Biotech

Technical Report

Characterization of Extractables from Gamma Irradiated HDPE Biocontainer Ports (Sample Report)

This sample report is intended to illustrate the type of information communicated in Pall USP <665> and BPOG extractables reports. This specific report is based on Pall Report VAL-AS-003177-ER(01) and additional laboratory studies since the report was published. Specific compound names and CAS numbers are omitted from this sample report, but can be found in the most current official version VAL-AS-003177-ER, available following completion of a confidentiality agreement.

Document Number:	VAL-AS-003177-SAMPLE
Revision Number:	00
Date	27-APR-2020
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Contents

1 Summary

HDPE ports are components of Pall single-use products such as 2D/3D biocontainers and mixers. This report summarizes the results from the extractables studies on HDPE biocontainer ports performed in accordance with published end-user recommendations[1] to support risk assessments of potential impurities that may migrate from process equipment into a fluid process stream. This extractables study is designed and intended to represent typical “worst-case” process conditions, which may exaggerate actual “in-process” or “final product” leachables.

Prior to extraction, the ports were gamma irradiated at 50 ± 5 kGy. Four ports were placed in a clean glass bottle, and extracted dynamically at approximately 1.8 cm^2/mL surface area to volume ratio with 6 different test fluids (Water, 5 M NaCl, 0.1 M H_3PO_4, 0.5 N NaOH, 50% Ethanol and 1% Polysorbate 80) and 4 incubation conditions (30 minutes at 25 ºC, 24 hours at 40 ºC, 21 days at 40 ºC and 70 days at 40 ºC). The general material properties of the ports and the extraction conditions employed in this study are summarized in Table 1**.**

Organic extractables analyses were performed on all samples by Direct injection GC/MS, Headspace GC/MS, and LC/PDA/MS (ESI+/-, APCI+/-), with a grand summary of these data shown in Table 2. All compounds detected at ≥ 0.1 µg/mL level are reported. Majority of the extractables detected were no more than 0.3 µg/cm^2. Extractables at > 0.3 µg/cm^2 include ICH Q3C Class 3 solvent 2-Propanol, antioxidant degradation products, fatty acids and their derivatives, a glycol related compound, and a siloxane degradation product. Bisphenol A (BPA) was not detected at all in any of the samples. Acetone, another ICH Q3C class 3 solvent, was also detected at < 0.2 µg/cm^2. All 7 day samples were assayed for 35 elemental impurities including all ICH Q3D elements by ICP/MS. Barium and Molybdenum were detected at no more than 0.020 µg/cm^2 but only in one of the two replicate Water extraction samples. A grand summary of the ICP/MS results is presented in Table 3.

The detailed summaries of the extractables data and assay parameters for all analytical methods are presented in Table 4 – Table 5 and Table 6 – Table 9**,** respectively. Biocontainer port and film surface areas for a wide range of Allegro™ biocontainer configurations, as well as example calculations for how worst-case levels of extractables may be expected to scale according to surface area are provided in the supplemental Appendices.

[1] Ding *et al.* “Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing,” *Pharmaceutical Engineering* Vol 34 No 6 (Nov/Dec 2014): 1-11.

2 Study Design

Table 1.

Material description and extraction conditions

Test article name	HPDE biocontainer ports	
Test article part number	619-31A (port)	
Number of lots tested	1	
Test article lot number(s)	S254M1-02, replicate extractions performed	
Extractables study number(s)	VAL-AS-003177	
Pretreatment of Test Article	**Variable(s)**	**Value(s)**
Gamma Irradiation		
Typical dose range during normal manufacturing	kGy	27 – 37
Received dose/dose range	kGy	48.3 – 50.2
Gamma date	DD-MMM-YYYY	16-DEC-2015 (70 day) 27-JAN-2016 (½ h, 24 h, 21 days)
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks)	Days	6 – 33
Pre-Flush		
Fluid identity, duration, temperature, volume	Name, min., °C, L	None
Test Article Extraction Conditions	**Value(s)**	
Description of extraction procedure	Four gamma irradiated HDPE biocontainer ports with a total fluid contact surface area of 274.3 cm^2 were placed in a clean 250 mL glass container (as shown above) and extracted dynamically using 150 mL solvent for a total surface area to volume ratio of 1.8 cm^2. The samples were agitated using an orbital shaker inside an incubator at approximately 100 rpm.	
Static or dynamic extraction	Dynamic	
Solvent start volume (mL)	150	
Solvent contact surface area (EFA for filter) (cm^2)	274.3	
Surface area to volume ratio (cm^2/mL)	1.83	
Extraction Solvents	**Included in Study**	**Average Solvent Loss (%)**
50% Ethanol	Yes	< 10%
0.5 N NaOH	Yes	< 10%
0.1 M H_3PO_4	Yes	< 10%
Water for injection (WFI)	Yes	< 10%
5 M NaCl	Yes	< 10%
1% Polysorbate 80 (PS80)	Yes	< 10%

Table 1. (Continued)

Time Points	Included in Study	Extraction Temperature (°C)
½ h	Yes	25
24 h	Yes	40
21 days	Yes	40
70 days	Yes	40
Analytical Methods	**Included in Study**	**Comment**
HS-GC-MS	Yes	Applied to all solvents
GC-MS	Yes	Applied to all solvents
LC-UV-MS ESI	Yes	Applied to all solvents
LC-UV-MS APCI	Yes	Applied to all solvents except 5 M NaCl
ICP-MS	Yes	Applied to all solvents
Others (NVR, TOC, pH)	Yes[1]	N/A
Supporting Information	**Variable(s)**	**Value(s)**
Material of construction	Contact	High Density Polyethylene (HDPE)

[1]*Non-compound-specific information may be included in laboratory study binder.*

3 Summary of Organic Extractables

Table 2.

Grand summary of organic extractables (ranked by abundance)

