Profiling Metal Content in Parenteral Grade Protein Stabilizers

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INTRODUCTION

Sucrose, Trehalose, Mannitol, and Maltose are four of the most commonly utilized carbohydrates for protein stabilization in drug formulations. As the demand for parenteral excipients continues to rise, the biopharma industry is considering guidance that would require more extensive analysis of a variety of minor constituents, including metals. Despite the high purity of many of these excipients, it is important for manufacturers to have an understanding of non-sugar moiety profiles and how they may vary with raw materials and processing. Herein, we present results of validated metal analysis performed on Pfanstiehl's injectable grade platform excipients. Specifically, multiple lots each of trehalose, sucrose, mannitol, and maltose were tested for levels of V, Cr, Mn, Fe, Ni, Cu, Zn, As, Mo, Ru, Rh, Pd, Cd, Os, Ir, Pt, Hg, and Pb. Observations from the data and proposed next steps are discussed.

MATERIALS & METHODS

For all assays, the parenteral grade carbohydrates (trehalose, sucrose, mannitol, maltose) used were manufactured by Pfanstiehl (Waukegan, IL USA). Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis was performed using a Thermo iCapQ ICP-MS instrument. Each 320-mg sample was diluted in 5% HNO_3 & 5% HCl prior to analysis. The peristaltic pump speed was 30rpm. Auto sampler rinse and wash were set to 90sec each. Additional method details can be provided upon request.

TABLE 1. TREHALOSE METALS PROFILE

Elements		V	Cr	Mn	Fe	Ni	Cu	Zn	As	Mo	Ru	Rh	Pd	Cd	Os	Ir	Pt	Hg	Pb
Limit (ppm)		1	2.5	25	130	2.5	10	130	0.15	1.0	1.0	1.0	1.0	0.25	1.0	1.0	1.0	0.15	0.5
Limit of Quantitation (ppm)		0.5	0.5	5	26	1	5	26	0.03	0.5	0.2	0.2	0.2	0.05	0.2	0.2	0.2	0.03	0.1
Trehalose	Lot 1	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	0.11	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 2	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 3	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 4	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 5	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 6	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 7	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 8	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 9	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 10	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1

TABLE 2. SUCROSE METALS PROFILE

Elements		V	Cr	Mn	Fe	Ni	Cu	Zn	As	Mo	Ru	Rh	Pd	Cd	Os	Ir	Pt	Hg	Pb
Limit (ppm)		1	2.5	25	130	2.5	10	130	0.15	1.0	1.0	1.0	1.0	0.25	1.0	1.0	1.0	0.15	0.5
Limit of Quantitation (ppm)		0.5	0.5	5	26	1	5	26	0.03	0.5	0.2	0.2	0.2	0.05	0.2	0.2	0.2	0.03	0.1
Sucrose	Lot 1	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 2	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 3	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 4	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 5	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 6	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 7	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 8	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 9	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1

TABLE 3. MANNITOL METALS PROFILE

Elements		V	Cr	Mn	Fe	Ni	Cu	Zn	As	Mo	Ru	Rh	Pd	Cd	Os	Ir	Pt	Hg	Pb
Limit (ppm)		1	2.5	25	130	2.5	10	130	0.15	1.0	1.0	1.0	1.0	0.25	1.0	1.0	1.0	0.15	0.5
Limit of Quantitation (ppm)		0.5	0.5	5	26	1	5	26	0.03	0.5	0.2	0.2	0.2	0.05	0.2	0.2	0.2	0.03	0.1
Mannitol	Lot 1	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	0.11	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 2	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 3	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1

TABLE 4. MALTOSE METALS PROFILE

Elements		V	Cr	Mn	Fe	Ni	Cu	Zn	As	Mo	Ru	Rh	Pd	Cd	Os	Ir	Pt	Hg	Pb
Limit (ppm)		1	2.5	25	130	2.5	10	130	0.15	1.0	1.0	1.0	1.0	0.25	1.0	1.0	1.0	0.15	0.5
Limit of Quantitation (ppm)		0.5	0.5	5	26	1	5	26	0.03	0.5	0.2	0.2	0.2	0.05	0.2	0.2	0.2	0.03	0.1
Maltose	Lot 1	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 2	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 3	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 4	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 5	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 6	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 7	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 8	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 9	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1
	Lot 10	<0.5	<0.5	<5	<26	<1	<5	<26	<0.03	<0.5	<0.2	<0.2	<0.2	<0.05	<0.2	<0.2	<0.2	<0.03	<0.1

RESULTS

The upper Limit was set as a harmonized limit based on the lower of the two levels suggested by the USP and/or EP. The data in each of the 4 tables illustrate that in all cases, these particular parenteral excipients have exceptionally low levels of the metals tested. In fact, there was only one instance in which a result was above the limit of quantitation. In that case, one lot of trehalose had a cadmium (Cd) level of 0.11ppm against a limit of quantitation of 0.05ppm and harmonized limit of 0.25ppm.

CONCLUSIONS

Given the very low levels of metals detected by these fully validated test methods, one can conclude that the materials assayed are unlikely to cause any safety concerns with respect to metal contribution. There is also virtually no risk of these particular excipients failing to pass metal limits proposed by USP/EP/ICH bodies in the future. This should provide a level of confidence for manufacturers and formulators using these excipients in existing processes and in pipeline development programs. The next step will be to try to correlate application data with these and other impurity profiles, and to map their impacts on formulation robustness and stability. At the very least, availability of such data should enable better decisions with respect to sourcing of critical raw materials for a variety of formulation applications, including media optimization, protein stabilization for liquid and lyophilized platforms, vaccine stabilization, and cell therapy. Pfanstiehl is actively developing more sensitive methods to quantitate trace metals and impurities in excipients well below existing industry standards.

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