

# Case Study

## Evaluation of a Drug Delivery System according to USP General Chapters <232> Elemental Impurities-Limits

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**CONFIDENTIAL**

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Please find enclosed the test results for samples described as:

1. *H<sub>2</sub>O Extraction of Bag*
2. *H<sub>2</sub>O Extraction of Filter*
3. *H<sub>2</sub>O Extraction of Tube*
4. *Saline (5 M) Extractions of Bag*
5. *Saline (5 M) Extractions of Filter*
6. *Saline (5 M) Extractions of Tube*
7. *Saline (5 M) Extractions of Assembled Bag-Filter-Tubing Device*
8. *H<sub>2</sub>O Blank*
9. *Saline (5 M) Blank*

The following test was performed:

1. Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)

## Objective

Nine (9) samples including three (3) H<sub>2</sub>O exactions, four (4) saline extractions and two (2) blanks (H<sub>2</sub>O and saline) were submitted for analyses by ICP-MS. ***The goal of this study was to determine the levels of elements identified as elemental impurities by USP General Chapters <232> Elemental Impurities-Limits in these extractions.***

## Summary of Results

The levels of twenty-four (24) elements identified as elemental impurities by *USP General Chapters <232> Elemental Impurities* were successfully determined by ICP-MS for both the water extractions and saline (5 M) extractions. Twenty-one (21) elements were detected in either H<sub>2</sub>O extraction samples or saline (5 M) extraction samples. A low level Detection Limit (DL) of 0.01 ng/mL (ppb) was achieved in the analyses.

## Individual Test Results

A summary of the individual test results is provided below. All accompanying data, including spectra, has been included in the data section of this report.

### ICP-MS

Nine (9) samples including seven (7) exaction samples and two (2) blank samples were analyzed using an Agilent 7900 ICP-MS. The samples consisted of H<sub>2</sub>O extractions of a Bag, Filters, and Tube; Saline (5 M) extractions of a Bag, Filters, and Tube and an assembled Bag-Filter-Tubing device; an H<sub>2</sub>O Blank; and a Saline Blank. The instrument was calibrated using Agilent multi-element prepared standards using 5.0% HNO<sub>3</sub>. The samples were diluted 1:10 with matrix matched 5.0% HNO<sub>3</sub> in a single analysis.

**Table 1** summarizes the results for all elements identified as elemental impurities for the risk assessment in accordance with USP General Chapters <232> Elemental Impurities-Limits. **Table 2** summarizes elements **detected** in samples which are identified as elemental impurities for the risk assessment in accordance with USP General Chapters <232> Elemental Impurities-Limits.

**Table 1**  
**ICP-MS Results for Elements to be Considered in the Risk Assessment<sup>1</sup>**  
**(ng/mL [ppb])**

Element Tested	Saline Extractions (10 x concentrated)					Water Extractions (10 x concentrated)			
	Filter	Tube	Bag	Device	Blank	Filter	Tube	Bag	Blank
Li	<DL <sup>2</sup>	<DL	<DL	<DL	<DL	<DL	<DL	<DL	<DL
V	0.048	0.012	0.021	0.026	0.015	0.007	<DL	<DL	<DL
Cr	0.076	0.049	0.043	<DL	0.039	0.029	<DL	<DL	<DL
Co	<DL	0.190	<DL	0.082	<DL	<DL	0.323	<DL	<DL
Ni	<DL	<DL	<DL	<DL	<DL	<DL	0.169	<DL	<DL
Cu	<DL	<DL	<DL	4.981	<DL	<DL	<DL	<DL	<DL
As	0.063	0.033	0.035	0.048	0.033	0.074	0.004	0.004	0.003
Se	0.014	<DL	<DL	<DL	<DL	<DL	<DL	<DL	<DL
Mo	0.243	0.184	0.173	0.227	0.201	0.009	0.011	<DL	0.007
Ru	0.000	0.000	0.000	0.001	0.001	0.000	0.000	0.000	0.000
Rh	0.003	<DL	0.001	0.001	<DL	0.001	<DL	<DL	<DL
Pd	0.002	0.002	0.002	0.002	0.001	0.002	0.001	0.001	<DL
Ag	2.431	2.742	1.637	0.261	0.063	0.260	0.047	0.144	0.028
Cd	<DL	0.009	0.005	<DL	<DL	<DL	0.017	0.011	<DL
Sn	0.019	0.024	0.022	<DL	<DL	<DL	<DL	<DL	<DL
Sb	105.496	0.042	1.052	0.260	0.013	20.267	0.007	<DL	<DL
Ba	0.307	0.311	0.588	0.016	0.302	0.199	0.057	0.102	<DL
Os	<DL	<DL	<DL	<DL	<DL	<DL	<DL	<DL	<DL
Ir	0.168	0.005	0.004	0.006	<DL	0.099	0.003	<DL	<DL
Pt	<DL	0.005	<DL	<DL	<DL	<DL	0.003	<DL	<DL
Au	0.028	0.022	0.020	0.035	0.011	0.015	0.022	0.011	0.012
Hg	0.024	0.017	0.012	0.023	0.004	0.012	0.012	0.012	0.007
Tl	<DL	<DL	<DL	<DL	<DL	<DL	<DL	<DL	<DL
Pb	0.010	0.022	0.024	0.085	0.015	<DL	0.013	0.027	<DL

<sup>1</sup>In accordance with USP General Chapters <232> Elemental Impurities-Limits

<sup>2</sup><DL= Below Detection Limit (0.01 ng/mL)

