confirm the reaction state. (DAB)

3) Purity

Test solution: Dissolve 2.5 g of sample in 100 mL of water

3.1) Clarity and coloration: Clear / Colourless

Using identical test-tubes of colourless, transparent, neutral glass with a flat base and an internal diameter of 15-25 mm, compare Test solution to be examined with a reference suspension freshly prepared as described below. Ensure that the depths of the layers in the 2 test-tubes are the same (about 40 mm). Compare the liquids in diffused daylight 5 min after preparation of the reference suspension, viewing vertically against a black background. Test solution is considered clear if its clarity is the same as that of water R or of the solvent used, or if its opalescence is not more pronounced than that of reference suspension I (Ph. Eur.2.2.1)

Using identical tubes of colourless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm, compare Test solution to be examined with water R or the solvent or the reference solution (see Tables of reference solutions) the depth of the layer being 40 mm. Compare the colours in diffused daylight viewing vertically against a white background. Test solution is colourless if it has the appearance of water R or the solvent or is not more intensely coloured than reference solution B9 (Ph. Eur. 2.2.2(II))

3.2) pH: 6.0 ~ 7.0

Weigh 2.5 g of the sample, dissolve in water to make 100 mL, and measure the pH. (Ph. Eur. 2.2.3)

3.3) Related substance: Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution

Precisely weighed 2.5 g of this solution into a 100mL volumetric flask, add 100 mL of water and dissolve. Use this solution as the sample solution. Take exactly 2 mL of the sample solution and dilute it with 100 mL of water. Use this solution as the standard solution. Dissolve 5 μ L of the above sample solution and standard solution on a thin plate made of silica gel for thin layer chromatography according to European Pharmacopoeia Thin Layer Chromatography. Next, it is developed at about 10 cm using water: acetic acid (98%): 1-butanol = 25: 25: 50 as a developing solvent, and then dried at 110 °C for 15 minutes. When the ninhydrin solution is evenly sprayed and dried at 110 °C for 10 minutes.

* Ninhydrin solution: 0.2 g of ninhydrin is completely dissolved in 94 mL of n-butanol and 6 mL of acetic acid. Shade to keep

3.4) Chloride: ≤ 300 ppm

- Sample solution: Take 6.7 mL of Test solution and dilute with 15 mL of water.
- To 15 mL of the Sample solution add 1 mL of dilute nitric acid R and pour the mixture as a single addition into a test-tube containing 1 mL of silver nitrate solution R2. Prepare a standard in the same manner using 10 mL of chloride standard solution (5 ppm Cl) R and 5 mL of water R. Examine the tubes laterally against a black background. After standing for 5 min protected from light, any opalescence in the Sample solution is not more intense than that in the standard. (Ph. Eur. 2.4.4)

3.5) Sulfate: ≤ 200 ppm

- Sample solution: Weigh 0.75 g of the sample, dissolve in water to make 15 mL.

▪ All solutions used for this test must be prepared with distilled water R. Add 3 mL of a 250 g/L solution of barium chloride R to 4.5 mL of sulfate standard solution (10 ppm SO₄) R1. Shake and allow to stand for 1 min. To 2.5 mL of this suspension add 15 mL of the Sample solution and 0.5 mL of acetic acid R. Prepare a standard in the same manner using 15 mL of sulfate standard solution (10 ppm SO₄) R instead of the prescribed solution. After 5 min, any opalescence in the test solution is not more intense than that in the standard. (Ph. Eur. 2.4.13)

3.6) Ammonium: ≤ 400 ppm

- Sample solution

25 mg of this product is placed on a watch glass with a diameter of 60 mm and dissolved or suspended by adding 0.5 ml of water R. 0.30 g heavy magnesium oxide R is added to the solution or suspension.

- Standard solution

In the same way, a reference mixture of 0.10 ml ammonium solution (100 ppm) R, 0.5 water R and 0.30 g heavy magnesium oxide R is prepared at the same time.

▪ Immediately after mixing, a second watch glass with a diameter of 60 mm, on the inner surface of which a red litmus paper R moistened with a drop of water R had previously been attached, is placed edge by edge on the first watch glass. The test and reference mix are warmed to 40 °C for 15 minutes. The litmus paper over the test mixture must not turn blue more intensely than the litmus paper over the reference mixture. (DAB N 2.4.1)

3.7) Iron: ≤ 30 ppm

- Sample solution

Dissolve 0.33 g of sample in 10 mL of dilute hydrochloric acid, add 10 mL of methyl isobutyl ketone each time, and extract it strongly (3 times) for 3 minutes. Separately, separate the methyl isobutyl ketone layer, add 10 mL of water, extrude strongly for 3 minutes, and use the aqueous layer as the Sample solution.

▪ Add 2 mL of a 200 g/L solution of citric acid monohydrate R and 0.1 mL of thioglycollic acid R. Mix, make alkaline with ammonia R and dilute to 20mL with water R. Prepare a standard in the same manner, using 10 mL of iron standard solution (1 ppm Fe) R. After 5 min, any pink colour in the test solution is not more intense than that in the standard. (Ph. Eur. 2.4.9)

3.8) Heavy metals: ≤ 10 ppm

▪Test solution: Place the 2 g of sample to be examined in a silica crucible with 4 mL of a 250 g/L solution of magnesium sulfate R in dilute sulfuric acid R. Mix using a fine glass rod. Heat cautiously. If the mixture is liquid, evaporate gently to dryness on a water-bath. Progressively heat to ignition and continue heating until an almost white or at most greyish residue is obtained. Carry out the ignition at a temperature not exceeding 800 °C. Allow to cool. Moisten the residue with a few drops of dilute sulfuric acid R. Evaporate, ignite again and allow to cool. The total period of ignition must not exceed 2 h. Take up the residue in 2 quantities, each of 5 mL, of dilute hydrochloric acid R. Add 0.1 mL of phenolphthalein solution R, then concentrated ammonia R until a pink colour is obtained. Cool, add glacial acetic acid R until the solution is decolorised and add 0.5 mL in excess. Filter if necessary and wash the filter. Dilute to 20 mL with water R.

▪Reference solution (standard).

Prepare as described for the Test solution, using the 2 mL of lead standard solution (10 ppm Pb) R instead of the substance to be examined. To 10 mL of the solution obtained add 2 mL of the Test solution.

▪Monitor solution. Prepare as described for the Test solution, adding to the substance to be examined the volume of lead standard solution (10 ppm Pb) R prescribed for preparation of the reference solution. To 10 mL of the solution obtained add 2 mL of the test solution.

▪Blank solution.

A mixture of 10 mL of water R and 2 mL of the test solution,

▪To 12 mL of each solution, add 2 mL of buffer solution pH 3.5 R. Mix and add to 1.2 mL of thioacetamide reagent R. Mix immediately. Examine the solutions after 2 min.

▪System suitability:

The reference solution shows a slight brown colour compared to the blank solution, the monitor solution is at least as intense as the reference.

▪Result: any brown colour in the test solution is not more intense than that in the reference solution. If the result is difficult to judge, filter the solutions through a suitable membrane filter (nominal pore size 0.45 um). Carry out the filtration slowly and uniformly, applying moderate and constant pressure to the piston. Compare the spots on the filters obtained with the different solutions. (Ph. Eur. 2.4.8)

3.9) Water: ≤ 7.0 %

Take 0.200g sample and test with Karl Fischer method. (Ph. Eur. 2.5.12) The sample is dissolved in 10mL of formamide at 50° C, the solution is mixed with 20mL of methanol(anhydrous) and cooled to room temperature. Perform a blank test.

3.10) Sulfated ash: ≤ 0.2 %

Ignite a suitable crucible (for example, silica, platinum, porcelain or quartz) at 600 ± 50 °C for 30 min, allow to cool in a desiccator over silica gel or other suitable desiccant and weigh. Place the 2.0 g of sample to be examined in the crucible and weigh. Moisten the substance to be examined with a small amount of sulfuric acid R (usually 1 mL) and heat gently at as low a temperature as until the sample is thoroughly charred. After cooling, moisten the residue with a small amount of sulfuric acid R (usually 1 mL), heat gently until white fumes are no longer evolved and ignite at $600 + 50$ °C until the residue is completely incinerated. Ensure that flames are not produced at any time during the procedure. Allow the crucible to cool in a desiccator over silica gel or other suitable desiccant, weigh it again and calculate the percentage of residue. If the amount of the residue so obtained exceeds the prescribed limit, repeat the moistening with sulfuric acid R and ignition, as previously, for 30min periods until 2 consecutive weighings do not differ by more than 0.5 mg or until the percentage of residue complies with the prescribed limit. (Ph. Eur. 2.4.14)

4) Assay (Anhydrous): 98.0 ~ 102.0 %

Precisely weigh 70 mg of the sample, dissolve in 5 mL of formic acid, add 50 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid. (Potentiometric titration) 0.1 mol/L Perchloric acid 1 mL = 8.84 mg C₉H₁₉N₃O₆

5) Residual solvent (MeOH): ≤ 3,000 ppm (0.3%)

Test solution

Take approximately 0.2g of this product, weigh it accurately, place it in a top empty bottle, add 2ml of water precisely to dissolve, and seal.

Reference solution

Take an appropriate amount of methanol, accurately weigh it, and dilute it with water to make a solution containing 75 µ g of methanol per 1ml. Precisely measure 2ml and place it in a top empty bottle, seal it.

Chromatographic conditions

A capillary column with 6% cyanopropylphenyl-94% dimethylpolysiloxane (or similar polarity) as the stationary liquid is used as the chromatographic column; Start at 35 °C and maintain for 20 minutes; The inlet temperature is 150 °C; The detector temperature is 250 °C; The equilibrium temperature of the headspace bottle is 80 °C, and the equilibrium time is 40 minutes.

Measurement method

Accurately measure the test solution and the reference solution, inject them into the headspace separately, and record the chromatogram.

Limit

According to the external standard method and peak area calculation, the residual amount of methanol should be $\leq 3000\text{ppm}$ (0.3%) 。

•Operation

Gas chromatography		Condition
Detector		Flame ionization(FID)
Column		DB-624 Capillary(G43), 0.25 mm x 30 m, 1.4 μm
Temp.	Detector	250 °C
	Column temperature	Start at 35 °C and maintain for 20 minutes
	inlet	150 °C
Carrier gas		nitrogen
Split Ratio		20 : 1
Flows		1) Hydrogen : 40 mL/min, 2) Air : 400.0 mL/min

Head-space	Condition
Sample equilibration temperature	80 °C
Quantitative loop temperature	100 °C
Transmission line temperature	110 °C
Equilibrating Time	40 min
Injection Time	1 min(mL)

•Calculation

$$\text{Residue of MeOH (ppm)} = \frac{\text{At} \times \text{Ws} \times 1 \times 10^6}{\text{As} \times 1000 \times \text{Wt}} \times \frac{\text{Ps}}{100}$$

At : Peak area of residual solvent in the sample solution

As : Peak area of residual solvent in standard solution

1: Dilution factor of sample

1000 : Dilution of standard solution

Wt : Weight of Sample (mg)

Ws : Weight of Standard (mg)

Ps : Purity of Standard

3.2.S.4.3 Validation of Analytical Procedures

1) 1) All tests on the product are in accordance with the German Pharmacopoeia and Methods

Validation is omitted.

2) Verification of GC method for residual solvent (Methanol)

Test method: 3.2.S.4.2

Test Item	Criteria	Validation results
System suitability test	The peak area measurement value RSD% (n=6) of repeated injection shall not exceed 10.0%; the number of theoretical plates (N) \geq 5000	Peak area repeatability RSD of 0.9% The minimum number of theoretical plates is 17842
Specificity	The blank solvent has no interference with methanol detection, and no other impurity peaks in the test solution interfere with each known impurity peak.	No interference
Detection of Quantitation	S/N is about 10, which can meet the testing requirements; Take the limit of quantification solution for 6 consecutive injections, and calculate the RSD of the peak area \leq 10.0% and the RSD of the retention time \leq 10.0%.	The limit of quantification is 1.510 μ g/ml, which is equivalent to the percentage content of the test product of 0.0015% The RSD for the limit of quantification precision was 2.6% RSD for retention time is 0%
Detection of Limit	S/N is about 3, which can meet the testing requirements	The detection limit is 0.453 μ g/ml, which is equivalent to 0.00045% of the test sample
Linearity and range	R \leq 0.990; The Y-axis intercept is within 25% of the 100% response value; Response factor RSD \leq 10%	Linear equation: y = 665.4x + 0.4822 R is 1 The percentage of Y-intercept to 100% response value is 0.91% Linear range 0.00150~0.3765mg/ml Response factor RSD of 2.1%
Accuracy test	According to the external standard method, the detected amount and recovery rate of each impurity were calculated. The average recovery rate is between 80% and 120%, and the relative standard deviation should not exceed 10.0%	50% recovery was 108%, RSD (n=3) of 0% 100% recovery was 108%, RSD (n=3) of 0.6% 150% recovery was 108%, RSD (n=3) of 0.6% The average recovery was 108%, and the RSD (n=9) was 0.5%
Precision	Repeatability: The RSD of the peak area for 6 consecutive injections of the reference solution is \leq 10.0%; the RSD of the	Repeatability: The RSD of the reference solution is 0.6% The RSD of the test solution is 1.0%



	<p>impurity content of the 6 samples of the test solution is $\leq 10.0\%$. Intermediate precision: Impurity content of the test solution RSD% (n=6) $\leq 10.0\%$, RSD% (n=12) $\leq 15.0\%$</p>	<p>Intermediate precision: The RSD of the test solution (n=6) is 0.7% The RSD of the test solution (n=12) is 2.0%</p>
Durability	<p>Under each condition, the RD of methanol content in the solution of the spiked test sample shall not exceed 15.0%)</p>	<p>When there is a slight change in the measurement conditions, the theoretical plate number (N) of the reference substance is more than 5000, and the RD is less than 10.0%, all of which meet the requirements, and the measurement results are within the acceptable range. Including: different flow rates (2.8~3.2ml/min), different detector temperatures (245~255°C), different inlet temperatures (145~155°C), different headspace equilibration times (35~45min), Different headspace temperature (75 ~ 85 °C).</p>

3.2.S.4.4 Batch Analysis

1) Batch Tested

3 consecutive batches were adopted to analyze batches and tested items are conformed. We report the data related to three batches as follows.

