PQRI Phase 2 Elemental Impurities Collaborative Study

Key Findings

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Study Participant labs

- Final tally of responding labs
  - Reproducibility analysis and comparison to reference data:

ICP-MS - Tablets	ICP-MS - Raw Materials	XRF
21 labs	13 labs	4 labs

  - Microwave type analysis:

SRC Microwave	IPV Microwave
12 labs	10 labs

  - Digestion method analysis:

Exhaustive Extraction	Total Digestion
19 labs	7 labs

Method variability - Preparation

Microwave Digestion method variability

	Max Temperature (°C)	Max Pressure (psi)	Ramp time (min)	Hold time (min)
Digestion method				
Total Digestion	210-250	85-2320	15-25	15-20
Exhaustive extraction	175-200	80-2321	10-20	0-25
Microwave system type				
SRC system	175-250	80-2321	10-25	0-20
IPV system	175-200	300-870	10-20	10-25

XRF labs

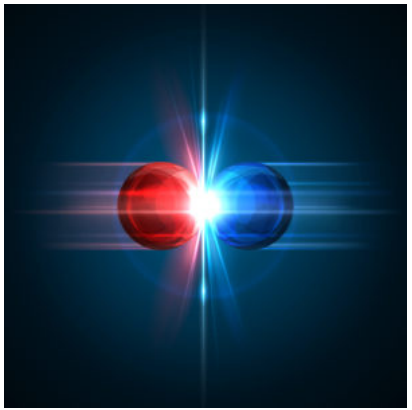
- 3 of 4 used (WDXRF) systems
  - Higher sensitivity than EDXRF
  - Wider range of elements than EDXRF.

Mix time	Oven temp	Oven time	Press load	Press time
120-1200 s	40-90 ℃	40-1260 min	10-35 ton	60-120 s

Method variability - Analysis

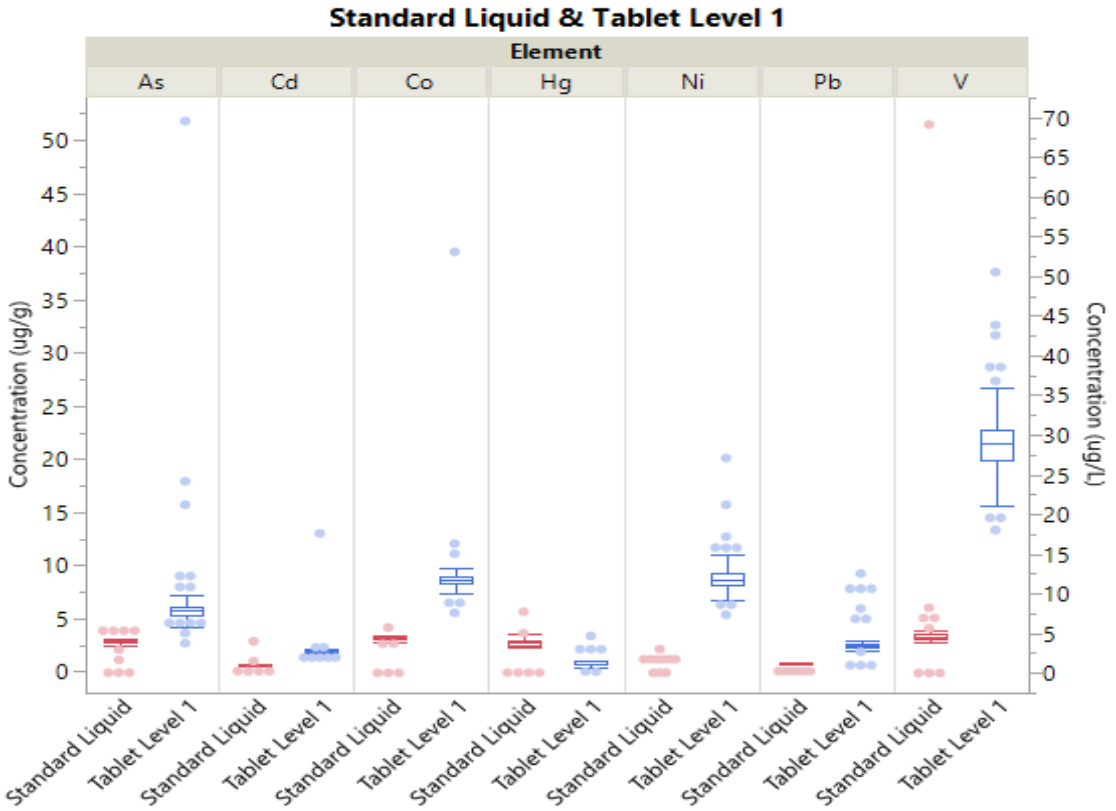
Element	As	Cd	Co	Hg	Ni	Pb	V
Collision cell gases	**He (16),** None (2) H_2 (1) O_2 (1) not spec. (1)	**None (17)** He (4)	**He (17)** None (3) not spec. (1)	**None (17)** He (4)	**He (17)** None (3) not spec. (1)	**None (16)** He (5)	He (15) None (2) **NH_3 (1)** H_2/He (1) not spec. (2)
Internal Standard	**Rh (12)** Ga (3) Sc (2) In (2) not spec. (2)	**Rh (16)** In (2) not spec. (3)	**Rh (12)** Ga (3) Sc (2) In (2) not spec. (2)	**Tl (14)** In (1) Bi (1) Rh (1) Pr (1) not spec. (3)	**Rh (12)** Ga (3) In (2) Sc (2) not spec. (2)	**Tl (14)** Bi (2) In (1) Rh (1) not spec. (3)	**Rh (11)** Ga (3) Sc (3) In (2) not spec. (2)

