Risk assessment on elemental impurities for Doxycycline Hyclate

We have performed a risk assessment on elemental impurities according to ICH Q3D guideline. For the drug substance, source may contribute elemental impurities come from manufacturing equipment, water, container closure system and intentionally added catalysts and inorganic reagents in the manufacturing process, etc.

1) Potential elemental impurities derived from intentionally added catalysts and inorganic reagents: Palladium is intentionally added in the manufacturing process.

2) Potential elemental impurities derived from manufacturing equipment made of stainless steel: main elemental in stainless steel are Ni, Co, V, Cu, Cr, Sb, Mn, Ti, Nb and Al. Equipment qualification and GMP controls ensure a low contribution form equipment. So Class 2A elemental impurities (Ni, Co, V) derive from equipment are considered in the risk assessment, class 3 and other elemental impurities (Cu, Cr, Sb, Mn, Ti, Nb, Al) are not considered in risk assessment.

3) Elemental impurities leached from container closure system: Considering Doxycycline hyclate drug substance and polyethylene bag are both solid, the probability of elemental leaching into drug substance is minimal, so further consideration in risk assessment is not required.

4) Elemental impurities derived from water: Potable water and purified water are both used in the manufacturing process, only purified water is used in the last step of synthesis, so elemental impurities in potable water is not considered in this risk assessment. Our purified water is comply with Chinese pharmacopeia and European pharmacopeia, the risk of inclusion of elemental impurities from water is reduced, so no further consideration is included in this risk assessment.

Base on above consideration, risk assessment summary is provided as below:

Intended route of administration/ Use of substance: Oral				
Element	Class	Intentionally added?	Considered in risk assessment?	Conclusion
Cd	**1**	**No**	**Yes**	≤ 30% of ICH Q3D option 1 limit
Pb	**1**	**No**	**Yes**	
As	**1**	**No**	**Yes**	
Hg	**1**	**No**	**Yes**	
Co	**2A**	**No**	**Yes**	≤ 30% of ICH Q3D option 1 limit
V	**2A**	**No**	**Yes**	
Ni	**2A**	**No**	**Yes**	
Ti	2B	No	No	/
Au	2B	No	No	/

Pd	2B	Yes	Yes	≤ 30% of ICH Q3D option 1 limit
Ir	2B	No	No	/
Os	2B	No	No	/
Rh	2B	No	No	/
Ru	2B	No	No	/
Se	2B	No	No	/
Ag	2B	No	No	/
Pt	2B	No	No	/
Li	3	No	No	/
Sb	3	No	No	/
Ba	3	No	No	/
Mo	3	No	No	/
Cu	3	No	No	/
Sn	3	No	No	/
Cr	3	No	No	/

Conclusion is based on test results of three commercial bathes of Doxycycline hyclate by ICP-MS, test method has been validated, and the validation report is in the site of Changzhou Pharmaceutical Factory. Detail test results are provided as below:

Batch No / Elemental	ED161008(μg/g)	ED170101 (μg/g)	ED170104 (μg/g)	Limit for option 1 in ICH Q3D (μg/g)	LOD (ng/g)	LOQ (ng/g)
Cd	N.D.	N.D.	N.D.	0.5	2.1	8.3
Pb	N.D.	N.D.	N.D.	0.5	3.5	14.0
As	0.03	N.D.	N.D.	1.5	91.3	365.2
Hg	N.D.	N.D.	N.D.	3	94.9	379.7
Co	N.D.	N.D.	N.D.	5	1.4	5.7
V	0.72	0.93	0.97	10	514.4	2057.4
Ni	N.D.	N.D.	N.D.	20	10.3	41.1
Pd	0.22	0.10	0.16	10	504.6	2018.3

All the elemental impurities level is below 30% of the calculated concentration limit based on the option1 (as per table A.2.2 of ICH Q3D guideline), so no control strategy is needed for these elemental impurities in Doxycycline hyclate.

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