	Batch Number	Batch Size	Manufacture Date	Analysis Date
PV1	C552202010	400.84 kg	2022.02.08	2022.02.10~2022.02.20
PV2	C552202011	400.84 kg	2022.02.09	2022.02.10~2022.02.20
PV3	C552202012	400.84 kg	2022.02.09	2022.02.11~2022.02.20

All three production batches produce were in Jingjing Pharmaceutical Co., Ltd. And conformity with the specification.

2) Result of Test

All three production batches studied were in conformity with the specification.

Batch number		C552202010	C552202011	C552202012
Manufacturing date		2022.02.08	2022.02.09	2022.02.09
Batch quantity		400.84kg	400.84kg	400.84kg
Testing Item	Standad	Result	Result	Result
Description	White crystal or crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder
pH	6.0 ~ 7.0	6.3	6.3	6.3
Identification	IR	should be consistent with the standard infrared spectrum	Consistent with standard infrared spectrum	Consistent with standard infrared spectrum
	Optical Rotation, °	+26.5 ~ +29.0	28.0	28.3
Clarity of the solution	≤No. 1 Turbidity Standard	<No. 1 Turbidity Standard	<No. 1 Turbidity Standard	<No. 1 Turbidity Standard
color of solution	≤ B9	<B9	<B9	<B9
Wate %	≤ 7.0	0.81	0.66	0.77

Residue on ignition	≤ 0.2	0.02	0.03	0.01
Chloride, ppm	≤ 300	< 300	< 300	< 300
Sulfate(ppm)	≤ 200	< 200	< 200	< 200
Ammonium ,ppm	≤ 400	< 400	< 400	< 400
Heavy metal, ppm	≤ 10	< 10	< 10	< 10
Iron, ppm	≤ 30	< 30	< 30	< 30
Other Amino Acids, %	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Compliance	Compliance	Compliance
Residual solvent methanol ppm	≤ 3000	91	95	89
Assay, %	98.0 ~ 102.0	98.6	98.9	99.0

3.2.S.4.5 Justification of Specifications

The specification of L-Ornithine-L-Aspartate is set in accordance with DAB in “Ornithinaspartat”. The acceptance criterion of residual solvent is set base on the permitted limit recommended in ICH Q3C. The analytical procedures are based on the DAB and Ph. Eur. general chapters. Residual solvent testing proceeds to the validated test method (3.2.S.4.3).

3.2.S.5 Reference Standards of Materials



3.2.S.5.1 Reference Standards of Materials

1) National standard products

National standard products are mainly used for testing and calibration of raw materials or finished products.

2) Working standard products

Working standard products are calibrated by national standard products or pharmacopoeia standard products and used for finished product testing or raw material testing. The preparation and calibration of working standard product can be referred to the preparation and calibration of SOP for each working standard product.

Normally, the validity period of the working standard product is one year. At the end of half a year, the calibration will be carried out again. The comparative test is carried out by the technical person in charge of each post, with the relative standard deviation less than 2%. Working standard products can only be used for testing if they are approved by the QC Department head. The comparative test results shall be recorded and the test report shall be issued.

3) Preservation of Standard product

The chemical standard product should be stored in refrigerator at 2-8 C. If the condition of preservation is indicated on the label, it should be preserved according to that condition.

3.5.S.5.2 List of standard substance

Standard substance	Source	Specifications	Content	Application
L-Ornithine L-Aspartate	National Institutes for Food and Drug Control	50 mg/bottle	96.6%	For identification and content determination



3.2.S.6 Container Closure System



3.2.S.6 Container Closure System

1) Type of Material

L-Ornithine-L-Aspartate (LOA) is double packed in polyethylene bags (inner container) and fiber drums (External container). The polyethylene bag and fiber drum container system used are representative of the container system used to package finished L-Ornithine-L-Aspartate (LOA).

2) Packing Methods

The LOA uses a polyethylene bag as the primary packaging material to the tight Container. It is wrapped in a fiber-drum which is resistant to external impact by secondary packaging. It is packaged in this way to prevent moisture and contamination from the outside, so as to maintain the quality of product during distribution / storage. Store at room temperature($\leq 30^{\circ}\text{C}$).

3) Inner Packaging-polyethylene bag

3.1) Specification of Inner Packing Material

Item	Standard
Appearance	The surface should be smooth and uniform in color, and there should be no perforation, foreign matter, odor, or adhesion. The heat-sealing part of the bag should be flat and free of false sealing.
identify	should be consistent with the control pattern
Specifications Dimensions	Length(mm) 900 Width(mm) 600 Thickness (mm) 0.08
Microbial limit	The total number of aerobic bacteria $\leq 1000\text{cfu/ml}$ The total number of mold and yeast $\leq 100\text{cfu/ml}$

3.2) Test methods

Visual appearance: The surface should be smooth and uniform in color, and there should be no perforation, foreign matter, odor, or adhesion. The heat-sealing part of the bag should be flat and free of false sealing.

Identification: Take 0.25g of the sample (cut into pieces), and reflux the sample with about 10ml of toluene at high temperature to dissolve the sample. The reflux liquid was coated on the potassium bromide wafer with a capillary while it was still hot, and after heating to evaporate the solvent, the infrared spectrum was collected by the transmission method. The infrared spectrum of this product should be consistent with the control spectrum.

Specifications and dimensions: use a calibrated ruler to test, the specifications and dimensions of medicinal low-density polyethylene bags should meet the requirements of Table 1

Check item	Tolerance scope (mm)			Weight (t)kg
	Width mm	Long mm	Thick mm	
Medicinal low density polyethylene bag	600±5	900±5	0.08±0.01	0.08

Microbial Limit:

Take 200ml of sterile 0.1% peptone solution, put it into a medicinal low-density polyethylene bag, and shake it up and down 10 times. Take 10ml of the solution and check it according to the "Standard Operating Procedures for Microbial Limit Inspection of Non-sterile products" SOP-012-JYF014, the total number of aerobic bacteria is ≤ 1000 cfu/ml, and the total number of mold and yeast is ≤ 100 cfu/ml.

Appendix 21: Incoming inspection report of plastic bags

4) External Packaging - Fiber drum**4.1) Specification of Fiber drum**

Test item	Specification
Appearance	<p>The paper barrel should be round and free of defects and cracks such as obvious out-of-roundness, concave deflation, skew, etc.</p> <p>The barrel body is smooth, no mechanical damage, no wrinkle, no glue opening. Paint spreads evenly. No paint leakage, no bubbles, no obvious sagging.</p> <p>Round curled edges without paper tongue.</p> <p>Closing and rear lid and barrel body are well sealed, and the barrel body is rolled with imported cardboard paper.</p> <p>The inside and outside of the barrel should be clean, free of impurities and oil stains.</p>
Dimensions	<p>Barrel body: $400\text{mm}\pm3\text{mm}$</p> <p>Inner height: $550\text{mm}\pm3\text{mm}$</p> <p>Outer height: $570\text{mm}\pm4\text{mm}$</p> <p>Weight: $3.15\pm0.3\text{kg}$</p>

Appendix 22: Drum Inspection Report

3.2.S.7 Stability



3.2.S.7.1 Stability Summary and Conclusions

1) Summary of type of studies conducted

Three production batches are used to evaluate stability characteristics of LOA.

1.1) Test condition and Period

Division	Condition	Period	Methods
Long-term stability	25±2°C, 60±10%RH	0,3,6,9,12, 18, 24,36 month	DAB
Accelerated stability	40±2°C, 75±5%RH	0,1,2,3,6 month	DAB

*According to ICH guideline ICH Topic Q1A(R2), ICH Topic Q1B)

Test items

content	Test items
Long-term stability	Appearance、Water、Clarity / Coloration、Related substance、Assay
Accelerated stability	Appearance、Water、Clarity / Coloration、Related substance、Assay

1.2) Sample information

Batch Number	Batch Size	Manufacture Date	Expiration Date
C552202010	400.84kg	2022.02.08	2024.02.07
C552202011	400.84kg	2022.02.09	2024.02.08
C552202012	400.84kg	2022.02.09	2024.02.08

1.3) Package of stability sample

Put the sample in a polyethylene bag(well-closed), seal it to prevent foreign matter from entering it, and put it in a packaging container of the same material as a commercial fiber-drum, and store it according to each set stability storage condition. All of stability Sample packing materials same as commercial product.

1.4) Conclusion regarding storage condition

Three batches of LOA (C552202010, C552202011, C552202012) produced with PV were tested for accelerated stability for 6 months and 6 months of long- term, and no significant changes have been observed to date. Continue to be tested in accordance with the stability Protocol.

In the case of South Korea, three years of expiration date has passed. Under normal storage conditions, L-ornithine-L-Aspartate is stable at room temperature $\leq 30^{\circ}\text{C}$.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

1) Stability Commitment

For PV 3 lots (C552202010, C552202011, C552202012) accelerated stability test will continue as planned for 6 months. And long-term Stability tests, we pledge to continue as planned for 36 months.

The stability of PV 3 lots will be progressed and the long-term stability tests will be conducted one lot each year. (On-going Stability Testing)

2) Post – approval Stability Protocol

2.1) Stability samples: commercial batches produced by the submitted process procedure.
(1batch annually)

2.2) Storage condition: (long-term Stability) $25\pm2^{\circ}\text{C}, 60\pm10\% \text{RH}$

2.3) Frequency: 0, 3, 6, 9, 12, 18 ,24, and 36 months

Frequency	Test date
Initial	2022.02.19
3M	2022.05.19
6M	2022.08.19
9M	2022.11.19
12M	2023.02.19
18M	2023.08.19
24M	2024.02.19
36M	2025.02.19

2.4) Specifications and analytical procedures: The test procedures are described for the specification (3.2.S.4.1), and the validation of the test methods are described in 3.2.S.4.2.

3.2.S.7.3 Stability data

1) Accelerated testing results

1.1) C552202010: 40±2°C, 75±5%RH(Accelerated)

Test	Specification	Initial	1 M	2M	3M	6M
		2022.02.1 9	2022.03.2 1	2022.04.2 1	2022.05.2 0	2022.08.2 0
Appearance	White crystalline powder or colorless crystals and well soluble in water	Conform	Conform	Conform	Conform	Conform
Identification	A. Specific rotation	+26.5 ~ +29.0 °	28.0	--	--	--
	B. IR	Corresponding to STD	Conform	--	--	--
Purity	1) Clarity/Coloration	Clear, Colourless	Conform	Conform	Conform	Conform
	2) pH	6.0 ~ 7.0	6.3	--	--	--
	3) Related substance (TLC)	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Conform	Conform	Conform	Conform
	4) Chloride	≤300 ppm	<300	--	--	--
	5) Sulfate	≤200 ppm	< 200	--	--	--
	6) Ammonium	≤400 ppm	<400	--	--	--
	7) Iron	≤30 ppm	< 30	--	--	--
	8) Heavy metals	≤10 ppm	< 10	--	--	--
	9) Water	≤7.0 %	0.81	0.78	0.80	1.31
	10) Sulfated ash	≤0.2 %	0.02	--	--	--
Assay	98.0 ~ 102.0 %	98.6	98.9	99.3	99.6	99.1
Residual solvent (Methanol, In-house)	≤ 3,000 ppm	91	--	--	--	--
shelf of life of L-Ornithine-L-Aspartate: 3years from the manufacturing date. Accelerated term test's all test are observed no significant changes.						

1.2) C552202011: 40±2°C, 75±5%RH(Accelerated)

Test	Specification	Initial	1 M	2M	3M	6M
		2022.02.19	2022.03.21	2022.04.21	2022.05.20	2022.08.20
Appearance	White crystalline powder or colorless crystals and well soluble in water	Conform	Conform	Conform	Conform	Conform
Identification	A. Specific rotation	+26.5 ~ +29.0 °	28.3	--	--	--
	B. IR	Corresponding to STD	Conform	--	--	--
Purity	1) Clarity/Coloration	Clear, Colourless	Conform	Conform	Conform	Conform
	2) pH	6.0 ~ 7.0	6.3	--	--	--
	3) Related substance (TLC)	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Conform	Conform	Conform	Conform
	4) Chloride	≤ 300 ppm	<300	--	--	--
	5) Sulfate	≤ 200 ppm	< 200	--	--	--
	6) Ammonium	≤ 400 ppm	<400	--	--	--
	7) Iron	≤ 30 ppm	< 30	--	--	--
	8) Heavy metals	≤ 10 ppm	< 10	--	--	--
	9) Water	≤ 7.0 %	0.66	0.81	0.79	0.977
	10) Sulfated ash	≤ 0.2 %	0.03	--	--	--
Assay	98.0 ~ 102.0 %	98.9	98.6	99.2	99.4	98.9
Residual solvent (Methanol, In-house)	≤ 3,000 ppm	95	--	--	--	--
	shelf of life of L-Ornithine-L-Aspartate: 3years from the manufacturing date. Accelerated term test's all test are observed no significant changes.					

1.3) C552202012: 40±2°C, 75±5%RH(Accelerated)

Test	Specification	Initial	1 M	2 M	3M	6M
		2022.02.1 9	2022.03.2 1	2022.04.2 1	2022.05.2 0	2022.08.2 0
Appearance	White crystalline powder or colorless crystals and well soluble in water	Conform	Conform	Conform	Conform	Conform
Identification	A. Specific rotation	+26.5 ~ +29.0 °	28.3	--	--	--
	B. IR	Corresponding to STD	Conform	--	--	--
Purity	1) Clarity/Coloration	Clear, Colourless	Conform	Conform	Conform	Conform
	2) pH	6.0 ~ 7.0	6.3	6.3	--	--
	3) Related substance (TLC)	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Conform	Conform	Conform	Conform
	4) Chloride	≤ 300 ppm	<300	--	--	--
	5) Sulfate	≤ 200 ppm	< 200	--	--	--
	6) Ammonium	≤ 400 ppm	<400	--	--	--
	7) Iron	≤ 30 ppm	< 30	--	--	--
	8) Heavy metals	≤ 10 ppm	< 10	--	--	--
	9) Water	≤ 7.0 %	0.77	1.27	0.90	1.07
	10) Sulfated ash	≤ 0.2 %	0.01	--	--	--
Assay	98.0 ~ 102.0 %	99.0	98.6	99.3	98.9	99.0
Residual solvent (Methanol, In-house)	≤ 3,000 ppm	89	--	--	--	--
	shelf of life of L-Ornithine-L-Aspartate: 3years from the manufacturing date. Accelerated term test's all test are observed no significant changes.					

