1.0 Purpose

This report provides documented evidence that alternate USP impurity limit test methods, using the Prodigy High Dispersion Simultaneous ICP Spectrometer with axial and halogen options, were validated as described in Giles method *L13-PR-100-050, USP ICP Method Validation Protocol* and all acceptance criteria were met as per USP 36 General Chapter <1225>. This also qualifies as a Performance Qualification for the ICP-OES.

2.0 Scope

This validation was performed according to the procedure outlined in Giles method *L13-PR-100-050, USP ICP Method Validation Protocol*. It covers Giles methods *L13-PR-100-057, USP ICP-OES Analysis*, and *L13-PR-100-058, USP ICP-OES Sample Preparation*, which comprise the total USP ICP method. The total USP ICP method represents alternate USP impurity limit tests for iron (USP 36 General Chapter <241>), selenium (USP 36 General Chapter <291>), and chloride (USP 36 General Chapter <221>). It also includes the elemental impurities method (USP 36 General Chapter <233>) as an alternative to the standard heavy metals procedure (USP 36 General Chapter <231>), which requires a simple verification of suitability.

3.0 Responsibility

QA Lab personnel are responsible for validation and revalidation of ICP methods.

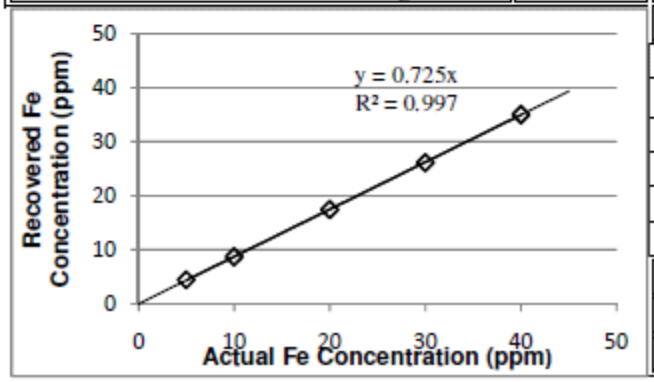
4.0 Results

Each alternate test for iron, selenium, and chloride was validated according to Giles method *L13-PR-100-050, USP ICP Method Validation Protocol* by testing five sets of three samples with concentrations ranging from a quarter of the USP limit to twice the USP limit. The elemental impurities test (USP 36 General Chapter <233>) was verified for suitability by testing three samples at the USP limit (USP 36 General Chapter <232>). Quality control checks of twice the USP limit passed (±20%) for the elemental impurities tests as specified in the monograph. In the results, "recovered concentration" is the "measured concentration" minus the "average unspiked concentration".

Iron Validation

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	-0.01082
0J #2 - 1	0.10372
0J #3 - 1	-0.0229
Average Unspiked Concentration	**0.023333333**

Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
0.25J #1 - 1	4.47092			5	4.447586667	88.95173333
0.25J #2 - 1	4.47273			5	4.449396667	88.98793333
0.25J #3 - 1	4.50866	0.0212859	0.4746979	5	4.485326667	89.70653333
0.5J #1 - 1	8.7842			10	8.760866667	87.60866667
0.5J #2 - 1	8.8551			10	8.831766667	88.31766667
0.5J #3 - 1	8.56647	0.1504108	1.7218818	10	8.543136667	85.43136667
1.0J #1 - 1	17.39286			20	17.36952667	86.84763333
1.0J #2 - 1	17.49087			20	17.46753667	87.33768333
1.0J #3 - 1	17.55208	0.0803157	0.4595085	20	17.52874667	87.64373333
1.5J #1 - 1	26.21476			30	26.19142667	87.30475556
1.5J #2 - 1	26.19215			30	26.16881667	87.22938889
1.5J #3 - 1	26.08109	0.0715463	0.273467	30	26.05775667	86.85918889
2.0J #1 - 1	35.22396			40	35.20062667	88.00156667
2.0J #2 - 1	35.04153			40	35.01819667	87.54549167
2.0J #3 - 1	34.93794	0.1448097	0.4129419	40	34.91460667	87.28651667
Average %RSD			**0.6684994**	**Average % Recovery:**		**87.67065722**
				Std. Dev.:		**1.035333936**