**Table 2**  
**ICP-MS Results Summary for Detected Elements**  
*(Levels < Detection Limit are shown in Blank)*

Sample	Extraction Solvent	V	Cr	Co	Ni	Cu	As	Se	Mo	Ru	Rh	Pd
Filter	Saline	X	X				X	X	X		X	X
	Water	X	X				X		X		X	X
Tube	Saline	X	X	X			X		X			X
	Water			X	X		X		X			X
Bag	Saline	X	X				X		X		X	X
	Water						X					X
Device	Saline	X		X		X	X		X	X	X	X
Sample	Extraction Solvent	Ag	Cd	Sn	Sb	Ba	Ir	Pt	Au	Hg	Pb	
Filter	Saline	X		X	X	X	X		X	X	X	
	Water	X			X	X	X		X	X		
Tube	Saline	X	X	X	X	X	X	X	X	X	X	
	Water	X	X		X	X	X	X	X	X	X	
Bag	Saline	X	X	X	X	X	X		X	X	X	
	Water	X	X			X			X	X	X	
Device	Saline	X			X	X	X		X	X	X	

# Analysis Conditions

## ICP-MS

Instrument: Agilent 7900 ICP-MS equipped with an Agilent SPS4 auto sampler.

### ICP-MS Conditions

Instrument	Agilent 7900 ICP-MS
Nebulizer	Micromist
Spray Chamber	Scott-type at 2 °C
Forward Power	1550 W
Sampling Depth	10 mm
Sampling Mode	He collision
Carrier Gas Flow Rate	1.03 L/min
Cell Gas Flow Rate	5.0 mL/min (He) 6.0 mL/min (H <sub>2</sub> )
KED Voltage	5.0 V (He) 3.0 V (H <sub>2</sub> )

### Calculated Detection Limits (ppb)

Mass	Name	MH DL	Calc DL	Mass	Name	MH DL	Calc DL	Mass	Name	MH DL	Calc DL
7	Li	0.22215	0.08388	60	Ni	0.00486	0.00199	137	Ba	0.00046	0.00039
9	Be	0.00000	0.00691	62	Ni	0.00365	0.00203	139	La	0.00005	0.00004
10	B	0.22760	0.39643	63	Cu	0.00235	0.00048	140	Ce	0.00008	0.00003
11	B	0.10713	0.19462	65	Cu	0.00133	0.00043	141	Pr	0.00003	0.00001
23	Na	0.08938	1.04746	66	Zn	0.02553	0.00515	146	Nd	0.00005	0.00007
24	Mg	0.00655	0.01127	69	Ga	0.00078	0.00017	147	Sm	0.00006	0.00002
26	Mg	0.02588	0.03600	71	Ga	0.00000	0.00017	157	Gd	0.00003	0.00002
27	Al	0.03023	0.02122	75	As	0.00007	0.00026	163	Dy	0.00002	0.00002
28	Si	4.58972	4.21094	77	Se	0.00000	0.01553	165	Ho	0.00001	0.00001
29	Si	6.22431	6.40883	77	Se	0.01290	0.00662	166	Er	0.00002	0.00003
31	P	1.53589	0.86923	78	Se	0.02619	0.02057	169	Tm	0.00002	0.00001
34	S	59.68298	205.81999	78	Se	0.00045	0.00014	172	Yb	0.00009	0.00007
39	K	0.05847	0.16713	80	Se	0.11203	0.21388	175	Lu	0.00130	0.00047
40	Ca	0.13407	0.00718	82	Se	0.12317	0.05629	178	Hf	0.00002	0.00006
42	Ca	0.21698	0.04237	82	Se	0.00285	0.00650	181	Ta	0.00001	0.00197
43	Ca	0.14149	0.05350	85	Rb	0.00023	0.00018	182	W	0.00007	0.00140
43	Ca	0.20596	0.02442	88	Sr	0.00112	0.00028	185	Re	0.00001	0.00001
44	Ca	0.03851	0.01518	90	Zr	0.00032	0.00025	191	Ir	0.00010	0.00055
44	Ca	0.12146	0.01032	93	Nb	0.00000	0.00023	193	Ir	0.00015	0.00058
47	Ti	0.01468	0.00440	95	Mo	0.00023	0.00069	194	Pt	0.00016	0.00006
48	Ti	0.00558	0.00163	97	Mo	0.00014	0.00104	195	Pt	0.00010	0.00009
51	V	0.00022	0.00014	101	Ru	0.00000	0.00005	197	Au	0.00001	0.00181
52	Cr	0.00043	0.00075	103	Rh	0.00002	0.00003	200	Hg	0.00001	0.00028
53	Cr	0.00116	0.00173	105	Pd	0.00002	0.00023	201	Hg	0.00003	0.00027
54	Fe	0.02520	0.00467	107	Ag	0.00017	0.00060	202	Hg	0.00003	0.00028
55	Mn	0.00208	0.00115	111	Cd	0.00004	0.00005	205	Tl	0.00019	0.00008
55	Mn	0.00131	0.00020	114	Cd	0.00012	0.00003	206	Pb	0.00010	0.00010
56	Fe	0.00409	0.00336	118	Sn	0.00045	0.00036	207	Pb	0.00027	0.00016
56	Fe	0.02245	0.00186	119	Sn	0.00059	0.00048	208	Pb	0.00026	0.00005
57	Fe	0.00762	0.01973	121	Sb	0.00016	0.00011	232	Th	0.00002	0.00002
57	Fe	0.02100	0.00300	123	Sb	0.00020	0.00015	238	U	0.00001	0.00001
59	Co	0.00027	0.00006	133	Cs	0.00004	0.00006				

## Closing Comments

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Sincerely,

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