2) Long-term testing results

2.1) C552202010: 25±2°C, 65±5%RH(long-term)

Test	Specification	Initial	3 M	6 M	9 M	12 M	18M	24 M	36 M
		2022.02.10	2022.05.20	2022.08.20	2022.11.23	2023.02.22	2023.08.20		
Appearance	White crystalline powder or colorless crystals and well soluble in water	Conform	Conform	Conform	Conform	Conform	Conform		
Identification	A. Specific rotation	+26.5 ~ +29.0 °	28.0	--	--	--	+28.0	--	
	B. IR	Corresponding to STD	Conform	--	--	--	Conform	--	
Purity	1) Clarity/Coloration	Clear, Colourless	Conform	Conform	Conform	Conform	Conform	Conform	
	2) pH	6.0 ~ 7.0	6.3	--	--	--	6.3	--	
	3) Related substance (TLC)	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Conform	Conform	Conform	Conform	Conform	Conform	
	4) Chloride	≤ 300 ppm	<300	--	--	--	<300	--	
	5) Sulfate	≤ 200 ppm	< 200	--	--	--	< 200	--	
	6) Ammonium	≤ 400 ppm	<400	--	--	--	<400	--	
	7) Iron	≤ 30 ppm	< 30	--	--	--	< 30	--	
	8) Heavy metals	≤ 10 ppm	< 10	--	--	--	< 10	--	
	9) Water	≤ 7.0 %	0.81	1.20	1.20	1.3	1.4	1.2	
	10) Sulfated ash	≤ 0.2 %	0.02	--	--	--	0.06	--	
Assay	98.0 ~ 102.0 %	98.6	99.4	99.3	99.7	99.8	99.6		
Residual solvent (Methanol, In-house)	≤ 3,000 ppm	91	--	--	--	87	--		
shelf life of L-Ornithine-L-Aspartate: 3 years from the manufacturing date.									
Long-term test shall be conducted for 36 months in accordance with the stability test plan.									

2.2) C552202011: 25±2°C, 65±5%RH(long-term)

Test	Specification	Initial	3 M	6 M	9 M	12 M	18M	24 M	36 M
		2022.02.10	2022.05.20	2022.08.20	2022.11.23	2023.02.22	2023.08.20		
Appearance	White crystalline powder or colorless crystals and well soluble in water	Conform	Conform	Conform	Conform	Conform	Conform		
Identification	A. Specific rotation B. IR	+26.5 ~ +29.0 ° Corresponding to STD	28.3 Conform	-- --	-- --	+28.0 Conform	-- --		
Purity	1) Clarity/Coloration 2) pH 3) Related substance (TLC) 4) Chloride 5) Sulfate 6) Ammonium 7) Iron 8) Heavy metals 9) Water 10) Sulfated ash	Clear, Colourless 6.0 ~ 7.0 Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution ≤ 300 ppm ≤ 200 ppm ≤ 400 ppm ≤ 30 ppm ≤ 10 ppm ≤ 7.0 % ≤ 0.2 %	Conform 6.3 Conform <300 < 200 <400 < 30 < 10 0.66 0.03	Conform -- Conform -- -- -- -- -- -- --	Conform -- Conform -- -- -- -- -- -- --	Conform -- Conform -- -- -- -- -- -- -- --	Conform 6.2 Conform -- Conform -- -- -- -- 0.77 0.02	Conform -- Conform -- -- -- -- -- -- -- 1.3 --	
Assay	98.0 ~ 102.0 %	98.9	99.8	99.4	99.5	99.4	99.6		
Residual solvent (Methanol, In-house)	≤ 3,000 ppm	95	--	--	--	87	--		
shelf life of L-Ornithine-L-Aspartate: 3years from the manufacturing date.									
Long-term test shall be conducted for 36 months in accordance with the stability test plan.									

2.3) C552202012: 25±2°C, 65±5%RH(long-term)

Test	Specification	Initial	3 M	6 M	9 M	12 M	18M	24 M	36 M
		2022.02.1 1	2022.05.2 0	2022.08.2 0	2022.11.2 3	2023.02.2 2	2023.08.2 0		
Appearance	White crystalline powder or colorless crystals and well soluble in water	Conform	Conform	Conform	Conform	Conform	Conform		
Identification	A. Specific rotation B. IR	+26.5 ~ +29.0 ° Corresponding to STD	28.3 Conform	-- --	-- --	-- Conform	+28.0 --		
Purity	1) Clarity/Coloration 2) pH 3) Related substance (TLC) 4) Chloride 5) Sulfate 6) Ammonium 7) Iron 8) Heavy metals 9) Water 10) Sulfated ash	Clear, Colourless 6.0 ~ 7.0 Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution ≤ 300 ppm ≤ 200 ppm ≤ 400 ppm ≤ 30 ppm ≤ 10 ppm ≤ 7.0 % ≤ 0.2 %	Conform 6.3 Conform < 300 < 200 < 400 < 30 < 10 0.77 0.01	Conform -- Conform -- -- -- -- -- 1.20	Conform -- Conform -- -- -- -- -- -- 1.40	Conform -- Conform -- -- -- -- -- -- 1.3	Conform 6.3 Conform -- < 300 < 200 < 400 < 30 < 10 1.4	Conform -- Conform -- -- -- -- -- -- 1.2	
Assay	98.0 ~ 102.0 %	99.0	99.2	99.2	99.7	99.8	99.4		
Residual solvent (Methanol, In-house)	≤ 3,000 ppm	89	--	--	--	85	--		

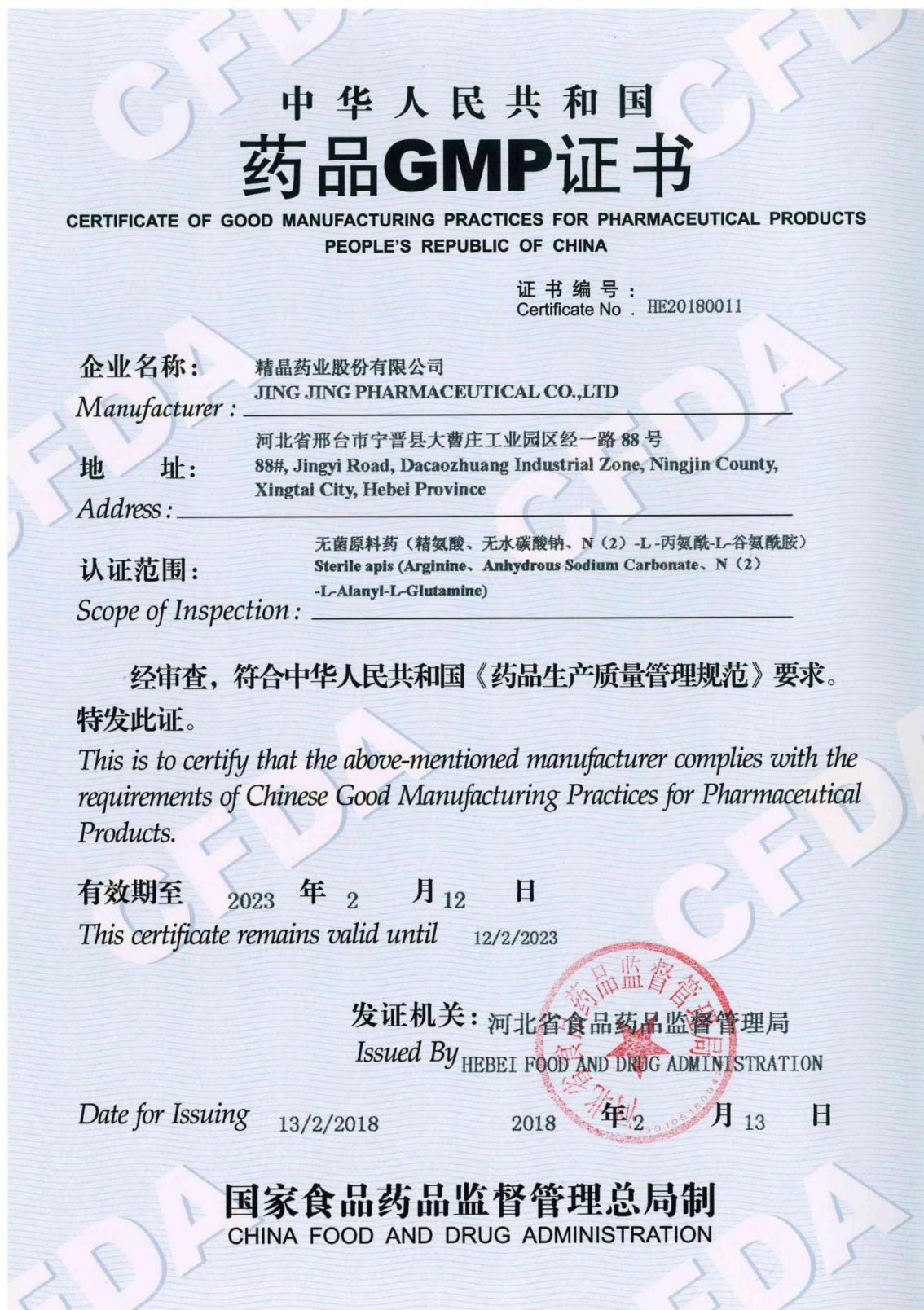
shelf life of L-Ornithine-L-Aspartate: 3years from the manufacturing date.
Long-term test shall be conducted for 36 months in accordance with the stability test plan.

APPENDIX

- Appendix 1: Drug Manufacturing License、GMP certificate
- Appendix 2: Arginine raw material inspection report
- Appendix 3: Aspartic Acid raw material inspection report
- Appendix 4: Activated carbon raw material inspection report
- Appendix 5: Process Verification (C552202010) Finished Product Inspection Report
- Appendix 6: Process Verification (C552202011) Finished Product Inspection Report
- Appendix 7: Process Verification (C552202012) Finished Product Inspection Report
- Appendix 8: Hydrogen spectrum analysis $^1\text{H-NMR}$
- Appendix 9: Sample hydrogen spectrum $^1\text{H-NMR}$
- Appendix 10: Standard carbon spectrum $^{13}\text{C-NMR}$
- Appendix 11: Sample carbon spectrum $^{13}\text{C-NMR}$
- Appendix 12: Mass spectrum
- Appendix 13 Elemental Analysis Spectrum
- Appendix 14: X-ray diffraction patterns of Sample
- Appendix 15: Standard X-ray diffraction patterns
- Appendix 16: Sample infrared spectrum
- Appendix 17: Standard infrared spectrum
- Appendix 18: L-ornithine-L-aspartate (C552202010) Elemental Analysis Test Report
- Appendix 19: L-ornithine-L-aspartate (C552202011) Elemental Analysis Test Report
- Appendix 20: L-ornithine-L-aspartate (C552202012) Elemental Analysis Test Report
- Appendix 21: Incoming inspection report of plastic bags
- Appendix 22: Drum Inspection Report

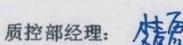
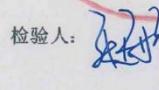
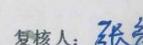
Appendix 1: Drug Manufacturing License, GMP certificate





Appendix 2: Arginine raw material inspection report

精晶药业股份有限公司		编码: SOP-012-YZC1291B-Rev-02 (01)			
精氨酸原料检验报告					
编码: 2201Y039-001J					
品名	精氨酸	批号	Y0392201001	数量	10075kg
来源	希杰(沈阳)生物科技有限公司	包装规格	25kg/袋		
留样数量	11.98g	检验日期	2022年01月19日		
检验目的	使用检验	报告日期	2022年01月21日		
检验依据	STP-011-YZCS1291B	有效期	2024年12月		
检验项目		检验标准	检验结果		
【性状】		白色结晶或结晶性粉末	白色结晶性粉末		
【鉴别】		应与对照图谱(1075图)一致	与对照图谱一致		
比旋度,		+26.9 ~ +27.9	+27.3		
【检查】					
碱度, pH		10.5 ~ 12.0	11.2		
透光率, %		≥98.0	98.7		
氯化物, %		≤0.02	<0.02		
硫酸盐, %		≤0.02	<0.02		
铁盐, ppm		≤10	<10		
砷盐, ppm		≤1	<1		
重金属, ppm		≤10	<10		
干燥失重, %		≤0.5	0.17		
炽灼残渣, %		≤0.3	0.12		
纯度, %		≥98.0	98.3		
【含量测定】%		≥98.5	99.9		
包装的完整性		应完整	完整		
包装的密封性		应密封	密封		
结论	本品依据 STP-011-YZCS1291B 检验  结果符合规定。				

质控部经理:  检验人:  复核人: 

Arginine raw material inspection report

Commodity Name :	Arginine	Batch No.	Y0392201001	Quantity:	10075 kg		
source	CJ (Shenyang) Biotechnology Co., Ltd.		Package	25kg/bag			
Number of retained samples	11.98g		Test Date	2022.01.19			
Inspection purpose	use test		Report Date	2022.01.21			
Test based on	SOP-012-YZC1291B		Expiry date	2024.12			
TEST	SPECIFICATION		RESULT				
Characters	White crystals or crystalline powder		White crystalline powder				
Specific rotation	+26.9° ~ +27.9°		+27.3°				
Identification	Comply to specification		Conforms				
pH	10.5~12.0		11.2				
Transmittance , %	≥ 98.0		98.7%				
Chloride , %	≤ 0.02		< 0.02				
Sulfate , %	≤ 0.02		< 0.02				
Iron , ppm	≤ 10		< 10				
Arsenic salt,ppm	≤1		< 1				
Heavy metals,ppm	≤ 10		< 10				
Loss on drying,%	≤ 0.5		0.17				
Residue on ignition	≤ 0.3		0.12				
purity,%	≥ 98.0		98.3				
Assay,%	≥98.5%		99.9%				
Packaging Integrity	should be complete		whole				
Packaging tightness	should be sealed		seal				
Conclusion	This product is tested according to STP-011-YZCS1291B , and the results meet the requirements						

