3.2.S.3.2 Impurity

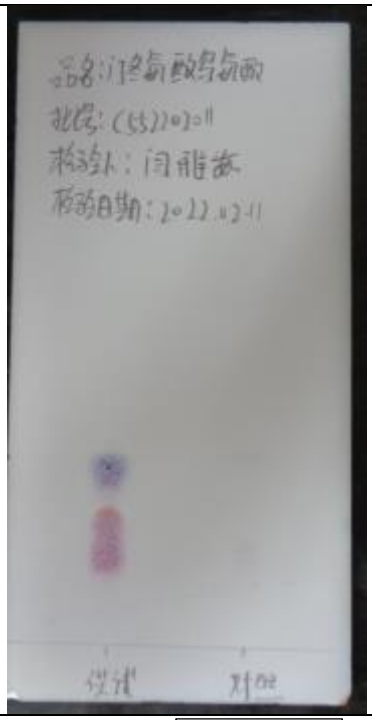
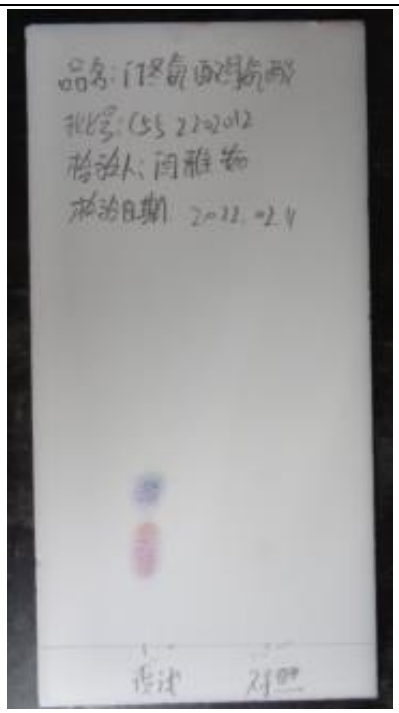
3.2.S.3.2.1 Relative substance

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 μL 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

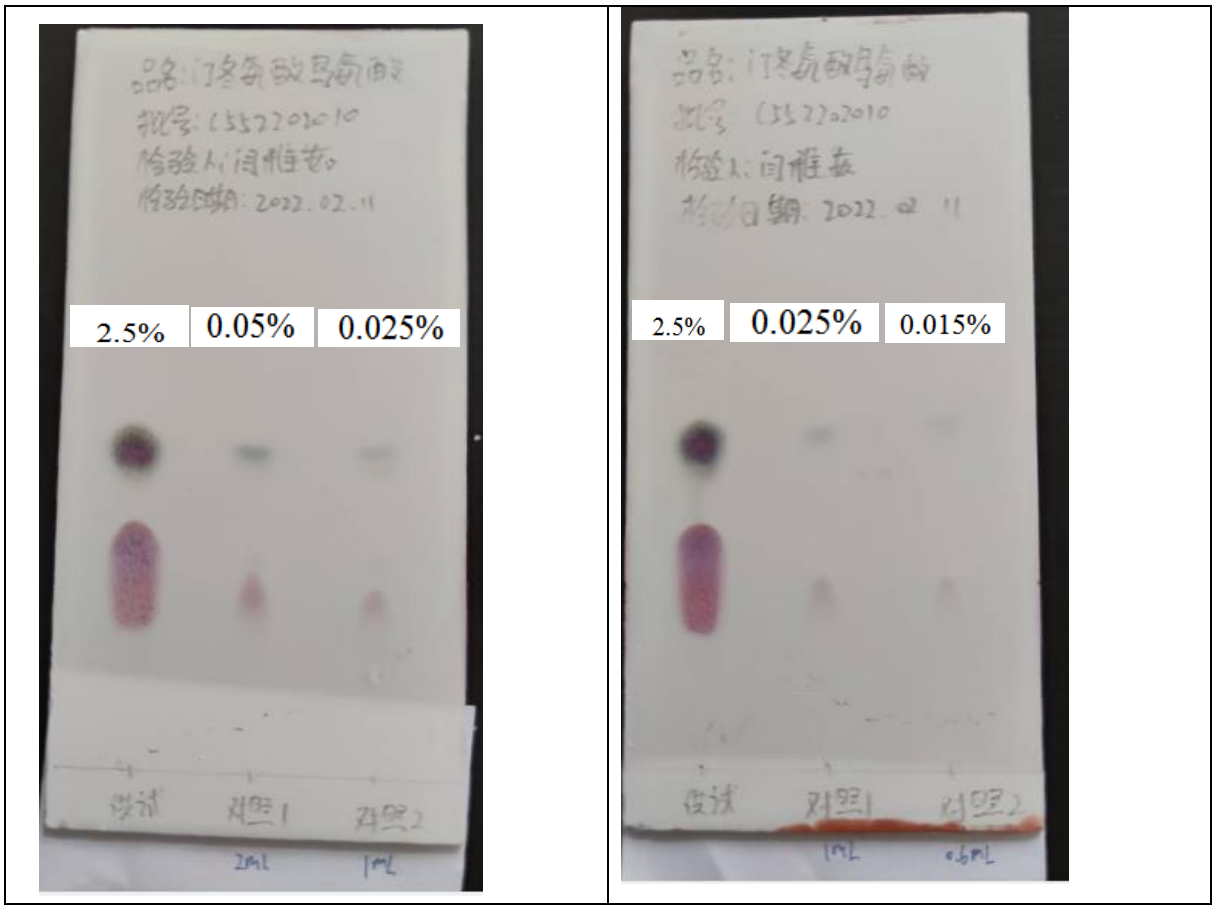
Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2g/day	0.05%	0.1%or1.0mg Per day intake (whichever is lower)	0.15% or 1.0mg Per day intake (whichever is lower)
＞ 2g/day	0.03%	0.05%	0.05%

[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.



sample solution	Standard solution (1ml)	sample solution	standard solution (1ml)	standard solution (0.6ml)

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 1CH 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 Administrauon/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.