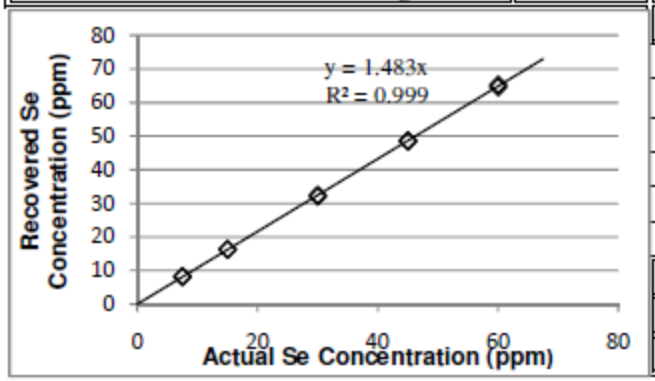


Slope	0.87421076
Std Err in Slope, S_b	0.001192512
Degrees of Freedom	13
Confidence Level	95%
Student t	2.160368652
Confidence Interval	0.003
Slope with CI	**0.874 ± 0.003**
Lower Confidence Limit	**0.872**
Upper Confidence Limit	**0.877**

Selenium Validation

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	1.07079
0J #2 - 1	0.62607
0J #3 - 1	0.3026
Average Unspiked Concentration	**0.666486667**

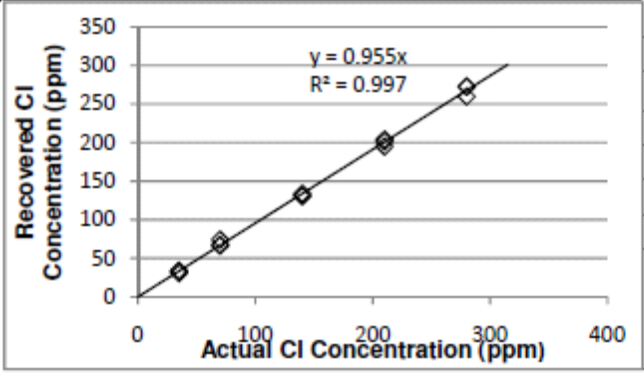
Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
0.25J #1 - 1	8.72974			7.5	8.063253333	107.5100444
0.25J #2 - 1	9.00094			7.5	8.334453333	111.1260444
0.25J #3 - 1	8.92251	0.1395594	1.5708373	7.5	8.256023333	110.0803111
0.5J #1 - 1	16.97345			15	16.30696333	108.7130889
0.5J #2 - 1	16.91877			15	16.25228333	108.3485556
0.5J #3 - 1	17.0264	0.0538173	0.3170784	15	16.35991333	109.0660889
1.0J #1 - 1	32.70195			30	32.03546333	106.7848778
1.0J #2 - 1	33.25479			30	32.58830333	108.6276778
1.0J #3 - 1	32.79387	0.2962343	0.8999468	30	32.12738333	107.0912778
1.5J #1 - 1	49.41441			45	48.74792333	108.3287185
1.5J #2 - 1	49.24977			45	48.58328333	107.9628519
1.5J #3 - 1	49.12551	0.1449196	0.2941739	45	48.45902333	107.6867185
2.0J #1 - 1	66.13626			60	65.46977333	109.1162889
2.0J #2 - 1	65.17981			60	64.51332333	107.5222056
2.0J #3 - 1	65.66173	0.4782298	0.7283507	60	64.99524333	108.3254056
		Average %RSD	**0.7620774**	**Average % Recovery:**		**108.4193437**
				Std. Dev.:		**1.132406905**
				Slope		1.081382828
				Std Err in Slope, S_b		0.001808501
				Degrees of Freedom		13
				Confidence Level		95%
				Student t		2.160368652
				Confidence Interval		0.004
				Slope with CI		**1.081 ± 0.004**
				Lower Confidence Limit		**1.077**
				Upper Confidence Limit		**1.085**



Chlorine Validation

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	26.54755
0J #2 - 1	22.87713
0J #3 - 1	26.34414
Average Unspiked Concentration	**25.25627333**

Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
0.25J #1 - 1	55.98569			35	30.72941667	87.79833333
0.25J #2 - 1	58.83384			35	33.57756667	95.93590476
0.25J #3 - 1	59.05845	1.712905	2.955357	35	33.80217667	96.57764762
0.5J #1 - 1	91.91891			70	66.66263667	95.2323381
0.5J #2 - 1	92.75248			70	67.49620667	96.42315238
0.5J #3 - 1	99.34297	4.0670641	4.2959773	70	74.08669667	105.8381381
1.0J #1 - 1	156.42347			140	131.1671967	93.69085476
1.0J #2 - 1	159.30672			140	134.0504467	95.75031905
1.0J #3 - 1	156.15669	1.7467585	1.110494	140	130.9004167	93.50029762
1.5J #1 - 1	220.37433			210	195.1180567	92.91336032
1.5J #2 - 1	226.68746			210	201.4311867	95.9196127
1.5J #3 - 1	229.25933	4.5718951	2.0279842	210	204.0030567	97.1443127
2.0J #1 - 1	298.01807			280	272.7617967	97.41492738
2.0J #2 - 1	285.14958			280	259.8933067	92.8190381
2.0J #3 - 1	297.68922	7.3365381	2.4986596	280	272.4329467	97.29748095
		Average %RSD	**2.5776944**	**Average % Recovery:**		**95.61704786**



Std. Dev.:	3.772578857
Slope	0.955772584
Std Err in Slope, S_b	0.006038483
Degrees of Freedom	13
Confidence Level	95%
Student t	2.160368652
Confidence Interval	0.013
Slope with CI	**0.956 ± 0.013**
Lower Confidence Limit	**0.943**
Upper Confidence Limit	**0.969**

Arsenic Verification

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	-0.04355
0J #2 - 1	-0.02035
0J #3 - 1	-0.00268
Average Unspiked Concentration	**-0.022193333**

Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
1.0J #1 - 1	0.00505			0.075	0.027243333	36.32444444
1.0J #2 - 1	0.05697			0.075	0.079163333	105.5511111
1.0J #3 - 1	0.05476	0.029359	**75.4209**	0.075	0.076953333	102.6044444
				Average % Recovery:		**81.49333333**

Lead Verification

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	-0.04572
0J #2 - 1	0.02953
0J #3 - 1	-0.00304
Average Unspiked Concentration	**-0.00641**

Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
1.0J #1 - 1	0.16546			0.25	0.17187	68.748
1.0J #2 - 1	0.19483			0.25	0.20124	80.496
1.0J #3 - 1	0.1689	0.016056	**9.1023**	0.25	0.17531	70.124
				Average % Recovery:		**73.12266667**

Cadmium Verification

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	0.0076
0J #2 - 1	0.00179
0J #3 - 1	0.00526
Average Unspiked Concentration	**0.004883333**

Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
1.0J #1 - 1	1.09687			1.25	1.091986667	87.35893333
1.0J #2 - 1	1.08895			1.25	1.084066667	86.72533333
1.0J #3 - 1	1.09224	0.003979	**0.3641**	1.25	1.087356667	86.98853333
					Average % Recovery:	**87.02426667**

Mercury Verification

Unspiked Sample Name	Measured Concentration (ppm)
0J #1 - 1	0.03459
0J #2 - 1	0.05119
0J #3 - 1	0.02913
Average Unspiked Concentration	**0.038303333**

Sample Name	Measured Concentration (ppm)	Standard Deviation	% RSD	Actual Concentration (ppm)	Recovered Concentration (ppm)	Recovery (%)
1.0J #1 - 1	0.67027			0.75	0.631966667	84.26222222
1.0J #2 - 1	0.64103			0.75	0.602726667	80.36355556
1.0J #3 - 1	0.63054	0.020589	**3.1809**	0.75	0.592236667	78.96488889
					Average % Recovery:	**81.19688889**

5.0 Conclusion

IRON – SELENIUM – CHLORINE

Each validation criterion for iron, selenium, and chlorine was met, as follows:

Accuracy–The 95% confidence limits of the slope of the recovered concentration vs. actual concentration equation for each element are within ±20% of 1.0 (in other words: the confidence interval for the slope is contained within a 20% interval around 1.0 for each element). This shows acceptable accuracy for each element.