Solvent	Compound	CAS	ICH Q3C	RT (min)	ID Level	Standard Used for Quantification	Method and Detection Mode	Highest Result of All Lots Tested (µg/cm²)				LOD (µg/mL)	LOQ (µg/mL)
								½ h	24 h	21 days	70 days		
Water	Compound 1	XX-XX-X	3	7.38	Confirmed	Standard 1	HS GC/MS, TIC	<LOD	<LOD	<LOQ	0.194	0.038	0.126
Water	Compound 2	XX-XX-X	N/A	2.18	Confirmed	Standard 2	LC/PDA/MS, ES+, TIC	0.00692	0.193	0.0980	0.126	0.007	0.024
Water	Compound 3	XX-XX-X	N/A	8.78	Confirmed	Standard 3	HS GC/MS, TIC	<LOD	<LOD	<LOQ	<LOQ	0.205	0.685
Water	Compound 4	N/A	N/A	5.45	Unknown	Standard 4	LC/PDA/MS, ES+, TIC	<LOD	<LOD	<LOQ	<LOD	0.090	0.301
Water	None detected at ≥ 0.1 µg/mL	N/A	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	DI GC/MS	<LOD	<LOD	<LOD	<LOD	0.032 0.022	0.106 0.074
0.1 M H_3PO_4	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, 114.2	0.00998	0.225	0.112	0.0851	0.005	0.018
0.1 M H_3PO_4	Compound 4	N/A	N/A	5.45	Unknown	Standard 4	LC/PDA/MS, ES+, TIC	<LOD	<LOQ	0.144	<LOQ	0.077	0.256
0.1 M H_3PO_4	Compound 3	XX-XX-X	N/A	8.77	Confirmed	Standard 3	HS GC/MS, TIC	<LOD	<LOD	<LOQ	<LOQ	0.147	0.490
0.1 M H_3PO_4	None detected at ≥ 0.1 µg/mL	N/A	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	DI GC/MS, TIC	< LOD	< LOD	< LOD	< LOD	0.039 0.025	0.132 0.084
0.5 N NaOH	Compound 5	N/A	N/A	5.07	Confident	Standard 4 (ES+)	LC/PDA/MS, PDA	<LOD	<LOD	0.407	1.19	0.015	0.052
0.5 N NaOH	Compound 6	N/A	N/A	5.64	Confident	Standard 4 (ES+)	LC/PDA/MS, PDA	<LOD	<LOD	0.531	1.04	0.015	0.052
0.5 N NaOH	Compound 4	N/A	N/A	5.45	Unknown	Standard 4	LC/PDA/MS, ES+, TIC	<LOD	0.141	0.304	0.250	0.015	0.052
0.5 N NaOH	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, 114.2	<LOQ	0.0622	<LOD	<LOD	0.009	0.030
0.5 N NaOH	Compound 3	XX-XX-X	N/A	8.78	Confirmed	Standard 3	HS GC/MS, TIC	<LOD	<LOD	<LOQ	<LOQ	0.268	0.893
0.5 N NaOH	Compound 7	XX-XX-X	N/A	23.57	Tentative	Standard 3	HS GC/MS, TIC	<LOQ	<LOD	<LOD	<LOD	0.268	0.893
0.5 N NaOH	Compound 8	XX-XX-X	N/A	16.51	Confirmed	Standard 5	DI GC/MS, TIC	<LOD	<LOQ	<LOQ	<LOQ	0.039	0.129
5 M NaCl	Compound 3	XX-XX-X	N/A	8.74	Confirmed	Standard 3	HS GC/MS, TIC	<LOD	<LOD	0.280	<LOD	0.139	0.463
5 M NaCl	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, 114.2	<LOQ	0.116	0.0684	0.0811	0.009	0.030
5 M NaCl	None detected at ≥ 0.1 µg/mL	N/A	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	DI GC/MS, TIC	< LOD	< LOD	< LOD	< LOD	0.043 0.001	0.143 0.002
50% Ethanol	Compound 9	XX-XX-X	N/A	7.81	Confirmed	Standard 6	LC/PDA/MS, ES-, 255.4	<LOD	0.463	2.44	3.18	0.027	0.088
50% Ethanol	Compound 10	XX-XX-X	N/A	11.44	Confirmed	Standard 7	DI GC/MS, TIC	<LOQ	0.921	1.98	2.89	0.017	0.057
50% Ethanol	Compound 11	XX-XX-X	3	7.97	Confirmed	Standard 8	HS GC/MS, TIC	1.50	1.49	1.51	0.979	0.441	1.471
50% Ethanol	Compound 12	XX-XX-X	N/A	8.08	Confirmed	Standard 9	LC/PDA/MS, ES-, 283.4	<LOD	0.201	1.22	1.44	0.007	0.024
50% Ethanol	Compound 13	XX-XX-X	N/A	4.44	Tentative	Standard 10	DI GC/MS, TIC	0.854	0.724	1.23	0.667	0.080	0.266
50% Ethanol	Compound 14	XX-XX-X	N/A	4.05	Confident	Standard 10	DI GC/MS, TIC	1.05	0.668	0.640	0.666	0.080	0.266
50% Ethanol	Compound 8	XX-XX-X	N/A	16.50	Confirmed	Standard 5	DI GC/MS, TIC	0.00204	0.0977	0.332	0.546	0.0003	0.001
50% Ethanol	Compound 15	XX-XX-X	N/A	7.63	Confirmed	Standard 4	LC/PDA/MS, ES+, TIC	0.0337	0.0473	0.0511	0.101	0.015	0.051
50% Ethanol	Compound 16	XX-XX-X	N/A	8.72	Confident	Standard 11	LC/PDA/MS, ES+ 663.6	0.00214	0.0402	0.0723	0.0614	0.0004	0.001
50% Ethanol	Compound 17	XX-XX-X	N/A	20.38	Confirmed	Standard 12	HS GC/MS, TIC	<LOQ	<LOQ	<LOQ	<LOD	0.211	0.704
50% Ethanol	Compound 18	XX-XX-X	N/A	28.19	Confident	Standard 7	HS GC/MS, TIC	<LOD	<LOD	<LOQ	<LOQ	0.053	0.178

Table 2. (Continued)

Solvent	Compound	CAS	ICH Q3C	RT (min)	ID Level	Standard Used for Quantification	Method and Detection Mode	Highest Result of All Lots Tested (µg/cm²)				LOD (µg/mL)	LOQ (µg/mL)
								½ h	24 h	21 days	70 days		
1% PS80	Compound 19*	XX-XX-X	N/A	12.84	Tentative	Standard 5	DI GC/MS, TIC	0.267	<LOQ	0.899	0.308	0.081	0.269
1% PS80	Compound 10	XX-XX-X	N/A	32.61	Confirmed	Standard 7	HS GC/MS, TIC	<LOQ	0.300	0.886	0.802	0.012	0.038
1% PS80	Compound 20	XX-XX-X	N/A	10.41	Tentative	Standard 13	DI GC/MS, TIC	0.121	<LOQ	0.459	<LOD	0.024	0.079
1% PS80	Compound 21*	XX-XX-X	N/A	24.31	Tentative	Standard 13	DI GC/MS, TIC	0.173	0.250	0.189	0.432	0.024	0.079
1% PS80	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, TIC	0.129	0.288	0.276	0.241	0.068	0.227
1% PS80	Compound 22	XX-XX-X	N/A	7.65	Tentative	Standard 14	DI GC/MS, TIC	0.122	0.0645	0.266	<LOQ	0.028	0.094
1% PS80	Compound 23*	XX-XX-X	N/A	22.90	Tentative	Standard 13	DI GC/MS, TIC	<LOQ	<LOQ	0.262	0.105	0.024	0.079
1% PS80	Compound 24*	XX-XX-X	N/A	23.44	Tentative	Standard 13	DI GC/MS, TIC	0.248	0.159	<LOQ	0.0843	0.024	0.079
1% PS80	Compound 25	XX-XX-X	N/A	14.91	Confirmed	Standard 15	DI GC/MS, TIC	<LOQ	0.0602	0.185	0.106	0.029	0.095
1% PS80	Compound 26	XX-XX-X	N/A	30.85	Confirmed	Standard 16	HS GC/MS, TIC	<LOQ	0.0561	0.101	0.0787	0.009	0.029
1% PS80	Compound 27*	XX-XX-X	N/A	31.45	Tentative	Standard 17	HS GC/MS, TIC	0.0535	0.0113	0.0371	0.0214	0.005	0.015

The worst-case results for each extractable are based on the total amount of that extractable from all time points (i.e. Total = Amount ½ h + Amount 24 h + Amount 21 days + Amount 70 days), whichever is higher between the two lots.

** PS80 degradation product*

4 Summary of Elemental Extractables

Table 3.