- Most used the recommended method
- Interested in “Unspecified” instances
  - Individual lab reports can show impact on results, spur discussion with labs around best practices



Standard Liquid Sample

- Most labs were accurate.
- High variation between labs
  - Biased by erroneous results from 2 labs.
- Variability is not instrument-based



ICP-MS vs Reference Lab – Tablet Materials

- Several elements were comparable to reference lab results
  - Exceptions: Cd, Hg, and V
- All labs, Exhaustive extraction only, and Total digestion only

Statistics refresher:
P-value – probability that difference is due to chance

All labs

Analyte	Material	Measurements >LOQ (n)	Reference concentration (ug/g)	Mean concentration (ug/g)	Geometric SD (ug/g)	95% confidence Interval	P value
As	Tablet Level 1	78	5.76	5.9	1.4	(5.5, 6.4)	0.485
	Tablet Level 2	78	17.2	17	1	(16, 17)	0.242
	Tablet Level 3	78	42.4	42	1	(40, 44)	0.723
Cd	Tablet Level 1	78	1.94	1.9	1.3	(1.8, 2.0)	0.252
	Tablet Level 2	75	4.82	4.6	1.2	(4.4, 4.7)	0.003
	Tablet Level 3	76	14.6	14	1	(13, 15)	0.049
Co	Tablet Level 1	78	8.92	8.7	1.2	(8.3, 9.1)	0.231
	Tablet Level 2	75	19.8	19	1	(18, 19)	0.002
	Tablet Level 3	76	39.8	39	1	(37, 40)	0.203
Hg	Tablet Level 1	28	3.64	0.8	1.7	(0.7, 1.0)	< 0.001
	Tablet Level 2	63	14.4	1.5	1.5	(1.4, 1.7)	< 0.001
	Tablet Level 3	69	41.0	3.3	2.6	(2.6, 4.1)	< 0.001
Ni	Tablet Level 1	72	8.59	8.7	1.2	(8.4, 9.1)	0.482
	Tablet Level 2	78	11.9	11	2	(9, 12)	0.100
	Tablet Level 3	78	15.3	14	2	(13, 16)	0.197
Pb	Tablet Level 1	78	2.49	2.5	1.5	(2.3, 2.8)	0.638
	Tablet Level 2	78	5.79	5.6	1.6	(5.0, 6.2)	0.533
	Tablet Level 3	78	15.1	14	2	(13, 16)	0.303
V	Tablet Level 1	75	22.8	21	1	(20, 22)	< 0.001
	Tablet Level 2	75	23.9	23	2	(20, 27)	0.798
	Tablet Level 3	54	1.25	1.6	2.0	(1.3, 1.9)	0.016

Key takeaways: Lab variability (ICP-MS)

- Good reproducibility for most analytes at high concentrations
  - Both within and between laboratories.

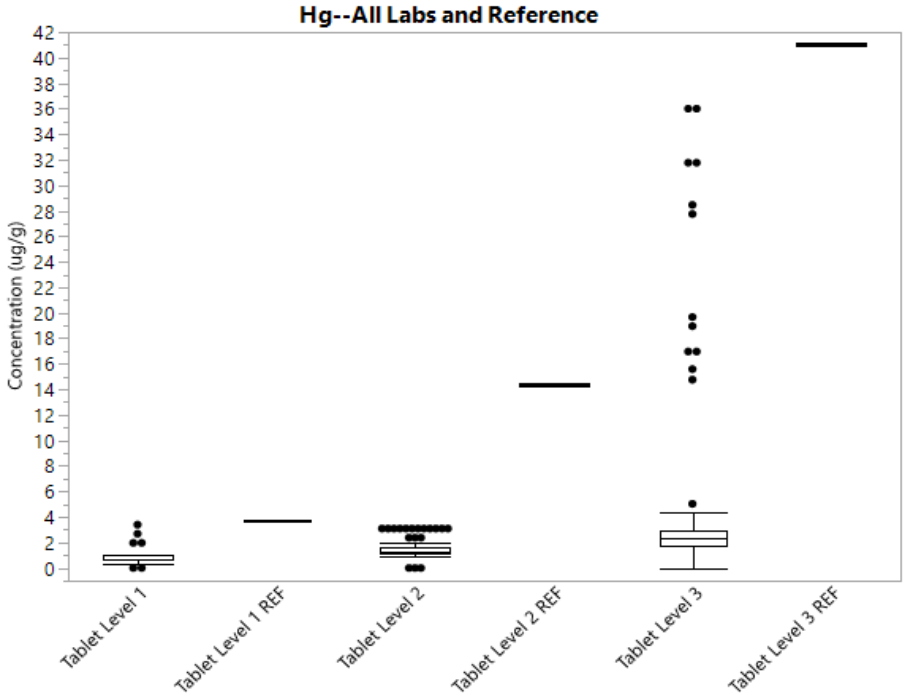
- Consistent results WITHIN labs, but higher variability between labs
  - Specific elements - **Hg, V**