Precision–The average % RSD for each element is less than 5%. This shows acceptable precision for each element.

Specificity–For each element, the percent recoveries for all spiked samples are between 80% and 120%, and the average % RSD is less than 5%. Because all USP impurities are present in the spiked samples, this demonstrates that each element is determined with appropriate accuracy and precision; showing acceptable specificity.

Detection Limit–Determination of actual detection limits is not necessary. Rather, the detection limit for each element is evaluated to be sufficiently low if the requirements for accuracy are met, and the percent recoveries for samples spiked with 0.25 times the impurity limit are between 80% and 120%. These criteria have been met for each element, showing that the detection limit for each is below 0.25 times the impurity limit.

Linearity–For each element, the coefficient of determination (R^2) for the recovered concentration vs. actual concentration equation is greater than 0.950. This shows acceptable linearity for each element.

Range–For each element, the range has be established to be the interval between 0.25 times the impurity limit and 2.0 times the impurity limit (including these levels), because these samples tested within this range show a suitable level of accuracy, precision, and linearity, as determined above.

Because of the nature of ICP-OES, the test for chloride is actually a test for total chlorine, of which chloride is a part. This test is a valid limit test for chloride because if the total chlorine is below the stated limit, then it can be assumed that the chloride (which is only part of the total chlorine) is also below the limit. If a sample is tested and found to be above the limit, the standard USP limit test will be employed to determine if this is actually due to chloride concentration alone.

ARSENIC – LEAD – CADMIUM – MERCURY

The elements to be determined using the elemental impurities method (USP general chapter <232>) include arsenic, lead, cadmium, and mercury. As these determinations are part of the overall method, the method needs to be verified to be suitable for these tests. The results for cadmium and mercury show an average recovery at each impurity limit between 80% and 120%, each with a % RSD less than 5%. Therefore, the tests for cadmium and mercury have been verified as suitable. The average recovery for lead is a little low, but still within a 30% range. The % RSD is also a little high, but still less than 10%. This is due to matrix effects, but is still acceptable if quality control checks pass as stipulated in USP 36 General Chapter <233>. The lead test has, therefore, been verified. The average recovery for arsenic is between 80% and 120%, but the % RSD is very high (75.42%). This is due to noise as the arsenic signal is weak, and the concentrations used in this verification are low (near the instrument detection limit). This is not sufficient precision to verify this test for the elemental impurities requirements of USP 36 general chapter <232> (0.075 ppm As). However, USP 36 general chapters <232> and <233> will not be implemented until May 1, 2014, so the current requirement is the heavy metals limit as specified in USP 36 general chapter <231>. This chapter specifies a heavy metals limit of 0.001% (10 ppm). This is a limit of 10 ppm for the total of arsenic, lead, cadmium, and mercury. If an out of specification limit is set at 1 ppm for each heavy metal, then even the arsenic test provides good enough precision to be verified for this determination.

6.0 Recommendations

It is recommended that a hydride generator be purchased by the end of the fourth quarter of 2013. This will provide better detection, and therefore precision in the determination of arsenic and lead using the ICP-OES. This will need to be done in order to meet USP general chapter <232> specifications for elemental impurities by the implementation date of May 1, 2014.

7.0 Reference Documents

USP ICP Method Validation Protocol *(L13-PR-100-050)*
USP ICP-OES Analysis *(L13-PR-100-057)*
USP ICP-OES Sample Preparation *(L13-PR-100-058)*

8.0 Approvals

Signing below indicates agreement that the USP ICP method comprised of Giles methods *L13-PR-100-057, USP ICP-OES Analysis*, and *L13-PR-100-058, USP ICP-OES Sample Preparation*, as well as the Performance Qualification of the ICP-OES have been validated, and all acceptance criteria met, according to the procedure outlined in Giles method *L13-PR-100-050, USP ICP Method Validation Protocol* and USP General Chapter <1225>.

Project Team Member	Functional Area	Signature	Date
Stephen Ballew	Quality/R&D		7/29/13
Deborah Durbin	Quality		7/29/13
Patrick Owen	Engineering		7/29/13
Matt Haynes	Operations		7/29/13