Grand summary of elemental impurities (ranked per ICH Q3D classification)

Element		ICH Q3D Class	Highest Result of All Lots Tested (µg/cm²) (70 days)					
			Water	0.1 M H_3PO_4	0.5 N NaOH	5 M NaCl	50% Ethanol	1% PS80
Cadmium	Cd	1	-	-	-	-	-	-
Lead	Pb	1	-	-	-	-	-	-
Arsenic	As	1	-	-	-	-	-	-
Mercury	Hg	1	-	-	-	-	-	-
Cobalt	Co	2A	-	-	-	-	-	-
Vanadium	V	2A	-	-	-	-	-	-
Nickel	Ni	2A	-	-	-	-	-	-
Thallium	Tl	2B	-	-	-	-	-	-
Gold	Au	2B	-	-	-	-	-	-
Palladium	Pd	2B	-	-	-	-	-	-
Iridium	Ir	2B	-	-	-	-	-	-
Osmium	Os	2B	-	-	-	-	-	-
Rhodium	Rh	2B	-	-	-	-	-	-
Ruthenium	Ru	2B	-	-	-	-	-	-
Selenium	Se	2B	-	-	-	-	-	-
Silver	Ag	2B	-	-	-	-	-	-
Platinum	Pt	2B	-	-	-	-	-	-
Lithium	Li	3	-	-	-	-	-	-
Antimony	Sb	3	-	-	-	-	-	-
Barium	Ba	3	0.020	-	-	-	-	-
Molybdenum	Mo	3	0.018	-	-	-	-	-
Copper	Cu	3	-	-	-	-	-	-
Tin	Sn	3	-	-	-	-	-	-
Chromium	Cr	3	-	-	-	-	-	-
Boron	B	N/A	0.029	-	-	-	-	-
Sodium	Na	N/A	1.288	0.017	N/A	N/A	-	0.031
Tungsten	W	N/A	-	-	-	-	-	-
Magnesium	Mg	N/A	0.055	-	-	-	-	-
Aluminum	Al	N/A	-	-	0.012	-	-	-
Calcium	Ca	N/A	0.201	-	-	-	-	-
Titanium	Ti	N/A	-	-	-	-	-	-
Manganese	Mn	N/A	-	-	-	-	-	-
Iron	Fe	N/A	-	-	-	-	-	-
Zinc	Zn	N/A	-	-	-	-	-	-
Potassium	K	N/A	0.027	-	-	-	-	-

"-" indicates < 20 ppb; N/A – not analyzed due to interference

5 Detailed Results

Table 4.

Detailed summary of organic extractables

Solvent	Compound	CAS	ICH Q3C	RT (min)	ID Level	Standard Used for Quantification	Method and Detection Mode	S254M1-02 Set 1 (µg/mL)				S254M1-02 Set 2 (µg/mL)				LOD (µg/mL)	LOQ (µg/mL)
								½ h	24 h	21 days	70 days	½ h	24 h	21 days	70 days		
Water	Compound 2	XX-XX-X	N/A	2.18	Confirmed	Standard 2	LC/PDA/MS, TIC	0.013	0.353	0.179	0.230	0.012	0.221	0.139	0.246	0.007	0.024
Water	Compound 4	N/A	N/A	5.45	Unknown	Standard 4	LC/PDA/MS, TIC	<0.090	<0.09	<0.301	<0.090	<0.090	<0.090	<0.301	<0.090	0.090	0.301
Water	None Detected	N/A	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	DI GC/MS, TIC	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.032 0.022	0.106 0.074
Water	Compound 1	XX-XX-X	3	7.38	Confirmed	Standard 1	HS GC/MS, TIC	<0.038	<0.038	0.132	<0.126	<0.038	<0.038	<0.126	0.354	0.038	0.126
Water	Compound 3	XX-XX-X	N/A	8.78	Confirmed	Standard 3	HS GC/MS, TIC	<0.205	<0.205	<0.685	<0.685	<0.205	<0.205	<0.685	<0.685	0.205	0.685
0.1 M H_3PO_4	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, 114.2	0.018	0.412	0.205	0.156	<0.018	0.267	0.200	0.155	0.005	0.018
0.1 M H_3PO_4	Compound 4	N/A	N/A	5.45	Unknown	Standard 4	LC/PDA/MS, TIC	<0.077	<0.256	<0.256	<0.256	<0.077	<0.256	0.264	<0.256	0.077	0.256
0.1 M H_3PO_4	None Detected	N/A	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	DI GC/MS, TIC	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.039 0.025	0.132 0.084
0.1 M H_3PO_4	Compound 3	XX-XX-X	N/A	8.77	Confirmed	Standard 3	HS GC/MS, TIC	<0.147	<0.147	<0.490	<0.490	<0.147	<0.147	<0.490	<0.490	0.147	0.490
0.5 N NaOH	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, 114.2	<0.009	0.094	<0.009	<0.009	<0.03	0.114	<0.009	<0.009	0.009	0.030
0.5 N NaOH	Compound 5	N/A	N/A	5.07	Confident	Standard 4 (ES+)	LC/PDA/MS, PDA; ES+, TIC	<0.015	<0.015	0.744	2.175	<0.015	<0.015	0.920	1.834	0.015	0.052
0.5 N NaOH	Compound 4	N/A	N/A	5.45	Unknown	Standard 4	LC/PDA/MS, ES+, TIC	<0.015	0.293	0.533	0.426	<0.015	0.258	0.557	0.457	0.015	0.052
0.5 N NaOH	Compound 6	N/A	N/A	5.64	Confident	Standard 4 (ES+)	LC/PDA/MS, PDA; ES+, TIC	<0.015	<0.015	0.972	1.902	<0.015	<0.015	0.859	1.949	0.015	0.052
0.5 N NaOH	Compound 8	XX-XX-X	N/A	16.51	Confirmed	Standard 5	DI GC/MS, TIC	<0.039	<0.129	<0.129	<0.129	<0.039	<0.129	<0.129	<0.129	0.039	0.129
0.5 N NaOH	Compound 3	XX-XX-X	N/A	8.78	Confirmed	Standard 3	HS GC/MS, TIC	<0.268	<0.268	<0.893	<0.893	<0.268	<0.268	<0.893	<0.893	0.268	0.893
0.5 N NaOH	Compound 7	XX-XX-X	N/A	23.57	Tentative	Standard 3	HS GC/MS, TIC	<0.268	<0.268	<0.268	<0.268	<0.893	<0.268	<0.268	<0.268	0.268	0.893
5 M NaCl	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, 114.2	<0.030	0.213	0.125	0.148	<0.009	0.136	0.126	0.221	0.009	0.030
5 M NaCl	None Detected	N/A	N/A	N/A	N/A	*n*-Decane, 2,4-Di-*tert*-butylphenol	DI GC/MS, TIC	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.043 0.001	0.143 0.002
5 M NaCl	Compound 3	75-65-0	N/A	8.74	Confirmed	Compound 3	HS GC/MS, TIC	<0.139	<0.139	0.513	<0.139	<0.139	<0.139	0.495	<0.139	0.139	0.463
50% Ethanol	Compound 15	N/A	N/A	7.63	Confirmed	Standard 4	LC/PDA/MS, ES+, TIC	<0.051	0.053	0.092	0.136	0.062	0.086	0.094	0.185	0.015	0.051
50% Ethanol	Compound 9	XX-XX-X	N/A	7.81	Confirmed	Standard 6	LC/PDA/MS, ES-, 255.4	<0.027	0.846	4.456	5.806	<0.027	0.785	4.076	5.671	0.027	0.088
50% Ethanol	Compound 12	XX-XX-X	N/A	8.08	Confirmed	Standard 9	LC/PDA/MS, ES- 283.4	<0.007	0.368	2.232	2.630	<0.007	0.416	1.897	2.424	0.007	0.024
50% Ethanol	Compound 16	XX-XX-X	N/A	8.72	Confident	Standard 11	LC/PDA/MS, ES+, 663.6	0.003	0.078	0.118	0.112	0.004	0.073	0.132	0.112	0.0004	0.001
50% Ethanol	Compound 14	XX-XX-X	N/A	4.05	Confident	Standard 10	DI GC/MS, TIC	1.916	1.222	1.170	1.219	0.929	1.793	1.268	1.377	0.080	0.266
50% Ethanol	Compound 13	XX-XX-X	N/A	4.44	Tentative	Standard 10	DI GC/MS, TIC	1.169	1.729	1.505	1.420	1.562	1.323	2.245	1.219	0.080	0.266
50% Ethanol	Compound 10	XX-XX-X	N/A	11.44	Confirmed	Stanard 7	DI GC/MS, TIC	<0.057	1.684	3.613	5.285	<0.057	1.524	3.939	4.537	0.017	0.057
50% Ethanol	Compound 8	XX-XX-X	N/A	16.50	Confirmed	Standard 5	DI GC/MS, TIC	0.006	0.188	0.630	0.933	0.004	0.179	0.606	0.999	0.0003	0.001
50% Ethanol	Compound 11	XX-XX-X	3	7.97	Confirmed	Standard 8	HS GC/MS, TIC	2.448	2.761	2.208	1.880	2.751	2.723	2.756	1.790	0.441	1.471
50% Ethanol	Compound 17	XX-XX-X	N/A	20.38	Confirmed	Standard 12	HS GC/MS, TIC	<0.704	<0.704	<0.704	<0.211	<0.704	<0.704	<0.704	<0.211	0.211	0.704
50% Ethanol	Compound 18	XX-XX-X	N/A	28.19	Confident	Standard 7	HS GC/MS, TIC	<0.053	<0.053	<0.178	<0.178	<0.053	<0.053	<0.178	<0.178	0.053	0.178

