.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: injection				
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	Yes	Absent

Sb	3	No	Yes	Absent
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
Fe	3	No	Equipment introduction	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	2	0.05	0.015
Pb	1	5	0.125	0.0375
As	1	15	0.375	0.1125
Hg	1	3	0.075	0.0225
Co	2A	5	0.125	0.0375
V	2A	10	0.25	0.075
Ni	2A	20	0.5	0.15
Li	3	250	6.25	1.875
Sb	3	90	2.25	0.675
Cu	3	300	7.5	2.25
Cr	3	1100	27.5	8.25
Fe	Other	500	12.5	3.75

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. 015	Not detected（＜0.002）	Not detected（＜0.002）	Not detected（＜0.002）
Pb	1	＜0. 0375	Not detected（＜0.02）	Not detected（＜0.02）	Not detected（＜0.02）
As	1	＜0. 1125	0.0078	Not detected（＜0.002）	Not detected（＜0.002）
Hg	1	＜0. 0225	Not detected（＜0.001）	Not detected（＜0.001）	Not detected（＜0.001）
Co	2A	＜0. 0375	0.00183	0.00147	0.00137
V	2A	＜0. 075	0.0022	0.0038	0.00235
Ni	2A	＜0. 15	0.0072	0.0062	0.0073
Li	3	＜1. 875	0.0016	0.0015	0.00014
Sb	3	＜0. 675	0.00047	0.00059	0.00059
Cu	3	＜2. 25	Not detected（＜0.05）	Not detected（＜0.05）	Not detected（＜0.05）
Cr	3	＜8. 25	0.0748	0.109	0.195
Fe	Other	＜3. 75	0.083	0.133	0.107

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.