Manager of Quality Control Department: Li Suxia

Inspector: Yujiao Zhang

Reviewer: Liang Zhang

Appendix 3: Aspartic Acid raw material inspection report

精晶药业股份有限公司		编码: SOP-012-YZC1292B-Rev-02 (01)	
天门冬氨酸原料检验报告			
编码: 2201Y031-001J			
品名	天门冬氨酸	批号	Y0312201001
来源	常州亚邦化学有限公司	包装规格	25 kg/袋
留样数量	12.41g	检验日期	2022年01月12日
检验目的	使用检验	报告日期	2022年01月16日
检验依据	STP-011-YZCS1292B	复验期	2023年12月
检验项目		检验标准	检验结果
【性状】		白色或类白色结晶性粉末	白色结晶性粉末
【鉴别】		应与对照图谱(913图)一致	与对照图谱一致
比旋度,		+24.0 ~ +26.0	+25.1
【检查】			
酸度, pH		2.5~3.5	3.0
透光率, %		≥98.0	98.4
氯化物, %		≤0.02	<0.02
硫酸盐, %		≤0.02	<0.02
铁盐, %		≤0.001	<0.001
砷盐, %		≤0.0001	<0.0001
重金属, ppm		≤10	<10
干燥失重, %		≤0.2	0.12
炽灼残渣, %		≤0.1	0.03
铵盐, %		≤0.04	<0.04
【含量测定】%		99.0~100.5	100.0
包装的完整性		应完整	完整
包装的密封性		应密封	密封
结论	本品依据 STP-011-YZCS1292B 检验, 结果符合规定。		
质控部经理:	张亮	检验人:	赵海林
			复核人: 李海林

Aspartic Acid raw material inspection report

Commodity Name	Aspartic Acid	Batch No.	Y0312201001	Quantity	16000 kg
source	Changzhou Yabang Chemical Co., Ltd.		Package	25kg/bag	
Number of retained samples	12.41g		Test Date	2022.01.12	
Inspection purpose	use test		Report Date	2022.01.16	
Test based on	SOP-012-YZC1292B		Expiry date	2023.12	
TEST	SPECIFICATION			RESULT	
Characters	White or off-white crystalline powder			White crystalline powder	
Specific rotation	+24.0° ~ +26.0°			+25.1°	
Identification	Should be consistent with the control map (Figure 913)			Conforms	
pH	2.5~3.5			3.0	
Transmittance , %	≥ 98.0			98.4%	
Chloride , %	≤ 0.02			< 0.02	
Sulfate , %	≤ 0.02			< 0.02	
Iron , %	≤ 0.001			< 0.001	
Arsenic salt,%	≤0.0001			< 0.0001	
Heavy metals,ppm	≤ 10			< 10	
Loss on drying,%	≤ 0.2			0.12	
Residue on ignition,%	≤ 0.1			0.03	
Ammonium,%	≤ 0.04			< 0.04	
Assay,%	99.0~100.5			100.0	
Packaging Integrity	should be complete			whole	
Packaging tightness	should be sealed			seal	
Conclusion	According to the internal control of the enterprise, the results meet the regulations				

Manager of Quality Control Department: Liang Zhang

Inspector: Yujiao Zhang

Reviewer: Haisong Li

Appendix 4: Activated carbon raw material inspection report

精晶药业股份有限公司		编码: SOP-012-YZC001-Rev-02 (05)			
活性炭检验报告					
编码: 2201F01-001J					
品名	活性炭	批号	F012201001	数量	2100kg
来源	南平原力活性炭有限公司		包装规格	12kg/箱	
留样数量	16.62g		检验日期	2022年01月14日	
检验目的	使用检验		报告日期	2022年01月19日	
检验依据	2020年版中国药典四部		有效期	2023年11月	
检验项目	检验标准			检验结果	
[性状]	黑色粉末			黑色粉末	
鉴别	应呈正反应			符合规定	
酸碱度	应显中性			符合规定	
氯化物, %	≤0.10			<0.10	
未炭化物	应符合规定			符合规定	
硫酸盐, %	≤0.05			<0.05	
硫化物	应符合规定			符合规定	
氰化物	应符合规定			符合规定	
乙醇中溶解物, mg	≤8			0.3	
荧光物质	小于对照溶液吸光度			小于对照溶液吸光度	
酸中溶解物, mg	≤8			1.7	
干燥失重, %	≤10.0			0.85	
炽灼残渣, %	≤3.0			0.91	
铁盐, %	≤0.02			<0.02	
锌盐, %	≤0.005			<0.005	
重金属, ppm	≤30			<30	
吸着力	应符合规定			符合规定	
细菌内毒素, EU/g	<2			<2	
活性炭对细菌内毒素吸附力, %	>99			>99	
需氧菌总数, cfu/g	≤1000			10	
霉菌和酵母菌总数, cfu/g	≤100			<10	
大肠埃希菌	不得检出			未检出	
沙门菌	不得检出			未检出	
包装的完整性	应完整			完整	
包装的密封性	应密封			密封	
结论	依据 2020 年版中国药典四部, 检验结果符合规定。				
质控部经理:	李晓东	检验人:	张丽娟	复核人:	孙玉玲

Activated carbon raw material inspection report

Commodity Name :	Activated carbon	Batch No.	F012201001	Quantity:	16000kg
source	Nanping Yuanli Activated Carbon Co., Ltd.		Package	12kg/carton	
Number of retained samples	16.62g		Test Date	2022.01.14	
Inspection purpose	use test		Report Date	2022.01.19	
Test based on	2020 edition of the four Chinese Pharmacopoeia		Expiry date	2023.11	
Item	Test standard		Result		
Properties	black powder		black powder		
Identification	should present positive reaction		Conforms		
pH	should present neutral reaction		Conforms		
Chloride (%)	≤ 0.1		< 0.1		
Sulfate (%)	≤ 0.05		< 0.05		
Uncarbonized substances	Comply with the regulations		Conforms		
Sulfide	Comply with the regulations		Conforms		
Cyanide	Comply with the regulations		Conforms		
Solutes in ethanol (mg)	≤ 8		0.3		
Fluorescent substance	Less than the absorbance of the control solution		Less than the absorbance of the control solution		
Acid soluble substances (mg)	≤ 8		1.7		
Loss on drying (%)	≤ 10.0		0.86		
Residue on ignition (%)	≤ 3.0		0.91		
Fe salt (%)	≤ 0.02		< 0.02		
Zinc salt (%)	≤ 0.005		< 0.005		
Heavy metal(ppm)	≤ 30		< 30		
Adsorbent capacity	Comply with the regulations		Conforms		
Total aerobic bacteria cfu/g	≤ 1000		< 1000		
Total mold and yeast cfu/g	≤ 100		< 100		
Escherichia coli	not be detected		not detected		
Salmonella	not be detected		not detected		
Bacterial endotoxin (EU/g)	<2		<2		
Adsorption capacity of activated carbon to bacterial endotoxin (%)	> 99		> 99		

Appendix 5: Process Verification (C552202010) Finished Product Inspection Report

精晶药业股份有限公司

编码: SOP-012-YZC1295B-Rev-02 (00)

门冬氨酸鸟氨酸成品检验报告（韩国）

编码: 2202C55-010J

品名	门冬氨酸鸟氨酸	批号	C552202010	批量	400.84kg
样品来源	生产车间	生产日期	2022年02月08日		
产品规格	25 kg/袋	检验日期	2022年02月10日		
报告日期	2022年04月06日	有效期至	2024年02月07日		
检验依据	企业内控				
检验项目	检验标准	检验结果			
【性状】	白色结晶或结晶性粉末	白色结晶性粉末			
【鉴别】					
(1) 比旋度, °	+26.5~+29.0	+28.0			
(2)	应与对照品图谱一致	与对照品图谱一致			
【检查】					
酸度	6.0~7.0	6.3			
溶液的澄清度	≤1号浊度标准	<1号浊度标准			
溶液的颜色	≤B9	<B9			
氯化物 (ppm)	≤300	<300			
硫酸盐 (ppm)	≤200	<200			
铵盐 (ppm)	≤400	<400			
水分 (%)	≤7.0	0.81			
炽灼残渣 (%)	≤0.2	0.02			
铁盐 (ppm)	≤30	<30			
重金属 (ppm)	≤10	<10			
其他氨基酸 (%)	应符合规定	符合规定			
残留溶剂 甲醇 (%)	≤0.30	0.0091			
【含量测定】 %	98.0~102.0	98.6			
结论	依据企业内控, 结果符合规定。				

质量负责人:

复核人:

Commodity Name	L-ornithine-L-aspartate	Batch No.	C552202010	Quantity:	400.84kg
source	production workshop		Production Date	2022.02.08	
Package	25kg/bag		Test Date	2022.02.10	
Report Date	2022.04.06		Expiry date	2024.02.07	
Test based on	In house				
TEST	SPECIFICATION			RESULT	
Description	White crystal or crystalline powder			White crystalline powder	
pH	6.0 ~ 7.0			6.3	
Identification	IR	should be consistent with the standard infrared spectrum			Consistent with standard infrared spectrum
	Optical Rotation, °	+26.5 ~ +29.0			28.0
Clarity of the solution	≤No. 1 Turbidity Standard			< No. 1 Turbidity Standard	
color of solution	≤B9			< B9	
Wate %	≤7.0			0.81	
Residue on ignition	≤0.2			0.02	
Chloride,ppm	≤300			< 300	
Sulfate (ppm)	≤200			< 200	
Ammonium ,ppm	≤400			< 400	
Heavy metal,ppm	≤10			< 10	
Iron, ppm	≤30			< 30	
Other Amino Acids,%	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution			Compliance	
Residual solvent methanol ppm	≤3000			91	
Assay, %	98.0 ~ 102.0			98.6	
Conclusion	According to the internal control of the enterprise, the results meet the regulations				

Appendix 6: Process Verification (C552202011) Finished Product Inspection Report

精晶药业股份有限公司

编码: SOP-012-YZC1295B-Rev-02(00)

门冬氨酸鸟氨酸成品检验报告（韩国）

编码: 2202C55-011J

品名	门冬氨酸鸟氨酸	批号	C552202011	批量	400.84kg
样品来源	生产车间	生产日期	2022年02月09日		
产品规格	25 kg/袋	检验日期	2022年02月10日		
报告日期	2022年04月06日	有效期至	2024年02月08日		
检验依据	企业内控				
检验项目	检验标准	检验结果			
【性状】	白色结晶或结晶性粉末	白色结晶性粉末			
【鉴别】					
(1) 比旋度, °	+26.5~+29.0	+28.3			
(2)	应与对照品图谱一致	与对照品图谱一致			
【检查】					
酸度	6.0~7.0	6.3			
溶液的澄清度	≤1号浊度标准	<1号浊度标准			
溶液的颜色	≤B9	<B9			
氯化物 (ppm)	≤300	<300			
硫酸盐 (ppm)	≤200	<200			
铵盐 (ppm)	≤400	<400			
水分 (%)	≤7.0	0.66			
炽灼残渣 (%)	≤0.2	0.03			
铁盐 (ppm)	≤30	<30			
重金属 (ppm)	≤10	<10			
其他氨基酸 (%)	应符合规定	符合规定			
残留溶剂 甲醇 (%)	≤0.30	0.0095			
【含量测定】 %	98.0~102.0	98.9			
结论	依据企业内控, 结果符合规定。				

质量负责人:

 检验人: 造红平

复核人: 钱勇

Commodity Name : source	L-ornithine-L-aspartate production workshop	Batch No. C552202011	Quantity: 400.84kg Production Date 2022.02.09
Package	25kg/bag	Test Date	2022.02.10
Report Date	2022.04.06	Expiry date	2024.02.07
Test based on	In house		
TEST	SPECIFICATION	RESULT	
Description	White crystal or crystalline powder	White crystalline powder	
Identification	IR	should be consistent with the standard infrared spectrum	Consistent with standard infrared spectrum
	Optical Rotation, °	+26.5 ~ +29.0	28.3
pH	6.0 ~ 7.0	6.3	
Clarity of the solution	≤No. 1 Turbidity Standard	< No. 1 Turbidity Standard	
color of solution	≤B9	< B9	
Wate %	≤7.0	0.66	
Residue on ignition	≤0.2	0.03	
Chloride,ppm	≤300	< 300	
Sulfate (ppm)	≤200	< 200	
Ammonium ,ppm	≤400	< 400	
Heavy metal,ppm	≤10	< 10	
Iron, ppm	≤30	< 30	
Other Amino Acids,%	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Compliance	
Residual solvent methanol ppm	≤3000	95	
Assay, %	98.0 ~ 102.0	98.9	
Conclusion	According to the internal control of the enterprise, the results meet the regulations		

Appendix 7: Process Verification (C552202012) Finished Product Inspection Report

精晶药业股份有限公司

编码: SOP-012-YZC1295B-Rev-02 (00)

门冬氨酸鸟氨酸成品检验报告 (韩国)