Table 4. (Continued)

Solvent	Compound	CAS	ICH Q3C	RT (min)	ID Level	Standard Used for Quantification	Method and Detection Mode	S254M1-02 Set 1 (µg/mL)				S254M1-02 Set 2 (µg/mL)				LOD (µg/mL)	LOQ (µg/mL)
								½ h	24 h	21 days	70 days	½ h	24 h	21 days	70 days		
1% PS80	Compound 2	XX-XX-X	N/A	2.17	Confirmed	Standard 2	LC/PDA/MS, ES+, TIC	0.236	0.527	0.504	0.441	0.263	0.410	0.504	0.394	0.068	0.227
1% PS80	Compound 22	XX-XX-X	N/A	7.65	Tentative	Standard 14	DI GC/MS, TIC	0.224	0.118	0.487	<0.094	0.168	0.133	0.487	<0.094	0.028	0.094
1% PS80	Compound 20	XX-XX-X	N/A	10.41	Tentative	Standard 13	DI GC/MS, TIC	0.222	<0.079	0.840	<0.024	0.109	<0.079	0.840	<0.024	0.024	0.079
1% PS80	Compound 19*	XX-XX-X	N/A	12.84	Tentative	Standard 5	DI GC/MS, TIC	0.487	<0.269	1.644	0.563	0.294	<0.269	1.644	0.359	0.081	0.269
1% PS80	Compound 25	XX-XX-X	N/A	14.91	Confirmed	Standard 15	DI GC/MS, TIC	<0.095	0.110	0.339	0.194	<0.095	0.114	0.339	0.129	0.029	0.095
1% PS80	Compound 23*	XX-XX-X	N/A	22.90	Tentative	Standard 13	DI GC/MS, TIC	<0.079	<0.079	0.479	0.192	<0.024	<0.079	0.479	<0.024	0.024	0.079
1% PS80	Compound 24*	XX-XX-X	N/A	23.44	Tentative	Standard 13	DI GC/MS, TIC	0.300	0.284	<0.079	0.157	0.454	0.290	<0.079	0.154	0.024	0.079
1% PS80	Compound 21*	XX-XX-X	N/A	24.31	Tentative	Standard 13	DI GC/MS, TIC	0.316	0.458	0.346	0.790	0.581	0.343	0.346	0.521	0.024	0.079
1% PS80	Compound 26	XX-XX-X	N/A	30.85	Confirmed	Standard 16	HS GC/MS, TIC	<0.029	0.096	0.089	0.142	<0.029	0.103	0.185	0.144	0.009	0.029
1% PS80	Compound 27*	XX-XX-X	N/A	31.45	Tentative	Standard 17	HS GC/MS, TIC	0.100	0.034	0.036	0.031	0.098	0.021	0.068	0.039	0.005	0.015
1% PS80	Compound 10	XX-XX-X	N/A	32.61	Confirmed	Standard 7	HS GC/MS, TIC	<0.038	0.577	0.487	1.451	<0.038	0.548	1.620	1.466	0.012	0.038

Compounds less than LOD or LOQ are reported as "<" the actual LOD/LOQ value of the relevant standard.

** PS80 degradation product*

Table 5.

Detailed summary of elemental impurities

Solvent	Element		ICH Q3D Class	LOD[a] (ppb)	LOQ[a] (ppb)	S254M1-02 Set 1 (ppb) 70 days	S254M1-02 Set 2 (ppb) 70 days
Water	Cadmium	Cd	1	0.007	0.023	0.087	<LOD
Water	Lead	Pb	1	0.001	0.003	0.102	<LOD
Water	Arsenic	As	1	0.025	0.082	1.768	1.092
Water	Mercury	Hg	1	0.015	0.049	<LOD	<LOD
Water	Cobalt	Co	2A	0.004	0.012	<LOQ	<LOD
Water	Vanadium	V	2A	0.005	0.017	0.029	<LOD
Water	Nickel	Ni	2A	0.015	0.050	0.061	<LOD
Water	Thallium	Tl	2B	0.0001	0.0004	<LOD	<LOD
Water	Gold	Au	2B	0.001	0.004	0.019	0.010
Water	Palladium	Pd	2B	0.004	0.013	<LOD	<LOD
Water	Iridium	Ir	2B	0.001	0.002	<LOD	<LOD
Water	Osmium	Os	2B	0.001	0.002	<LOD	<LOD
Water	Rhodium	Rh	2B	0.0002	0.001	<LOD	<LOD
Water	Ruthenium	Ru	2B	0.002	0.006	<LOD	<LOD
Water	Selenium	Se	2B	0.033	0.111	8.220	5.620
Water	Silver	Ag	2B	0.002	0.007	<LOD	<LOD
Water	Platinum	Pt	2B	0.002	0.007	<LOD	<LOD
Water	Lithium	Li	3	0.005	0.016	0.442	<LOD
Water	Antimony	Sb	3	0.001	0.005	0.353	0.051
Water	Barium	Ba	3	0.003	0.011	35.992	17.631
Water	Molybdenum	Mo	3	0.004	0.014	32.231	3.965
Water	Copper	Cu	3	0.006	0.019	0.848	0.263
Water	Tin	Sn	3	0.025	0.083	<LOD	<LOD
Water	Chromium	Cr	3	0.052	0.174	<LOD	<LOD
Water	Boron	B	N/A	0.004	0.013	53.283	36.291
Water	Sodium	Na	N/A	0.036	0.119	2356	191
Water	Tungsten	W	N/A	0.003	0.009	0.037	<LOD
Water	Magnesium	Mg	N/A	0.029	0.098	101	42.817
Water	Aluminum	Al	N/A	0.027	0.089	10.583	0.417
Water	Calcium	Ca	N/A	0.010	0.033	367	184
Water	Titanium	Ti	N/A	0.024	0.081	0.291	<LOD
Water	Manganese	Mn	N/A	0.019	0.064	1.611	0.579
Water	Iron	Fe	N/A	0.066	0.220	5.900	<LOD
Water	Zinc	Zn	N/A	0.059	0.197	8.417	0.710
Water	Potassium	K	N/A	0.061	0.203	49.803	38.684

[a] Instrument LOD and LOQ. Elements less than LOD or LOQ are reported as "<" the instrument LOD/LOQ value of the relevant standard. For risk assessment of elements reported at < LOD or < LOQ, values can be used "as is" as there was no dilution during sample preparation.

