

## **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)  $25\pm 2^{\circ}\text{C}$ ,  $60\pm 10\%\text{RH}$

**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
			2022.02.19	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 °	28.0	--	--	--	--
	B. IR	Corresponding to STD	Conform	--	--	--	--
Purity	1) Clarity/Coloration	Clear, Colourless	Conform	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	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	1.1
	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	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	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	0.76
	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
			2022.02.19	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	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
	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	0.83
	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 2022.02.10	3 M 2022.05.20	6 M 2022.08.20	9 M 2022.11.23	12 M 2023.02.22	18M 2023.08.20	24 M	36 M
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 of 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.										

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

Test		Specification	Initial 2022.02.10	3 M 2022.05.20	6 M 2022.08.20	9 M 2022.11.23	12 M 2023.02.22	18M 2023.08.20	24 M	36 M
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 °	28.3	--	--	--	+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	--	--	--	6.2	--		
	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 %	0.66	1.20	1.10	1.0	0.77	1.3		
	10) Sulfated ash	≤ 0.2 %	0.03	--	--	--	0.02	--		
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 of 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	+26.5 ~ +29.0 °	28.3	--	--	--	+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 %	0.77	1.20	1.40	1.3	1.4	1.2		
	10) Sulfated ash	≤ 0.2 %	0.01	--	--	--	0.05	--		
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 of 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.										