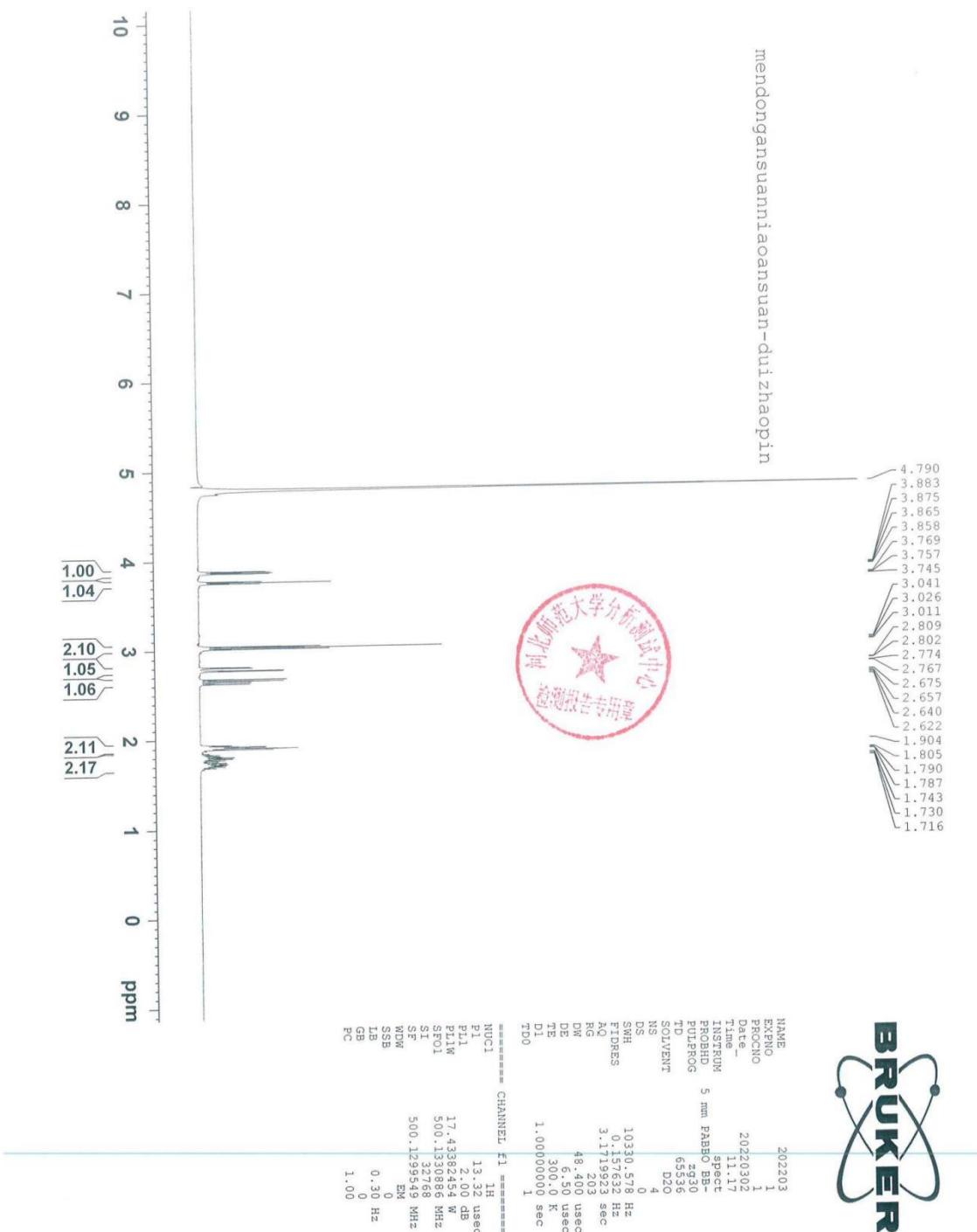
编码: 2202C55-012J

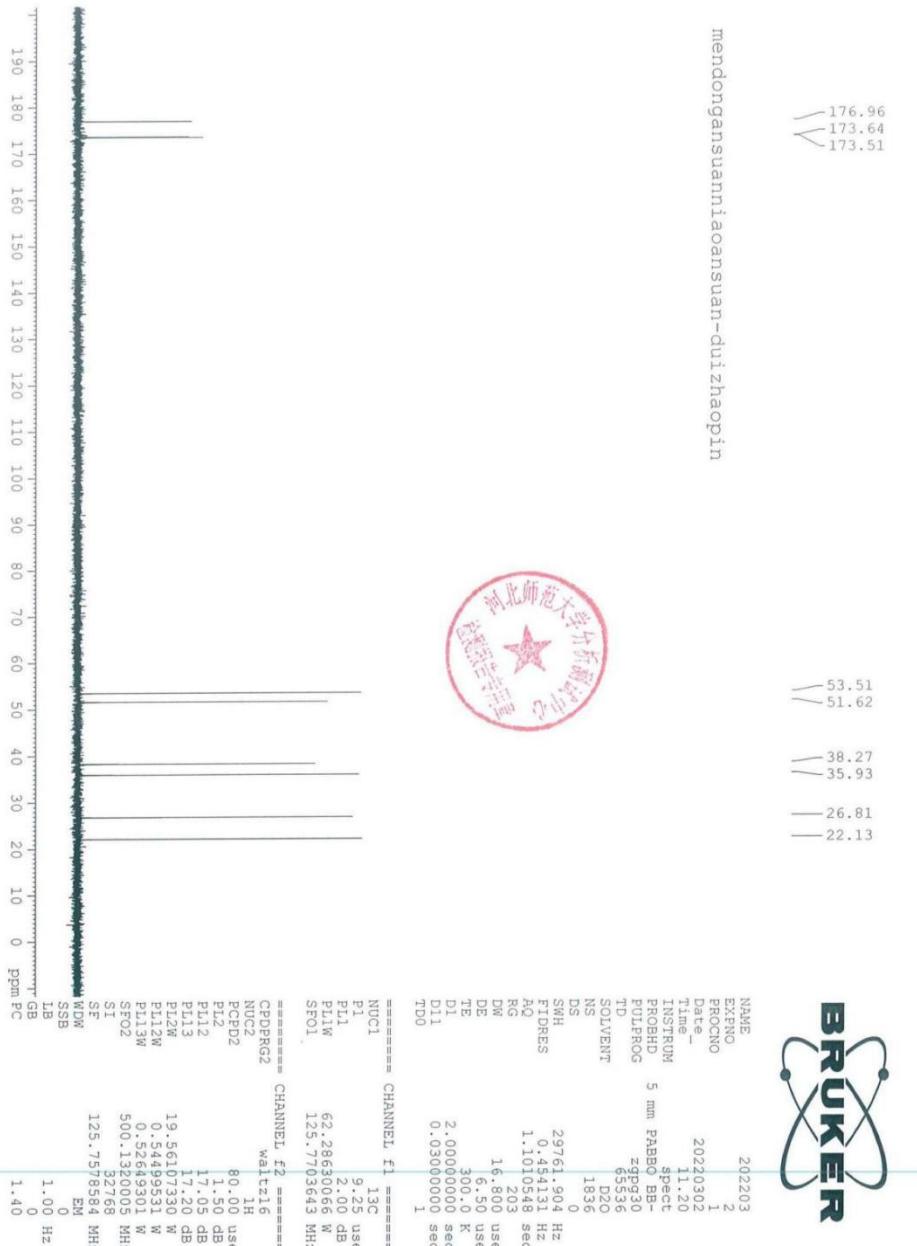
品名	门冬氨酸鸟氨酸	批号	C552202012	批量	400.84kg
样品来源	生产车间	生产日期	2022年02月09日		
产品规格	25 kg/袋	检验日期	2022年02月11日		
报告日期	2022年04月06日	有效期至	2024年02月08日		
检验依据	企业内控				
检验项目	检验标准	检验结果			
【性状】	白色结晶或结晶性粉末	白色结晶性粉末			
【鉴别】					
(1) 比旋度, °	+26.5~+29.0	+28.3			
(2)	应与对照品图谱一致	与对照品图谱一致			
【检查】					
酸度	6.0~7.0	6.3			
溶液的澄清度	≤1号浊度标准	<1号浊度标准			
溶液的颜色	≤B9	<B9			
氯化物 (ppm)	≤300	<300			
硫酸盐 (ppm)	≤200	<200			
铵盐 (ppm)	≤400	<400			
水分 (%)	≤7.0	0.77			
炽灼残渣 (%)	≤0.2	0.01			
铁盐 (ppm)	≤30	<30			
重金属 (ppm)	≤10	<10			
其他氨基酸 (%)	应符合规定	符合规定			
残留溶剂 甲醇 (%)	≤0.30	0.0089			
【含量测定】 %	98.0~102.0	99.0			
结论	依据企业内控, 结果符合规定。				

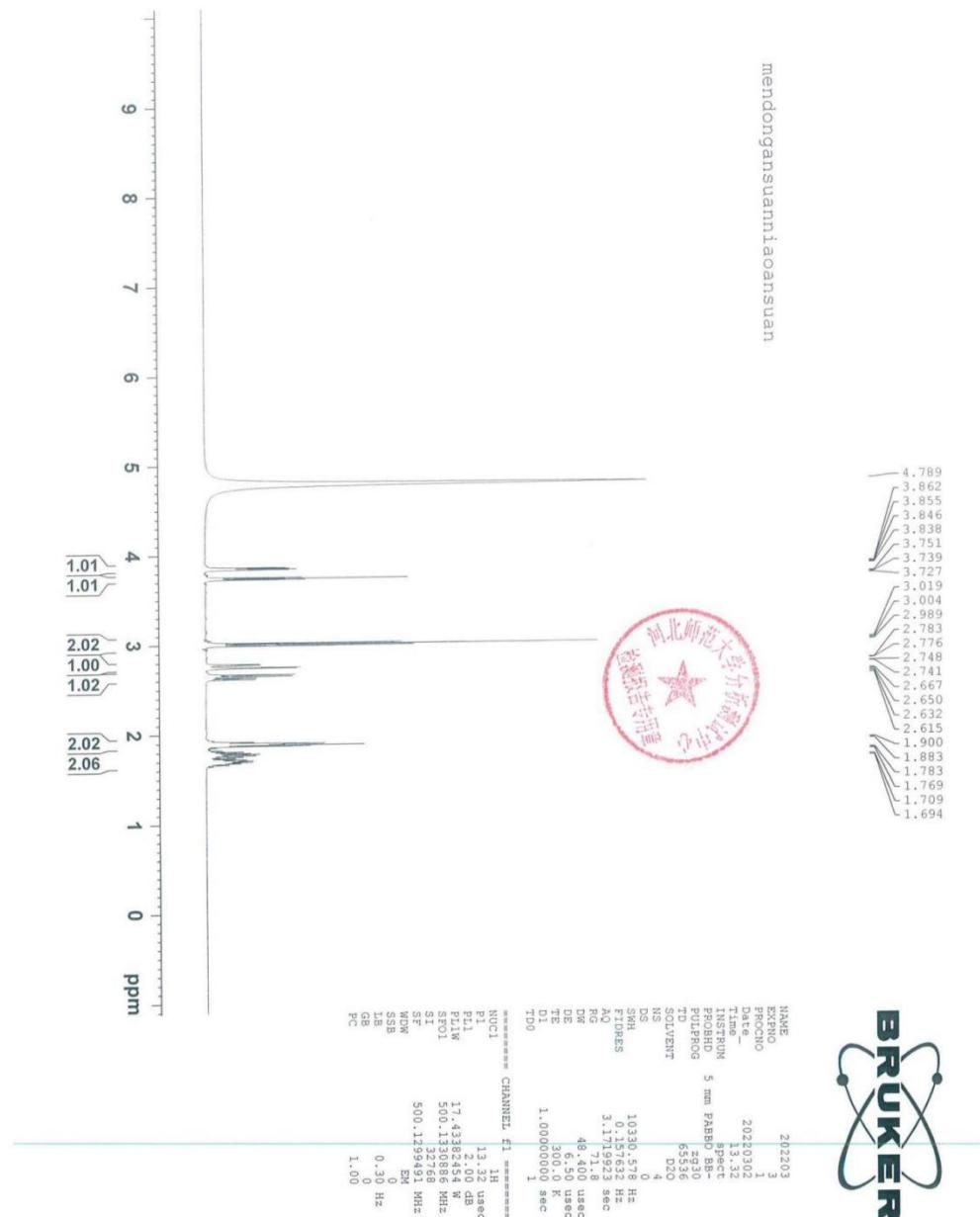
质量负责人:  检验人: 范峰

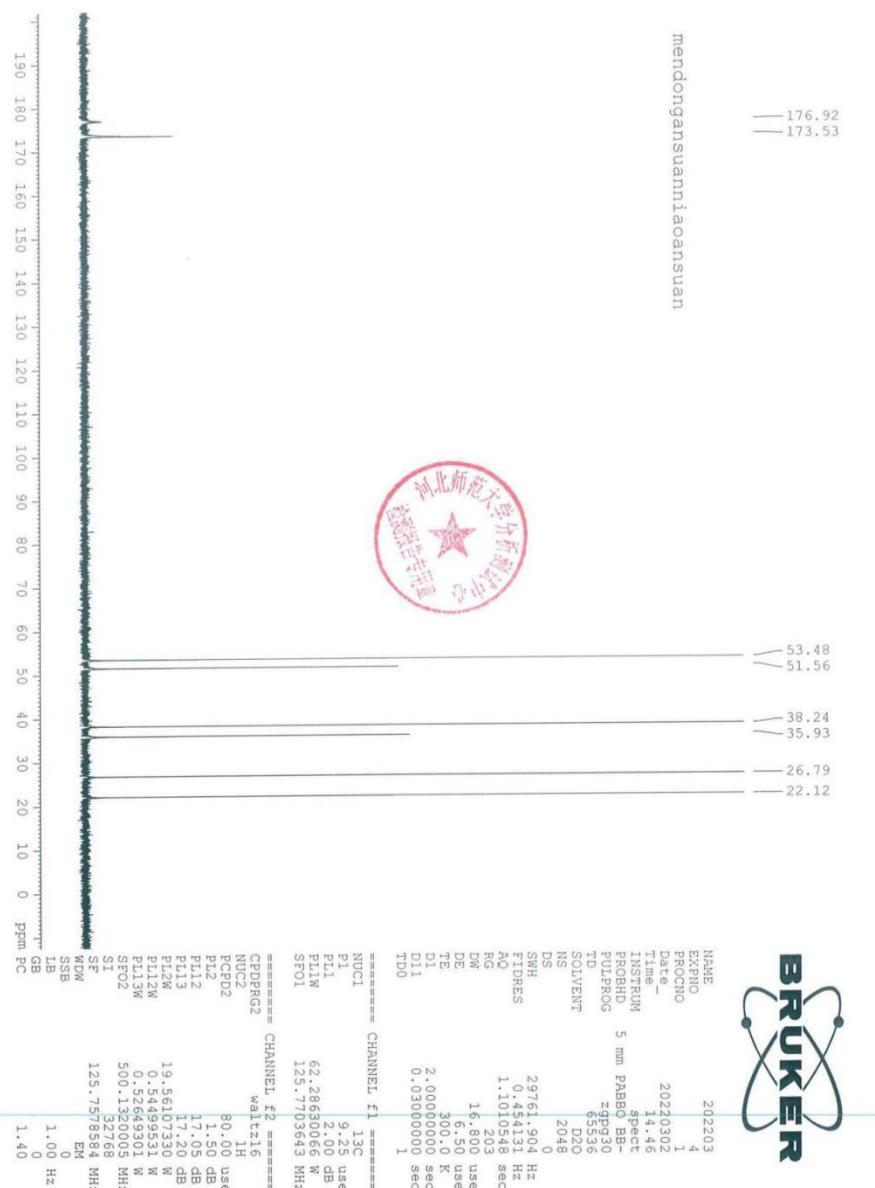
复核人: 刘东

Commodity Name : source	L-ornithine-L-aspartate production workshop	Batch No. C552202012	Quantity: 400.84kg Production Date 2022.02.09
Package	25kg/bag	Test Date	2022.02.11
Report Date	2022.04.06	Expiry date	2024.02.07
Test based on	In house		
TEST	SPECIFICATION	RESULT	
Description	White crystal or crystalline powder	White crystalline powder	
Identification	IR	should be consistent with the standard infrared spectrum	Consistent with standard infrared spectrum
	Optical Rotation, °	+26.5 ~ +29.0	28.3
pH	6.0 ~ 7.0	6.3	
Clarity of the solution	≤No. 1 Turbidity Standard	< No. 1 Turbidity Standard	
color of solution	≤B9	< B9	
Wate %	≤7.0	0.77	
Residue on ignition	≤0.2	0.01	
Chloride,ppm	≤300	< 300	
Sulfate (ppm)	≤200	< 200	
Ammonium ,ppm	≤400	< 400	
Heavy metal,ppm	≤10	< 10	
Iron, ppm	≤30	< 30	
Other Amino Acids,%	Spots other than the main spots in the test solution are not larger than the spots obtained in the standard solution	Compliance	
Residual solvent methanol ppm	≤3000	89	
Assay, %	98.0 ~ 102.0	99.0	
Conclusion	According to the internal control of the enterprise, the results meet the regulations		