Table 5. (Continued)

Solvent	Element		ICH Q3D Class	LOD[a] (ppb)	LOQ[a] (ppb)	S254M1-02 Set 1 (ppb) 70 days	S254M1-02 Set 2 (ppb) 70 days
0.1 M H_3PO_4	Cadmium	Cd	1	0.007	0.023	0.003	0.001
0.1 M H_3PO_4	Lead	Pb	1	0.001	0.003	<LOD	<LOD
0.1 M H_3PO_4	Arsenic	As	1	0.025	0.082	<LOD	0.103
0.1 M H_3PO_4	Mercury	Hg	1	0.015	0.049	<LOD	<LOD
0.1 M H_3PO_4	Cobalt	Co	2A	0.004	0.012	<LOD	<LOD
0.1 M H_3PO_4	Vanadium	V	2A	0.005	0.017	<LOD	<LOD
0.1 M H_3PO_4	Nickel	Ni	2A	0.015	0.050	<LOD	0.006
0.1 M H_3PO_4	Thallium	Tl	2B	0.0001	0.0004	<LOD	<LOD
0.1 M H_3PO_4	Gold	Au	2B	0.001	0.004	<LOD	<LOD
0.1 M H_3PO_4	Palladium	Pd	2B	0.004	0.013	<LOD	<LOD
0.1 M H_3PO_4	Iridium	Ir	2B	0.001	0.002	<LOD	<LOD
0.1 M H_3PO_4	Osmium	Os	2B	0.001	0.002	0.994	<LOD
0.1 M H_3PO_4	Rhodium	Rh	2B	0.0002	0.001	<LOD	<LOD
0.1 M H_3PO_4	Ruthenium	Ru	2B	0.002	0.006	<LOD	<LOD
0.1 M H_3PO_4	Selenium	Se	2B	0.033	0.111	<LOD	<LOD
0.1 M H_3PO_4	Silver	Ag	2B	0.002	0.007	<LOD	<LOD
0.1 M H_3PO_4	Platinum	Pt	2B	0.002	0.007	<LOD	<LOD
0.1 M H_3PO_4	Lithium	Li	3	0.005	0.016	0.003	0.002
0.1 M H_3PO_4	Antimony	Sb	3	0.001	0.005	<LOD	<LOD
0.1 M H_3PO_4	Barium	Ba	3	0.003	0.011	0.044	0.436
0.1 M H_3PO_4	Molybdenum	Mo	3	0.004	0.014	0.049	0.055
0.1 M H_3PO_4	Copper	Cu	3	0.006	0.019	<LOD	<LOD
0.1 M H_3PO_4	Tin	Sn	3	0.025	0.083	0.003	<LOD
0.1 M H_3PO_4	Chromium	Cr	3	0.052	0.174	0.002	0.003
0.1 M H_3PO_4	Boron	B	N/A	0.004	0.013	<LOD	0.160
0.1 M H_3PO_4	Sodium	Na	N/A	0.036	0.119	11.100	30.800
0.1 M H_3PO_4	Tungsten	W	N/A	0.003	0.009	<LOD	<LOD
0.1 M H_3PO_4	Magnesium	Mg	N/A	0.029	0.098	<LOD	1.200
0.1 M H_3PO_4	Aluminum	Al	N/A	0.027	0.089	<LOD	0.337
0.1 M H_3PO_4	Calcium	Ca	N/A	0.010	0.033	<LOD	2.430
0.1 M H_3PO_4	Titanium	Ti	N/A	0.024	0.081	<LOD	<LOD
0.1 M H_3PO_4	Manganese	Mn	N/A	0.019	0.064	<LOD	0.002
0.1 M H_3PO_4	Iron	Fe	N/A	0.066	0.220	<LOD	<LOD
0.1 M H_3PO_4	Zinc	Zn	N/A	0.059	0.197	<LOD	<LOD
0.1 M H_3PO_4	Potassium	K	N/A	0.061	0.203	0.036	0.365

[a] Instrument LOD and LOQ. Elements less than LOD or LOQ are reported as "<" the instrument LOD/LOQ value of the relevant standard. For risk assessment of elements reported at < LOD or < LOQ, values can be used "as is" as there was no dilution during sample preparation.

Table 5. (Continued)

Solvent	Element		ICH Q3D Class	LOD[a] (ppb)	LOQ[a] (ppb)	S254M1-02 Set 1 (ppb) 70 days	S254M1-02 Set 2 (ppb) 70 days
0.5 N NaOH	Cadmium	Cd	1	0.007	0.023	<LOD	<LOD
0.5 N NaOH	Lead	Pb	1	0.001	0.003	<LOD	<LOD
0.5 N NaOH	Arsenic	As	1	0.025	0.082	0.275	<LOD
0.5 N NaOH	Mercury	Hg	1	0.015	0.049	0.019	<LOD
0.5 N NaOH	Cobalt	Co	2A	0.004	0.012	<LOD	<LOD
0.5 N NaOH	Vanadium	V	2A	0.005	0.017	<LOD	<LOD
0.5 N NaOH	Nickel	Ni	2A	0.015	0.05	<LOD	<LOD
0.5 N NaOH	Thallium	Tl	2B	0.0001	0.0004	<LOD	<LOD
0.5 N NaOH	Gold	Au	2B	0.001	0.004	0.002	<LOD
0.5 N NaOH	Palladium	Pd	2B	0.004	0.013	<LOD	<LOD
0.5 N NaOH	Iridium	Ir	2B	0.001	0.002	<LOD	<LOD
0.5 N NaOH	Osmium	Os	2B	0.001	0.002	<LOD	<LOD
0.5 N NaOH	Rhodium	Rh	2B	0.0002	0.001	<LOD	<LOD
0.5 N NaOH	Ruthenium	Ru	2B	0.002	0.006	<LOD	<LOD
0.5 N NaOH	Selenium	Se	2B	0.033	0.111	<LOD	<LOD
0.5 N NaOH	Silver	Ag	2B	0.002	0.007	<LOD	<LOD
0.5 N NaOH	Platinum	Pt	2B	0.002	0.007	<LOD	<LOD
0.5 N NaOH	Lithium	Li	3	0.005	0.016	<LOD	<LOD
0.5 N NaOH	Antimony	Sb	3	0.001	0.005	0.153	<LOD
0.5 N NaOH	Barium	Ba	3	0.003	0.011	3.500	<LOD
0.5 N NaOH	Molybdenum	Mo	3	0.004	0.014	0.105	<LOD
0.5 N NaOH	Copper	Cu	3	0.006	0.019	0.006	<LOD
0.5 N NaOH	Tin	Sn	3	0.025	0.083	<LOD	<LOD
0.5 N NaOH	Chromium	Cr	3	0.052	0.174	<LOD	<LOD
0.5 N NaOH	Boron	B	N/A	0.004	0.013	15.100	<LOD
0.5 N NaOH	Sodium	Na	N/A	0.036	0.119	<LOD	<LOD
0.5 N NaOH	Tungsten	W	N/A	0.003	0.009	0.002	<LOD
0.5 N NaOH	Magnesium	Mg	N/A	0.029	0.098	3.340	<LOD
0.5 N NaOH	Aluminum	Al	N/A	0.027	0.089	22.400	<LOD
0.5 N NaOH	Calcium	Ca	N/A	0.01	0.033	0.651	<LOD
0.5 N NaOH	Titanium	Ti	N/A	0.024	0.081	0.024	<LOD
0.5 N NaOH	Manganese	Mn	N/A	0.019	0.064	<LOD	<LOD
0.5 N NaOH	Iron	Fe	N/A	0.066	0.22	0.066	<LOD
0.5 N NaOH	Zinc	Zn	N/A	0.059	0.197	0.533	<LOD
0.5 N NaOH	Potassium	K	N/A	0.061	0.203	15.200	<LOD

[a] Instrument LOD and LOQ. Elements less than LOD or LOQ are reported as "<" the instrument LOD/LOQ value of the relevant standard. For risk assessment of elements reported at < LOD or < LOQ, values can be used "as is" as there was no dilution during sample preparation.