Appendix 8: Hydrogen spectrum analysis $^1\text{H-NMR}$ 

Appendix 9: Sample hydrogen spectrum $^1\text{H-NMR}$ 

Appendix 10: Standard carbon spectrum ^{13}C -NMR

Appendix 11: Sample carbon spectrum ^{13}C -NMR

Appendix 12: Mass spectrum

SDFC/ZJ116

检测报告

冀师检(化)字(2022)第02002号

委托单位: 精晶药业股份有限公司

委托名称: 门冬氨酸鸟氨酸

检测类别: 委托检测

承担检测的技术机构: 河北师范大学分析测试中心



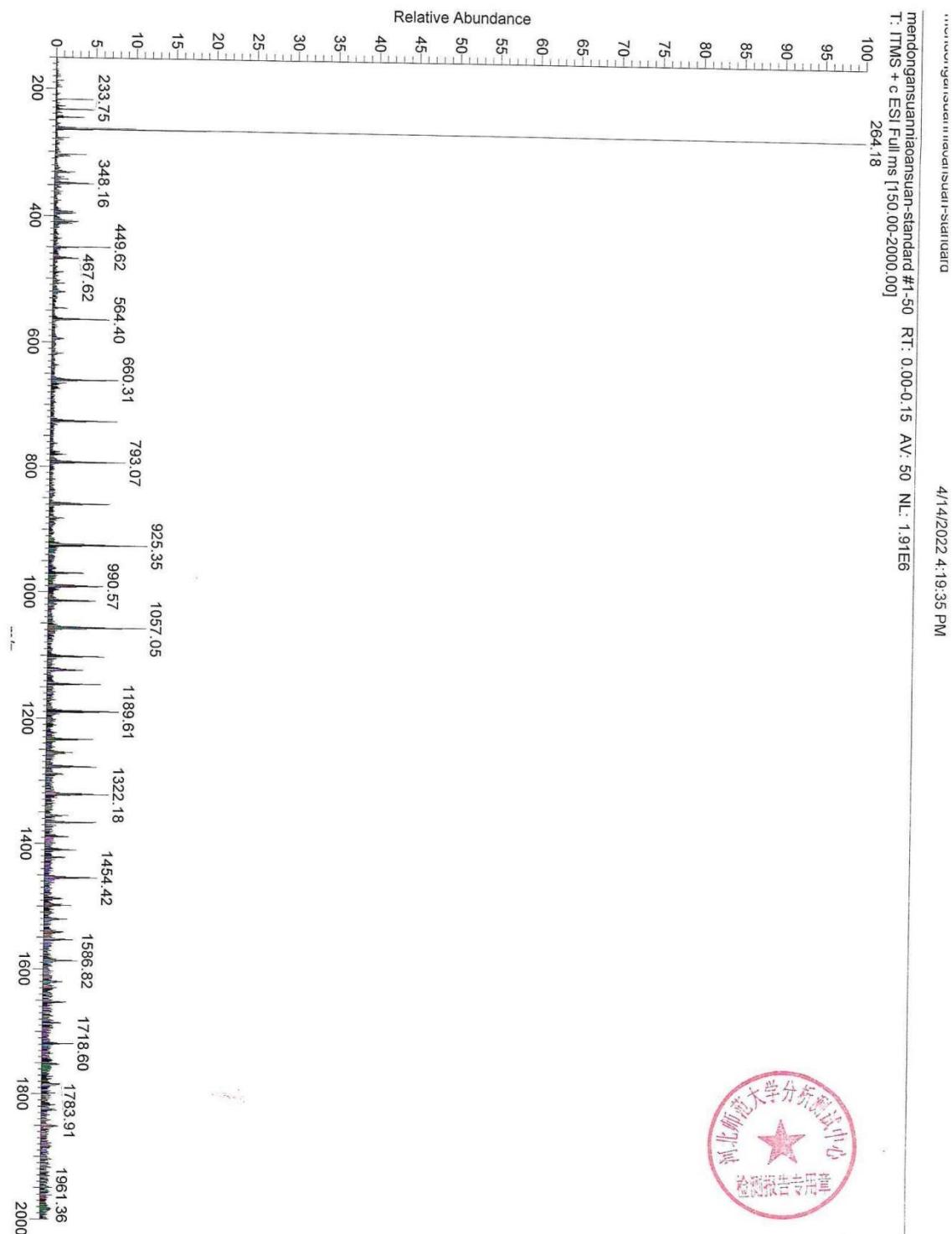
报告编号:

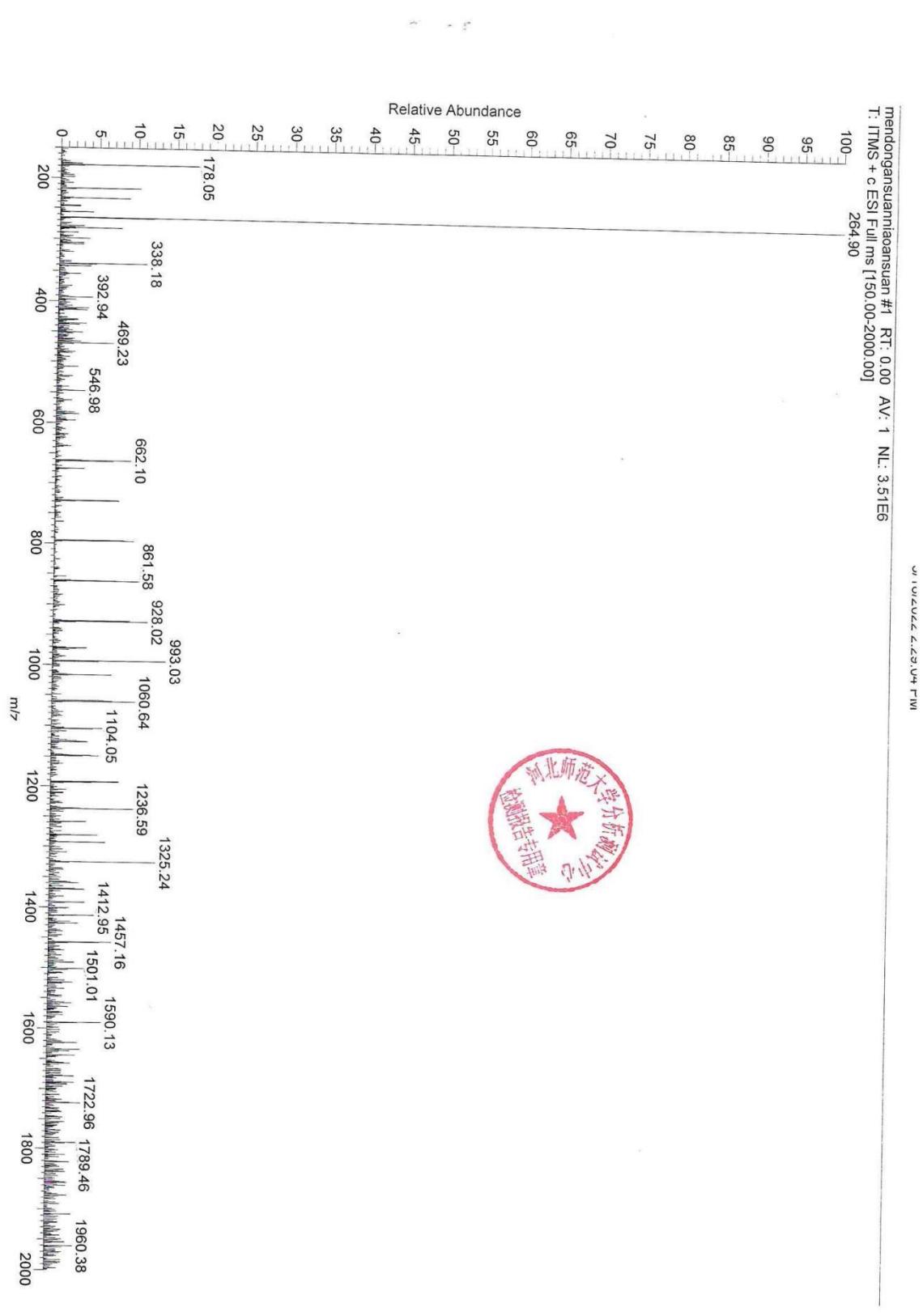
检测报告

冀师检(化)字(2022)第02002号

第1页 共1页

样品名称	门冬氨酸鸟氨酸		样品状态	固体粉末
			样品来源	委托检测
委托单位	精晶药业股份有限公司		型号规格	g/袋
委托时间	2022年02月11日		抽样地点	/
委托人	宴玲		抽样时间	/
样品编号	样品、对照品		抽样人	/
检测时间	2022年03月17日		样品数量	2管×1g/管
检测项目	质谱			
检测依据	《中国药典》2015年版四部 通则 0431 质谱法			
检测所使用的 主要仪器 设备	设备名称	规格型号	设备编号	
	质谱仪	Thermo LTQ	/	
	/	/	/	
	/	/	/	
检测环境	温度 20℃, 湿度 47% RH			
检测结论	该样品按照以上标准检测, 实测结果见附图。			
主检	胡玉红	审核	韩亚楠	批准人 常彦忠 日期 2022.3.18
注	本结果仅对此次来样负责			





Appendix 13: Elemental Analysis Spectrum

SDFC/ZJ116

检 测 报 告

冀师检(化)字(2022)第02002号

送样单位: 精晶药业股份有限公司
样品名称: 门冬氨酸鸟氨酸
检测类别: 委托检测

承担检测的技术机构: 河北师范大学分析测试中心



检 测 报 告

冀师检(化)字(2022)第02002号

第 1 页 共 2 页

样品名称	门冬氨酸鸟氨酸	型号规格	白色粉末
		样品来源	委托检测
送样单位	精晶药业股份有限公司	型号规格	试剂包装完好
送样时间	2022年02月11日	抽样地点	/
送 样 人	晏玲	抽样时间	/
样品编号	07125-SLBW4848、C552202010	抽 样 人	/
检测时间	2022年03月10日	样品数量	2袋
检测要求	元素分析		
检测依据			
检测所使用的主要仪器设备	设备名称	规格型号	设备编号
	元素分析仪	Vario ELIII	20064873
检测环境	室温		
检测结论	实测结果见第2页。		
主检	孙晓光	审核	王丽娜 批准人 常彦忠 日期 20220311
备注	样品未处理，本结果仅对此次来样负责		

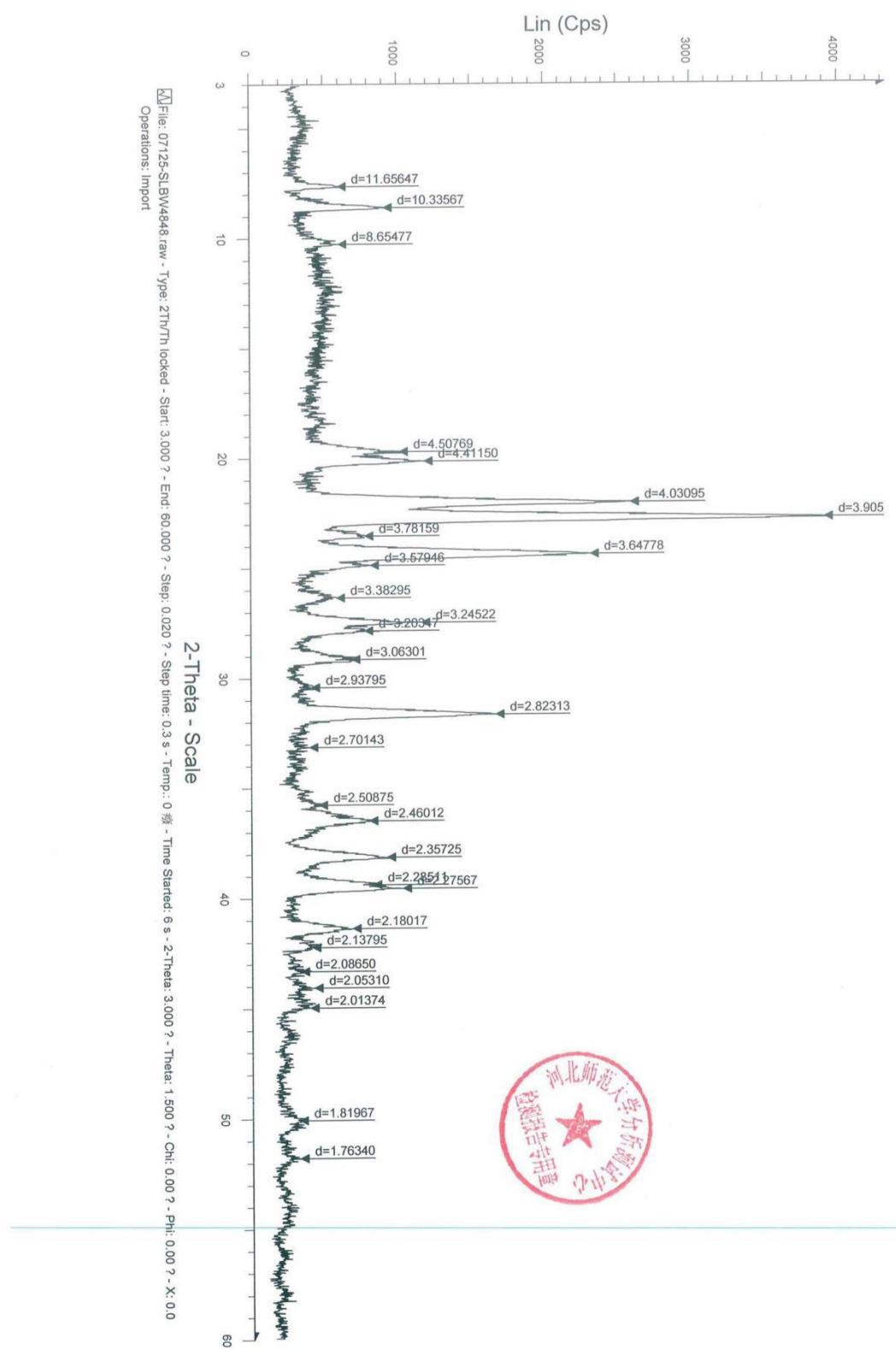


检 测 结 果

冀师检(化)字(2022)第02002号

第 2 页 共 2 页

Appendix 14: X-ray diffraction patterns of Sample

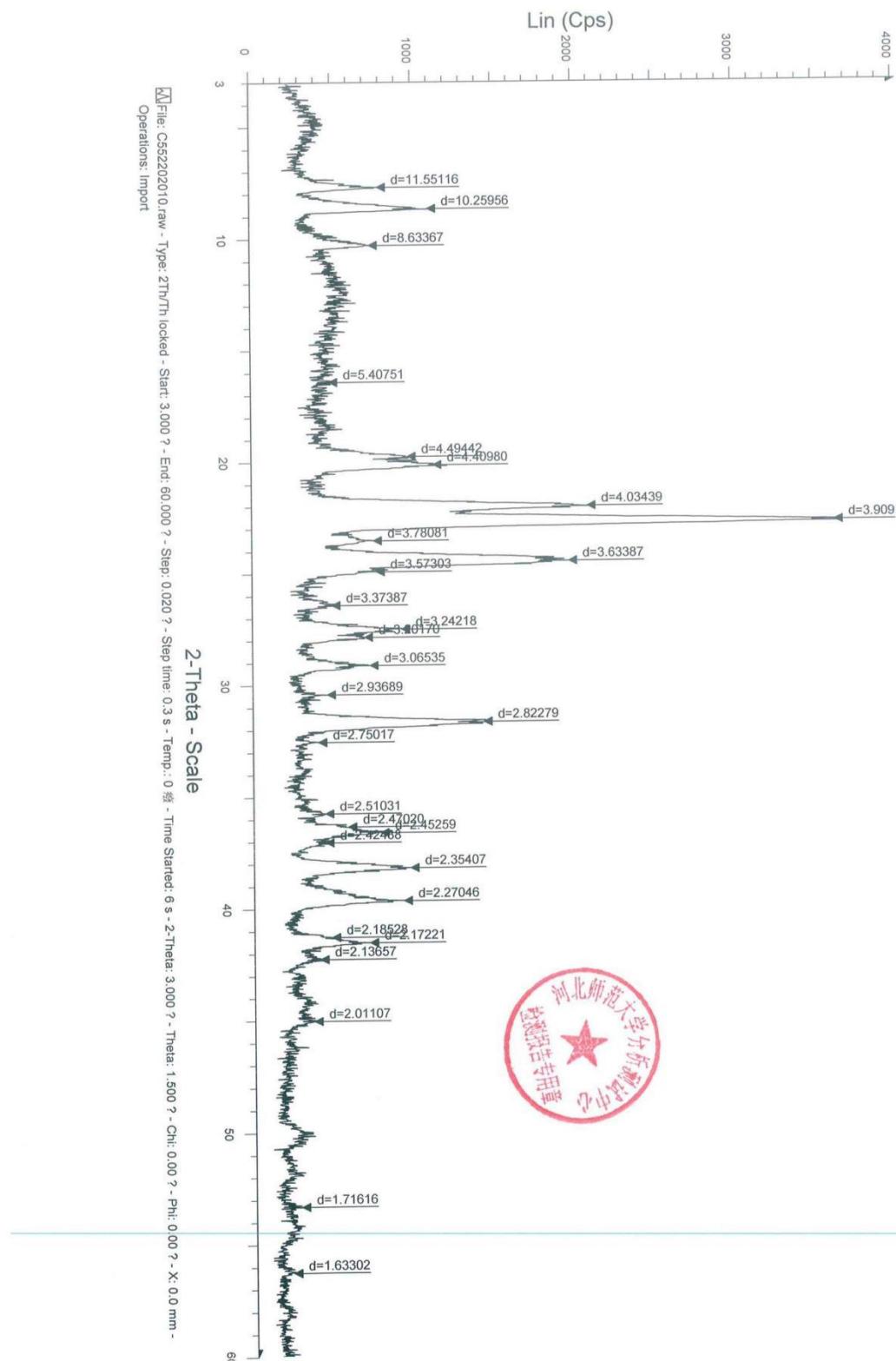


07125-SLBW4848.raw

Caption	Angle 2-Theta ?	d value Angstrom	Intensity Cps	Intensity %
d=11. 65647	7. 578	11. 65647	590	15. 1
d=10. 33567	8. 548	10. 33567	903	23
d=8. 65477	10. 213	8. 65477	593	15. 1
d=4. 50769	19. 679	4. 50769	1007	25. 7
d=4. 41150	20. 112	4. 4115	1177	30
d=4. 03095	22. 034	4. 03095	2597	66. 2
d=3. 90571	22. 749	3. 90571	3920	100
d=3. 78159	23. 506	3. 78159	770	19. 6
d=3. 64778	24. 382	3. 64778	2317	59. 1
d=3. 57946	24. 855	3. 57946	807	20. 6
d=3. 38295	26. 324	3. 38295	573	14. 6
d=3. 24522	27. 462	3. 24522	1157	29. 5
d=3. 20347	27. 827	3. 20347	767	19. 6
d=3. 06301	29. 131	3. 06301	677	17. 3
d=2. 93795	30. 4	2. 93795	400	10. 2
d=2. 82313	31. 668	2. 82313	1663	42. 4
d=2. 70143	33. 135	2. 70143	387	9. 9
d=2. 50875	35. 763	2. 50875	450	11. 5
d=2. 46012	36. 494	2. 46012	797	20. 3
d=2. 35725	38. 147	2. 35725	913	23. 3
d=2. 28511	39. 4	2. 28511	820	20. 9
d=2. 27567	39. 57	2. 27567	1023	26. 1
d=2. 18017	41. 381	2. 18017	677	17. 3
d=2. 13795	42. 237	2. 13795	400	10. 2
d=2. 08650	43. 33	2. 0865	323	8. 2
d=2. 05310	44. 072	2. 0531	413	10. 5
d=2. 01374	44. 98	2. 01374	387	9. 9
d=1. 81967	50. 089	1. 81967	310	7. 9
d=1. 76340	51. 803	1. 7634	313	8



Appendix 15: Standard X-ray diffraction patterns

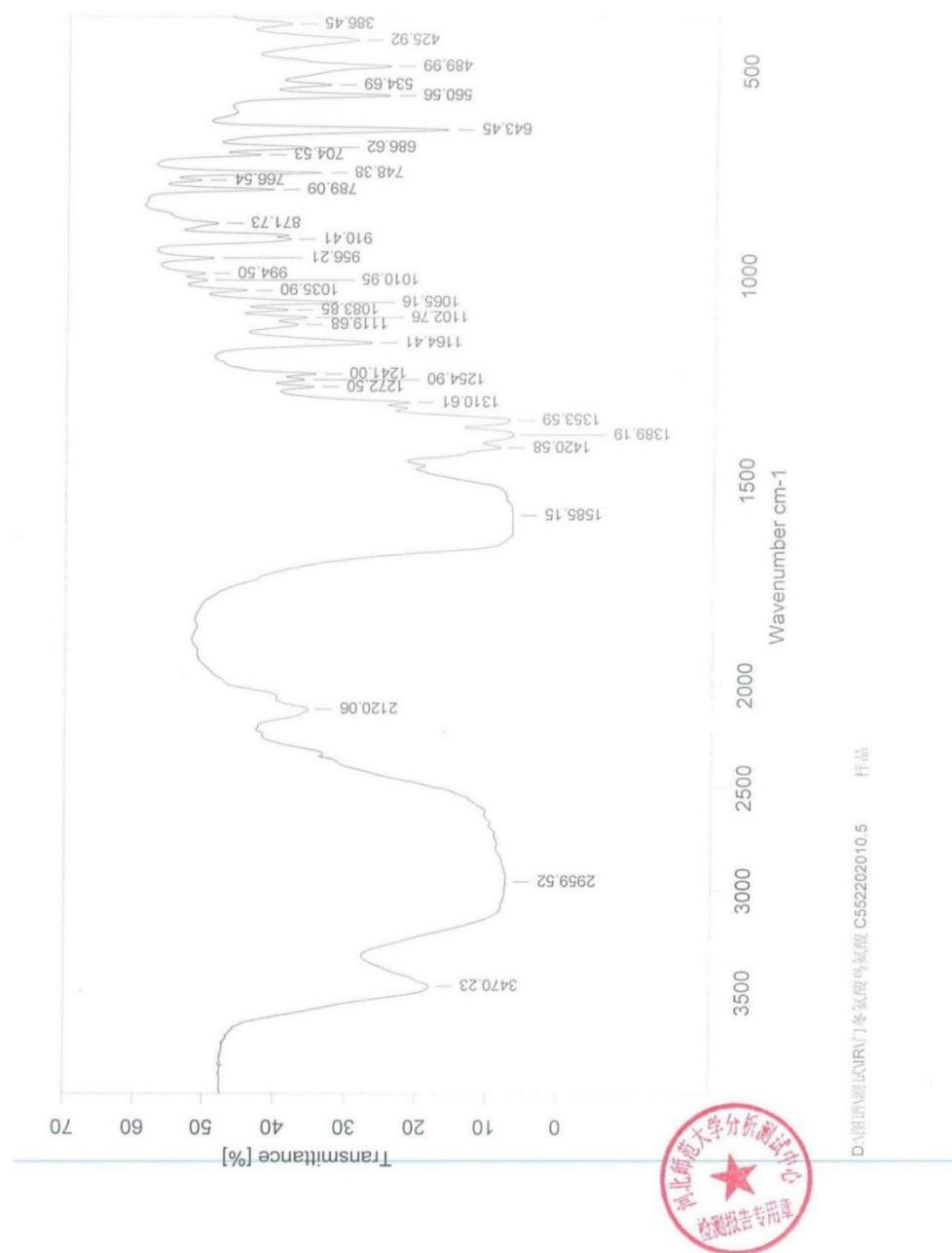


C552202010.raw

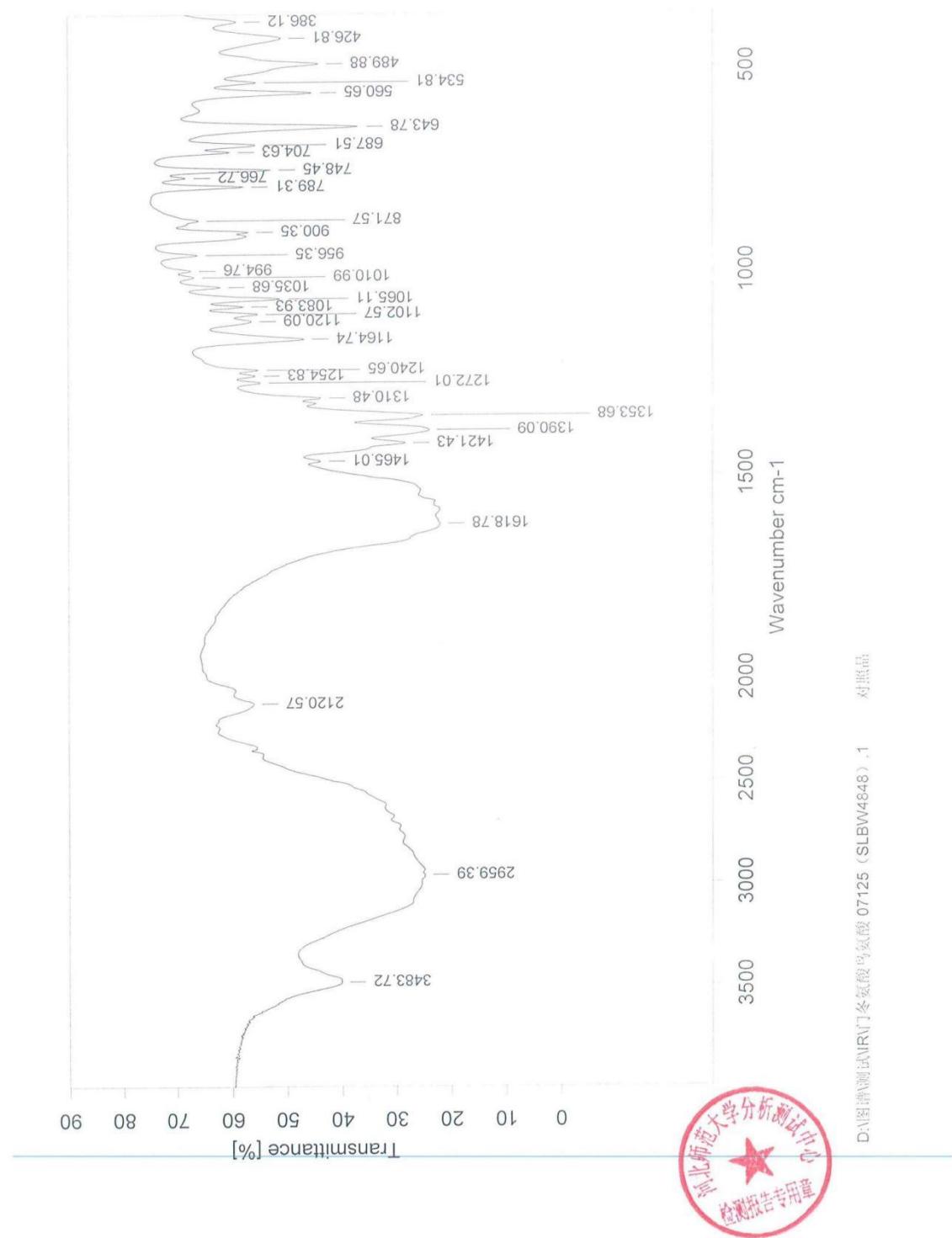
Caption	Angle 2-Theta ?	d value Angstrom	Intensity Cps	Intensity %
d=11. 55116	7. 647	11. 55116	787	21. 6
d=10. 25956	8. 612	10. 25956	1100	30. 2
d=8. 63367	10. 238	8. 63367	733	20. 1
d=5. 40751	16. 379	5. 40751	480	13. 2
d=4. 49442	19. 737	4. 49442	967	26. 6
d=4. 40980	20. 12	4. 4098	1127	31
d=4. 03439	22. 015	4. 03439	2097	57. 6
d=3. 90933	22. 728	3. 90933	3640	100
d=3. 78081	23. 511	3. 78081	750	20. 6
d=3. 63387	24. 477	3. 63387	1977	54. 3
d=3. 57303	24. 9	3. 57303	767	21. 1
d=3. 37387	26. 396	3. 37387	490	13. 5
d=3. 24218	27. 488	3. 24218	923	25. 4
d=3. 20170	27. 843	3. 2017	690	19
d=3. 06535	29. 108	3. 06535	723	19. 9
d=2. 93689	30. 411	2. 93689	457	12. 5
d=2. 82279	31. 672	2. 82279	1437	39. 5
d=2. 75017	32. 531	2. 75017	400	11
d=2. 51031	35. 74	2. 51031	440	12. 1
d=2. 47020	36. 34	2. 4702	583	16
d=2. 45259	36. 61	2. 45259	783	21. 5
d=2. 42488	37. 044	2. 42488	440	12. 1
d=2. 35407	38. 2	2. 35407	970	26. 6
d=2. 27046	39. 665	2. 27046	927	25. 5
d=2. 18528	41. 28	2. 18528	477	13. 1
d=2. 17221	41. 54	2. 17221	713	19. 6
d=2. 13657	42. 266	2. 13657	403	11. 1
d=2. 01107	45. 043	2. 01107	363	10
d=1. 71616	53. 34	1. 71616	277	7. 6
d=1. 63302	56. 29	1. 63302	223	6. 1