Table 5. (Continued)

Solvent	Element		ICH Q3D Class	LOD[a] (ppb)	LOQ[a] (ppb)	S254M1-02 Set 1 (ppb) 70 days	S254M1-02 Set 2 (ppb) 70 days
5 M NaCl	Cadmium	Cd	1	0.007	0.023	<LOD	<LOD
5 M NaCl	Lead	Pb	1	0.001	0.003	0.045	<LOD
5 M NaCl	Arsenic	As	1	0.025	0.082	<LOD	<LOD
5 M NaCl	Mercury	Hg	1	0.015	0.049	<LOD	<LOD
5 M NaCl	Cobalt	Co	2A	0.004	0.012	<LOD	<LOD
5 M NaCl	Vanadium	V	2A	0.005	0.017	<LOD	<LOD
5 M NaCl	Nickel	Ni	2A	0.015	0.05	<LOD	<LOD
5 M NaCl	Thallium	Tl	2B	0.0001	0.0004	<LOD	<LOD
5 M NaCl	Gold	Au	2B	0.001	0.004	<LOD	<LOD
5 M NaCl	Palladium	Pd	2B	0.004	0.013	<LOD	<LOD
5 M NaCl	Iridium	Ir	2B	0.001	0.002	<LOD	<LOD
5 M NaCl	Osmium	Os	2B	0.001	0.002	<LOD	<LOD
5 M NaCl	Rhodium	Rh	2B	0.0002	0.001	0.072	<LOD
5 M NaCl	Ruthenium	Ru	2B	0.002	0.006	<LOD	<LOD
5 M NaCl	Selenium	Se	2B	0.033	0.111	<LOD	<LOD
5 M NaCl	Silver	Ag	2B	0.002	0.007	<LOD	<LOD
5 M NaCl	Platinum	Pt	2B	0.002	0.007	<LOD	<LOD
5 M NaCl	Lithium	Li	3	0.005	0.016	0.003	<LOD
5 M NaCl	Antimony	Sb	3	0.001	0.005	<LOD	<LOD
5 M NaCl	Barium	Ba	3	0.003	0.011	0.211	<LOD
5 M NaCl	Molybdenum	Mo	3	0.004	0.014	0.035	<LOD
5 M NaCl	Copper	Cu	3	0.006	0.019	0.069	<LOD
5 M NaCl	Tin	Sn	3	0.025	0.083	<LOD	<LOD
5 M NaCl	Chromium	Cr	3	0.052	0.174	<LOD	<LOD
5 M NaCl	Boron	B	N/A	0.004	0.013	0.307	<LOD
5 M NaCl	Sodium	Na	N/A	0.036	0.119	<LOD	<LOD
5 M NaCl	Tungsten	W	N/A	0.003	0.009	<LOD	<LOD
5 M NaCl	Magnesium	Mg	N/A	0.029	0.098	<LOD	<LOD
5 M NaCl	Aluminum	Al	N/A	0.027	0.089	<LOD	<LOD
5 M NaCl	Calcium	Ca	N/A	0.01	0.033	<LOD	<LOD
5 M NaCl	Titanium	Ti	N/A	0.024	0.081	<LOD	<LOD
5 M NaCl	Manganese	Mn	N/A	0.019	0.064	0.019	<LOD
5 M NaCl	Iron	Fe	N/A	0.066	0.22	<LOD	<LOD
5 M NaCl	Zinc	Zn	N/A	0.059	0.197	<LOD	<LOD
5 M NaCl	Potassium	K	N/A	0.061	0.203	<LOD	<LOD

[a] Instrument LOD and LOQ. Elements less than LOD or LOQ are reported as "<" the instrument LOD/LOQ value of the relevant standard. For risk assessment of elements reported at < LOD or < LOQ, values can be used "as is" as there was no dilution during sample preparation.

Table 5. (Continued)

Solvent	Element		ICH Q3D Class	LOD[a] (ppb)	LOQ[a] (ppb)	S254M1-02 Set 1 (ppb) 70 days	S254M1-02 Set 2 (ppb) 70 days
50% Ethanol	Cadmium	Cd	1	0.007	0.023	<LOD	<LOD
50% Ethanol	Lead	Pb	1	0.001	0.003	<LOD	<LOD
50% Ethanol	Arsenic	As	1	0.025	0.082	0.025	<LOD
50% Ethanol	Mercury	Hg	1	0.015	0.049	<LOD	<LOD
50% Ethanol	Cobalt	Co	2A	0.004	0.012	<LOD	<LOD
50% Ethanol	Vanadium	V	2A	0.005	0.017	<LOD	<LOD
50% Ethanol	Nickel	Ni	2A	0.015	0.05	<LOD	<LOD
50% Ethanol	Thallium	Tl	2B	0.0001	0.0004	<LOD	<LOD
50% Ethanol	Gold	Au	2B	0.001	0.004	<LOD	<LOD
50% Ethanol	Palladium	Pd	2B	0.004	0.013	<LOD	<LOD
50% Ethanol	Iridium	Ir	2B	0.001	0.002	<LOD	<LOD
50% Ethanol	Osmium	Os	2B	0.001	0.002	0.494	0.256
50% Ethanol	Rhodium	Rh	2B	0.0002	0.001	<LOD	<LOD
50% Ethanol	Ruthenium	Ru	2B	0.002	0.006	<LOD	<LOD
50% Ethanol	Selenium	Se	2B	0.033	0.111	<LOD	<LOD
50% Ethanol	Silver	Ag	2B	0.002	0.007	<LOD	<LOD
50% Ethanol	Platinum	Pt	2B	0.002	0.007	<LOD	<LOD
50% Ethanol	Lithium	Li	3	0.005	0.016	0.002	0.001
50% Ethanol	Antimony	Sb	3	0.001	0.005	<LOD	<LOD
50% Ethanol	Barium	Ba	3	0.003	0.011	0.003	<LOD
50% Ethanol	Molybdenum	Mo	3	0.004	0.014	0.395	0.085
50% Ethanol	Copper	Cu	3	0.006	0.019	<LOD	<LOD
50% Ethanol	Tin	Sn	3	0.025	0.083	<LOD	<LOD
50% Ethanol	Chromium	Cr	3	0.052	0.174	<LOD	<LOD
50% Ethanol	Boron	B	N/A	0.004	0.013	0.197	<LOD
50% Ethanol	Sodium	Na	N/A	0.036	0.119	6.350	<LOD
50% Ethanol	Tungsten	W	N/A	0.003	0.009	<LOD	<LOD
50% Ethanol	Magnesium	Mg	N/A	0.029	0.098	0.239	0.345
50% Ethanol	Aluminum	Al	N/A	0.027	0.089	<LOD	<LOD
50% Ethanol	Calcium	Ca	N/A	0.01	0.033	0.558	1.190
50% Ethanol	Titanium	Ti	N/A	0.024	0.081	<LOD	<LOD
50% Ethanol	Manganese	Mn	N/A	0.019	0.064	<LOD	<LOD
50% Ethanol	Iron	Fe	N/A	0.066	0.22	<LOD	<LOD
50% Ethanol	Zinc	Zn	N/A	0.059	0.197	<LOD	<LOD
50% Ethanol	Potassium	K	N/A	0.061	0.203	<LOQ	<LOD

[a] Instrument LOD and LOQ. Elements less than LOD or LOQ are reported as "<" the instrument LOD/LOQ value of the relevant standard. For risk assessment of elements reported at < LOD or < LOQ, values can be used "as is" as there was no dilution during sample preparation.

Table 5. (Continued)

Solvent	Element		ICH Q3D Class	LOD[a] (ppb)	LOQ[a] (ppb)	S254M1-02 Set 1 (ppb) 70 days	S254M1-02 Set 2 (ppb) 70 days
1% PS80	Cadmium	Cd	1	0.007	0.023	<LOD	<LOD
1% PS80	Lead	Pb	1	0.001	0.003	<LOD	0.257
1% PS80	Arsenic	As	1	0.025	0.082	<LOQ	<LOD
1% PS80	Mercury	Hg	1	0.015	0.049	<LOD	<LOD
1% PS80	Cobalt	Co	2A	0.004	0.012	<LOD	<LOD
1% PS80	Vanadium	V	2A	0.005	0.017	<LOD	<LOD
1% PS80	Nickel	Ni	2A	0.015	0.050	<LOD	<LOD
1% PS80	Thallium	Tl	2B	0.0001	0.0004	<LOD	<LOD
1% PS80	Gold	Au	2B	0.001	0.004	<LOD	<LOD
1% PS80	Palladium	Pd	2B	0.004	0.013	<LOD	<LOD
1% PS80	Iridium	Ir	2B	0.001	0.002	<LOD	<LOD
1% PS80	Osmium	Os	2B	0.001	0.002	<LOD	<LOD
1% PS80	Rhodium	Rh	2B	0.0002	0.001	<LOD	<LOD
1% PS80	Ruthenium	Ru	2B	0.002	0.006	<LOD	<LOD
1% PS80	Selenium	Se	2B	0.033	0.111	<LOD	<LOD
1% PS80	Silver	Ag	2B	0.002	0.007	<LOD	<LOD
1% PS80	Platinum	Pt	2B	0.002	0.007	<LOD	<LOD
1% PS80	Lithium	Li	3	0.005	0.016	<LOD	<LOD
1% PS80	Antimony	Sb	3	0.001	0.005	<LOD	<LOD
1% PS80	Barium	Ba	3	0.003	0.011	0.124	0.514
1% PS80	Molybdenum	Mo	3	0.004	0.014	0.032	0.109
1% PS80	Copper	Cu	3	0.006	0.019	<LOD	0.041
1% PS80	Tin	Sn	3	0.025	0.083	<LOD	<0.025
1% PS80	Chromium	Cr	3	0.052	0.174	<LOD	<LOD
1% PS80	Boron	B	N/A	0.004	0.013	<LOD	0.483
1% PS80	Sodium	Na	N/A	0.036	0.119	<LOD	56.034
1% PS80	Tungsten	W	N/A	0.003	0.009	<LOD	<LOD
1% PS80	Magnesium	Mg	N/A	0.029	0.098	1.021	1.084
1% PS80	Aluminum	Al	N/A	0.027	0.089	<LOD	0.747
1% PS80	Calcium	Ca	N/A	0.010	0.033	0.980	1.509
1% PS80	Titanium	Ti	N/A	0.024	0.081	<LOD	<LOD
1% PS80	Manganese	Mn	N/A	0.019	0.064	<LOD	<LOD
1% PS80	Iron	Fe	N/A	0.066	0.220	0.661	0.405
1% PS80	Zinc	Zn	N/A	0.059	0.197	<LOD	<LOD
1% PS80	Potassium	K	N/A	0.061	0.203	<LOD	<LOQ

[a] Instrument LOD and LOQ. Elements less than LOD or LOQ are reported as "<" the instrument LOD/LOQ value of the relevant standard. For risk assessment of elements reported at < LOD or < LOQ, values can be used "as is" as there was no dilution during sample preparation.

6 Analytical Methods

Table 6.

Assay performance parameters for LC with Ultraviolet and Mass Spectrometric Detection (LC-UV-MS)

Standards	Bisphenol A (BPA), Irganox 1010, *Bis*(2-ethylhexyl)phthalate (DEHP), Erucamide (see notes below)		
Limit of detection (LOD)	Signal-to-noise ratio ≥ 3 (all standards)		
Limit of quantitation (LOQ)	Signal-to-noise ratio ≥ 10 (all standards)		
Pre-treatment	10-fold dilution for 1% PS80 samples only		
Precision	RSD ≤ 2% (Retention Time) and ≤ 20% (Area Counts) (n = 6) For PDA and ES+/-, 1 – 5 ppm (all standards) For APCI+/-, 10 ppm (Irganox 1010 only)		
Spike recovery	80 – 120% For PDA and ES+/-, 1.2 – 4.5 ppm (all standards) For APCI+/-, 9 - 12 ppm (Irganox 1010 only)		
Sample bracketing	Every 10 sample injections (all standards), % Difference ≤ 25%.		
Column	Waters Acquity UPLC BEH C18, 1.7 µm, 2.1 x 50 mm		
Column temperature	60 ºC		
Injection volume	8 µL		
Flow rate	0.45 mL/min		
Mobile Phase A	Water with 0.01% Formic acid (v/v) + 3 mM Ammonium formate		
Mobile Phase B	Methanol with 0.01% Formic acid (v/v) + 3 mM Ammonium formate		
Gradient	Time	% A	% B
	0.0	98	2
	1.0	98	2
	8.0	0	100
	10.0	0	100
	10.2	98	2
PDA range	210 - 400 nm		
m/z range, amu	70 – 1400		
Ionization modes	ESI +/-, APCI +/- (ESI - Electrospray Ionization; APCI - Atmospheric Pressure Chemical Ionization) (See notes below)		

PDA for BPA and DEHP; ES+, TIC for Erucamide; ES-, TIC, APCI+/-,TIC for Irganox 1010 (TIC – Total Ion Current)

APCI +/- data are only reported for unique compounds not detected by ES.

For 1% PS80, only unique peaks in the sample (i.e. not detected in the negative control, not known PS80 degradants) were reported.

Table 7.

Assay performance parameters for Direct Injection GC with Mass Spectrometric Detection (DI-GC-MS)

Standards	*n*-Decane and 2,4-*Di-tert*-butylphenol		
Limit of detection (LOD)	Signal-to-noise ratio ≥ 3 (all standards)		
Limit of quantitation (LOQ)	Signal-to-noise ratio ≥ 10 (all standards)		
Internal standard	2 ppm Phenanthrene-d_{10}		
Pre-treatment	Liquid-liquid extraction with Dichloromethane (1x for 50% Ethanol, 3x for all other solvents). In addition, 7-day samples were concentrated 50x.		
Precision	RSD ≤ 2% (Retention Time) and ≤ 20% (Area Counts) (n = 6), 0.5 – 1 ppm (all standards)		
Spike recovery	80 – 120%, 1 ppm BHT (all solvents)		
Sample bracketing	Every 10 sample injections (all standards), % Difference ≤ 20%.		
Column	Agilent DB-1 MS, 60 m x 0.25 mm, 0.25 µm		
Injection port temperature	200 °C		
Injection volume	1.0 µL		
GC temperature program	Rate (°C/min)	Temperature (°C)	Hold Time (min)
	N/A	50.0	1.50
	17.0	135.0	5.50
	12.0	300.0	6.50
m/z range, amu	35 – 650		

Table 8.

Assay performance parameters for Headspace GC with Mass Spectrometric Detection (HS-GC-MS)

Standards	2-Propanol and Methyl ethyl ketone (MEK)		
Limit of detection	Signal-to-noise ratio ≥ 3 (all standards)		
Limit of quantitation	Signal-to-noise ratio ≥ 10 (all standards)		
Internal standard	None		
Precision	RSD ≤ 2% (Retention Time) and ≤ 20% (Area Counts) (n = 6), 1 – 10 ppm		
Spike recovery	80 – 120%, 1 – 8 ppm (all solvents)		
Sample bracketing	Every 10 sample injections (all standards), % Difference ≤ 20%.		
Column	Agilent DB-624 MS, 60 m x 0.25 mm, 1.4 µm		
Injection port temperature	250 °C		
Headspace vial temperature	70 °C		
Injection volume	1.0 µL		
GC temperature program	Rate (°C/min)	Temperature (°C)	Hold Time (min)
	N/A	40.0	4.00
	5.0	50.0	5.00
	5.0	65.0	5.00
	15.0	200.0	5.00
m/z range, amu	35 - 650		

Table 9.