Appendix 16: Sample infrared spectrum



Appendix 17: Standard infrared spectrum



Appendix 18: L-ornithine-L-aspartate (C552202010) Elemental Analysis Test Report

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国际互认
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TESTING
CNAS L8223

正本

检测报告

No. HC20220210515A-1



样品名称: 门冬氨酸鸟氨酸

委托单位名称: 精晶药业股份有限公司
河北省邢台市宁晋县大曹庄
委托单位地址: 工业园区经一路88号

潍坊海润华辰检测技术有限公司

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Email: info@harrens.com

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0536-2119106

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0532-80981700

潍坊实验室: 潍坊市食品谷总部基地L座

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杭州实验室: 杭州市下城区华中南路668号2幢501室

0571-56505915

美国实验室: 3860 Bay Center Pl, Hayward, CA 94545

成都实验室: 成都市龙泉驿区(经开区)成龙大道二段1666号C3栋 028-88612161



报告编号 Report ID: HC20220210515A-1

检 测 报 告

Test Report

承检机构名称 Lab Name: 潍坊海润华辰检测技术有限公司

承检机构地址 Lab Add.: 潍坊市寒亭区开元街道中国食品谷总部基地L座

样品信息 Sample:

样品名称 Sample Name	门冬氨酸鸟氨酸	生产日期/批号 Prod. Date/Code	2022.02.08/C552202010
样品编号 Sample No.	HC20220210515	规格 Specification	/
商标 Trademark	/	数量/重量 Quantity/Weight	50g
样品描述 Sample Desc.	袋装门冬氨酸鸟氨酸	生产商 Manufacturer	精晶药业股份有限公司
接收日期 Receiving Date	2022-02-15	检测日期 Testing Date	2022-02-15 至 2022-02-22
备注Notes	此报告为编号HC20220210515检测报告的补充（或更正），报告发出后，原报告自动作废。		

报告编制人 Editor: 徐山九

批准人 Approved by:

审核人 Verifier: 孙洪川

签发日期 Issuing Date: 2022-03-09

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Email: info@harrens.com

第 1 页/共 2 页

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杭州实验室: 杭州市下城区华中南路668号2幢501室0532-80655806
0532-80981700
0571-56505915潍坊实验室: 潍坊市食品谷总部基地L座 0536-2119106
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成都实验室: 成都市龙泉驿区(经开区)成龙大道二段1666号C3栋 028-88612161



报告编号 Report ID: HC20220210515A-1

检测结果 Test Results

序号 NO.	检测项目 Testing Items		检测结果及单位 Result&Unit	检测方法 Testing Method
	英文 English	中文 Chinese		
1	Cadmium	镉	未检出(<0.002mg/kg)	GB 5009. 268-2016(第一法)
2	Lead	铅	未检出(<0.02mg/kg)	GB 5009. 268-2016(第一法)
3	Arsenic	砷	0.00782mg/kg	GB 5009. 268-2016(第一法)
4	Mercury	汞	未检出(<0.001mg/kg)	GB 5009. 268-2016(第一法)
5	Cobalt	钴	0.00183mg/kg	GB 5009. 268-2016(第一法)
6	Vanadium	钒	0.00220mg/kg	GB 5009. 268-2016(第一法)
7	Nickel	镍	未检出(<0.2mg/kg)	GB 5009. 268-2016(第一法)
8	Chromium	铬	0.0748mg/kg	GB 5009. 268-2016(第一法)
9	Copper	铜	未检出(<0.05mg/kg)	GB 5009. 268-2016(第一法)

*****报告结束 END*****



青岛海润检测股份有限公司：青岛西海岸新区望江路23号海润园区 0532-80981700

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第 2 页 / 共 2 页

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杭州实验室：杭州市下城区华中南路668号2幢501室

潍坊实验室：潍坊市食品谷总部基地L座
美国实验室：3860 Bay Center Pl. Hayward, CA 94545 +1 (510) 8878885
成都实验室：成都市龙泉驿区(经开区)成龙大道二段1666号C3栋 028-88612161

Appendix 19: L-ornithine-L-aspartate (C552202011) Elemental Analysis Test Report

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检测报告

No. HC20220211705

样品名称: 门冬氨酸鸟氨酸

委托单位名称: 精晶药业股份有限公司

河北省邢台市宁晋县大曹庄
委托单位地址: 工业园区经一路88号



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杭州实验室: 杭州市下城区华中南路668号2幢501室

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潍坊实验室: 潍坊市食品谷总部基地1座 0536-2119106
美国实验室: 3860 Bay Center Pl. Hayward, CA 94545 +1 (510) 8878885
成都实验室: 成都市龙泉驿区(经开区)成龙大道二段1666号C3栋: 028-88612161



报告编号 Report ID: HC20220211705

检 测 报 告

Test Report

承检机构名称 Lab Name: 潍坊海润华辰检测技术有限公司

承检机构地址 Lab Add.: 潍坊市寒亭区开元街道中国食品谷总部基地L座

样品信息 Sample:

样品名称 Sample Name	门冬氨酸鸟氨酸	生产日期/批号 Prod. Date/Code	2022.02.09/C552202011
样品编号 Sample No.	HC20220211705	规格 Specification	/
商标 Trademark	/	数量/重量 Quantity/Weight	50g
样品描述 Sample Desc.	袋装门冬氨酸鸟氨酸	生产商 Manufacturer	精晶药业股份有限公司
接收日期 Receiving Date	2022-02-28	检测日期 Testing Date	2022-02-28 至 2022-03-07
备注Notes	*项目不在CNAS认可范围内。		

报告编制人 Editor: 徐山九

批准人 Approved by:

审核人Verifier: 孙洪川

签发日期 Issuing Date: 2022-03-07

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0532-80981700
0571-56505915潍坊实验室: 潍坊市食品谷总部基地L座 0536-2119106
美国实验室: 3860 Bay Center Pl, Hayward, CA 94545 +1 (510) 8878885
成都实验室: 成都市龙泉驿区(经开区)成龙大道二段1666号C3栋 028-88612161



报告编号 Report ID: HC20220211705

检 测 结 果

Test Results

序号 No.	检测项目 Testing Items		检测结果及单位 Result&Unit	检测方法 Testing Method
	英文 English	中文 Chinese		
1	Cadmium	镉	未检出(<0.002mg/kg)	GB 5009.268-2016(第一法)
2	Lead	铅	未检出(<0.02mg/kg)	GB 5009.268-2016(第一法)
3	Arsenic	砷	未检出(<0.002mg/kg)	GB 5009.268-2016(第一法)
4	Mercury	汞	未检出(<0.001mg/kg)	GB 5009.268-2016(第一法)
5	Cobalt	钴*	0.00147mg/kg	GB 5009.268-2016(第一法)
6	Vanadium	钒*	0.00380mg/kg	GB 5009.268-2016(第一法)
7	Nickel	镍	未检出(<0.2mg/kg)	GB 5009.268-2016(第一法)
8	Chromium	铬	0.109mg/kg	GB 5009.268-2016(第一法)
9	Copper	铜	未检出(<0.05mg/kg)	GB 5009.268-2016(第一法)

*****报告结束 END*****



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第 2 页 / 共 2 页

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Appendix 20: L-ornithine-L-aspartate (C552202012) Elemental Analysis Test Report

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国际互认
检测
TESTING
CNAS L8223

正本

检 测 报 告

No. HC20220211706样 品 名 称: 门冬氨酸鸟氨酸委 托 单 位 名 称: 精晶药业股份有限公司委托单位地址: 河北省邢台市宁晋县大曹庄
工业园区经一路88号

潍坊海润华辰检测技术有限公司

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报告编号 Report ID: HC20220211706

检 测 报 告

Test Report

承检机构名称 Lab Name: 潍坊海润华辰检测技术有限公司

承检机构地址 Lab Add.: 潍坊市寒亭区开元街道中国食品谷总部基地L座

样品信息 Sample:

样品名称 Sample Name	门冬氨酸鸟氨酸	生产日期/批号 Prod. Date/Code	2022.02.09/C552202012
样品编号 Sample No.	HC20220211706	规格 Specification	/
商标 Trademark	/	数量/重量 Quantity/Weight	50g
样品描述 Sample Desc.	袋装门冬氨酸鸟氨酸	生产商 Manufacturer	精晶药业股份有限公司
接收日期 Receiving Date	2022-02-28	检测日期 Testing Date	2022-02-28 至 2022-03-07
备注Notes	*项目不在CNAS认可范围内。		

报告编制人 Editor: 徐山九

批准人 Approved by:

审核人Verifier: 孙洪川

签发日期 Issuing Date: 2022-03-07

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第 1 页/共 2 页

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报告编号 Report ID: HC20220211706

检测结果 Test Results

序号 No.	检测项目 Testing Items		检测结果及单位 Result&Unit	检测方法 Testing Method
	英文 English	中文 Chinese		
1	Cadmium	镉	未检出(<0.002mg/kg)	GB 5009. 268-2016(第一法)
2	Lead	铅	未检出(<0.02mg/kg)	GB 5009. 268-2016(第一法)
3	Arsenic	砷	未检出(<0.002mg/kg)	GB 5009. 268-2016(第一法)
4	Mercury	汞	未检出(<0.001mg/kg)	GB 5009. 268-2016(第一法)
5	Cobalt	钴*	0.00137mg/kg	GB 5009. 268-2016(第一法)
6	Vanadium	钒*	0.00235mg/kg	GB 5009. 268-2016(第一法)
7	Nickel	镍	未检出(<0.2mg/kg)	GB 5009. 268-2016(第一法)
8	Chromium	铬	0.195mg/kg	GB 5009. 268-2016(第一法)
9	Copper	铜	未检出(<0.05mg/kg)	GB 5009. 268-2016(第一法)

*****报告结束 END*****



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成都实验室：成都市龙泉驿区(经开区)成龙大道二段1666号C3栋 028-88612161

Appendix 21: Incoming inspection report of plastic bags

精晶药业股份有限公司		编码: SOP-014-BCS023-Rev-02(00)	
精晶药业股份有限公司 包材检验报告			
编码: 2201B017-002J			
品名	塑料袋 (食品级)	物料编码	B017-2201002
批量	40000 条	请验日期	2022 年 01 月 15 日
包装规格	200 条/包	检验日期	2022 年 01 月 15 日
来源	河北正兴包装制品有限公司	报告日期	2022 年 01 月 21 日
检验目的	进厂检验	检验依据	企业内控
检验项目	检验标准	检验结果	单项判定
【尺寸】	长: 900mm±10 mm 宽: 600mm±10 mm 厚: 0.08mm±0.01mm	898mm-901mm 607mm-608mm 0.09mm-0.09mm	符合规定 符合规定 符合规定
【外观】	无明显水纹和云雾, 不得有气泡、穿孔及破裂, 无明显条纹。	无水纹和云雾, 无气泡、穿孔及破裂, 条纹不明显	符合规定
	杂质: >2mm 个/m ² 不允许有 0.3~0.6mm≤20 个	符合规定 符合规定	符合规定 符合规定
	分散度: ≤5 个/10cm×10cm	符合规定	符合规定
	平整度: 不允许有活褶, 无明显暴筋, 簇面卷绕基本整齐	无活褶, 无明显暴筋, 簇面卷绕基本整齐	符合规定
【微生物菌检】	需氧菌总数≤1000cfu/100c m ² 霉菌及酵母菌总数≤100cfu/ 100c m ² 大肠埃希菌 不得检出	0 0 未检出	符合规定 符合规定 符合规定
判定	按照企业内控标准检验, 结果符合规定。 		
质量负责人:	李素霞	检验人:	刘京梅
			复核人: 王小利

Appendix 22: Drum Inspection Report

精品药业股份有限公司		编码: SOP-012-BCS007-Rev-02 (01)			
纸桶检验报告					
编码: 2201B77-002J					
品名	纸桶	批号	B772201002	数量	195个
来源	赵县东明制桶有限公司		包装规格		
检验日期	2022年01月28日		报告日期	2022年01月28日	
检验目的	使用检验		复验期	2022年12月	
检验依据	STP-011-BCSS007				
检验项目	检验标准			检验结果	
规格尺寸	桶身: 400mm±3mm 内高: 550mm±3mm 外高: 570mm±4mm 重量: 3.15±0.3kg			401~403mm 550~552mm 571~573mm 3.08~3.10kg	
外观	纸桶应圆整, 无明显失圆、凹瘪、歪斜等缺陷和龟裂。 桶体光滑、无机械损伤、无皱褶、无开胶。油漆涂布均匀。 无漏漆、无泡、无明显流挂。 圆卷边无纸舌。 闭合后桶盖与桶体封闭良好。 桶身用进口箱板纸卷制。 桶体内外应清洁, 无杂质, 无油渍。			符合规定	
结论	本品依据STP-011-BCSS007检验, 结果符合规定。				


 质量检验专用章(2)

质控部经理: 李晓东 检验人: 牛晓东 复核人: 张海平