Assay performance parameters for Inductively Coupled Plasma with Mass Spectrometric Detection (ICP-MS)

Standards	All elements tested except for Osmium (Os). Os standard was not available during testing.
Limit of detection*	< 0.07 ppb
Limit of quantitation*	< 0.3 ppb
Spike recovery	80 – 120% (all elements in all solvents)
Quantification	Calibration curve (5 standard concentrations per element) except for Os, which was semi-quantified using Ir.

Recovery of Se was not meaningful due to matrix interference (i.e. $Ar^{40}Cl^{37}$). Se is not known to be intentionally added into the port materials.

** Instrument LOD and LOQ. To determine method LOD/LOQ, values must be multiplied by the sample preparation dilution factor (DF = 50 for all solvents except for water and 0.1 M H_3PO_4 which have DF = 1).*

7 Deviations

Table 10.

Protocol deviations

Category	Description
Surface area to volume ratio (SAVR)	SAVR of 6.0 cm^2/mL was not used during testing as the three-dimensional geometry of the HDPE port limited the practical SAVR that could be achieved at 1.83 cm^2/mL. This ratio is still much higher than the fluid contact surface area of the port per biocontainer extraction volume if the testing had been performed with the port attached, leading to an improved characterization.
Analytical method	5 M NaCl samples were not analyzed by LC/MS-APCI due to impact of high concentration of salt on the APCI ion source.

8 Appendices

8.1 Extraction Setup Diagram

Figure 1.

HPDE port - extraction set-up

8.2 Abbreviations

Full Name	Abbreviation
High Density Polyethylene	HDPE
Electrospray Ionization	ESI
Atmospheric Pressure Chemical Ionization	APCI
Gas Chromatography Mass Spectrometry	GC-MS
Headspace Gas Chromatography Mass Spectrometry	HS-GC-MS
Direct Injection Gas Chromatography Mass Spectrometry	DI-GC-MS
Liquid Chromatography Ultraviolet Mass Spectrometry	LC-UV-MS
Inductively Coupled Plasma Mass Spectrometry	ICP-MS
High Performance Liquid Chromatography	HPLC
Non-volatile Residue	NVR
Total Organic Carbon	TOC
Total Ion Current	TIC
Limit of Detection	LOD
Limit of Quantitation	LOQ

8.3 Part Numbers and Scaling Parameters

In order to facilitate scaling of extractables data to various sized components, extractables data are reported in units of μg/mL and summarized in units of μg/cm^2 of fluid contact surface area. The tables below show approximate fluid contact surface areas of the components of the Large Scale Drain Valve, the part numbers of bioreactors with which these drain valves are intended to be used, and example calculations.

Table 11.

2D Allegro biocontainers

Product	Total Volume (L)	Film Contact Area (cm^2)	Port Contact Area (cm^2)	Part Number
50 mL	0.05	180	24	LGR0050ML770
500 mL	0.5	523	24	LGR0500ML770
1 L	1	894	24	LGR1000ML770
5 L	5	2331	44	LGR0005L6600 LGR0005L7700 LGR0005L8800 LGR0005L8800TF
10 L	10	3758	44	LGR0010L6600 LGR0010L7700 LGR0010L8800 LGR0010L8800TF
20 L	20	5881	44	LGR0020L6600 LGR0020L6600CAP LGR0020L7700 LGR0020L8800
50 L	50	10283	44	LGR0050L6600 LGR0050L6600CAP LGR0050L7700 LGR0050L8800

Table 12.

3D Allegro biocontainers

Product	Total Volume (L)	Film Contact Area (cm^2)	Port Plate Area (cm^2)	Drain Flange Area (cm^2)	Part Number
100 L	100	14556	117	97	LGR0100L5550, LGR0100L6660, LGR0100L8880, LGR0100L9990
200 L	200	21500	117	97	LGR0200L5550, LGR0200L6660, LGR0200L8880, LGR0200L9990
500 L	500	38307	117	97	LGR0500L5550, LGR0500L5660, LGR0500L6660, LGR0500L8880, LGR0500L9990
1000 L	1000	62966	117	97	LGR1000L5550, LGR1000L5660, LGR1000L5880, LGR1000L5990, LGR1000L6550, LGR1000L6660, LGR1000L6880, LGR1000L6990, LGR1000L8550, LGR1000L8660, LGR1000L8880, LGR1000L8990, LGR1000L9550, LGR1000L9660, LGR1000L9880, LGR1000L9990,
1500 L	1500	81963	117	97	LGR1500L5550, LGR1500L6660, LGR1500L8880, LGR1500L9990
100 L	100	14556	117	97	LGR0100L5550, LGR0100L6660, LGR0100L8880, LGR0100L9990,
200 L	200	21500	117	97	LGR0200L5550, LGR0200L6660, LGR0200L8880, LGR0200L9990

8.4 Example Risk Assessment

As an example of how compounds are typically scaled, the table below illustrates how the most abundant 5 organic extractables in 50% Ethanol and the ICH Q3D elements detected would scale according to fluid contact surface area. Under these typical worst-case, actual use conditions (e.g. 40 ºC for 70 days), levels of potential leachables are expected to be below most detection and reporting thresholds.

Table 13.

Example calculation showing final concentration of port extractables in filled 1 L and 20 L Allegro 2D biocontainers

Compound	Worst-Case Amount (µg/cm^2)	Port Contact Area in Biocontainer (cm^2)		Worst-Case Amount in Filled Biocontainer (µg/mL)	
		1 L	20 L	1 L	20 L
Compound 9	3.18	24	44	0.0763	0.0070
Compound 10	2.89	24	44	0.0694	0.0064
Compound 11	1.51	24	44	0.0362	0.0033
Compound 12	1.44	24	44	0.0346	0.0032
Compound 13	1.23	24	44	0.0295	0.0027
Ba	0.020	24	44	< 0.001	< 0.0001
Mo	0.018	24	44	< 0.001	< 0.0001

[a] *Worst-case amount in filled biocontainer = [Worst-case Amount (µg/cm^2) x Port Contact Area] / Total Volume*

9 Quality Statement

Pall SLS Validation & Laboratory Operations consists of a team of highly trained scientists and subject matter experts, with major laboratories based in the following locations:

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An SLS Global Quality Management System (QMS) is in place for key activities and laboratory standard test methods to ensure that processes are harmonized across facilities.

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9. Recording & reporting of data
10. Management of laboratory equipment
11. Non-conformances
12. Continuous improvement

Site QMS are also in place for processes aligned to wider site specific activities.

Hard copy generated raw data is retained for a period of 10 years, then scanned and retained indefinitely. Electronic documents are archived to a centralized project database, whereas instrument specific analytical data, including GC/MS and LCUV/MS data, are archived via redundant local backups.
In addition, validation services are aligned with regulatory guidelines and industry standards, and are engaged in internationally recognized industry associations including PDA, BPSA, BPOG, ASTM and USP.

Jonathan Blount Director, DBS and Quality Operations

10 Revision History

Revision Number	Date	Prepared by	Approved by	Approved by
00	27-APR-2020	Gilbert Tumambac, Ph.D.	James Hathcock, Ph.D.	Jonathan P. Blount

Amendments Made:

None

Reasons for Revision:

Initial release of this sample report, which is based on VAL-AS-003177-ER(01) including additional information that will be included in a subsequent revision.

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