Material	Analyte	Total Measurements	Mean $\log_{10}$(concentration+1) (µg/g)	Within lab Std Dev	Within lab RSD (%)	Across lab Std Dev	Across lab RSD (%)	Reproducibility Ratio
Tablet Level 1	As	87	0.842	0.057	6.8	0.247	29.3	4.40
	Cd	87	0.462	0.082	17.8	0.073	15.8	0.859
	Co	87	0.987	0.066	6.6	0.108	11.0	1.70
	Hg	81	0.276	0.084	30.3	0.192	69.7	5.49
	Ni	87	0.991	0.054	5.5	0.104	10.5	1.97
	Pb	87	0.556	0.047	8.5	0.234	42.0	5.83
	V	84	1.349	0.047	3.5	0.109	8.1	2.32
Tablet Level 2	As	87	1.254	0.048	3.8	0.095	7.6	1.96
	Cd	87	0.723	0.036	5.0	0.286	39.6	1.91
	Co	87	1.251	0.047	3.8	0.489	39.1	1.92
	Hg	81	0.382	0.028	7.4	0.249	65.1	5.99
	Ni	87	1.078	0.117	10.8	0.224	20.8	1.87
	Pb	87	0.827	0.073	8.8	0.307	37.1	4.74
	V	84	1.387	0.240	17.3	0.271	19.5	1.12
Tablet Level 3	As	87	1.635	0.032	2.0	0.160	9.8	5.03
	Cd	87	1.141	0.042	3.7	0.399	34.9	9.97
	Co	87	1.564	0.107	6.8	0.477	30.5	5.38
	Hg	81	0.613	0.072	11.7	0.693	113.0	9.37
	Ni	87	1.190	0.084	7.1	0.266	22.4	3.02
	Pb	87	1.190	0.024	2.1	0.392	32.9	16.3
	V	81	0.393	0.085	21.7	0.324	82.4	3.51

Key takeaways: Lab variability (cont'd)

Analysis of tablets by ICP-MS

- Consistent results WITHIN labs, but higher variability between labs
  - Specific elements - **Hg, V**



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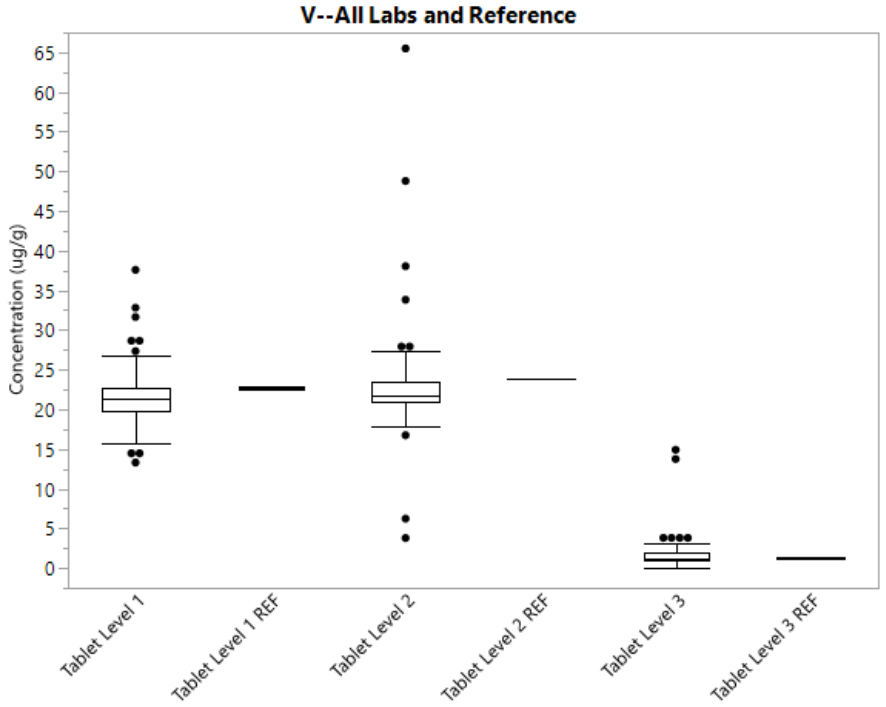
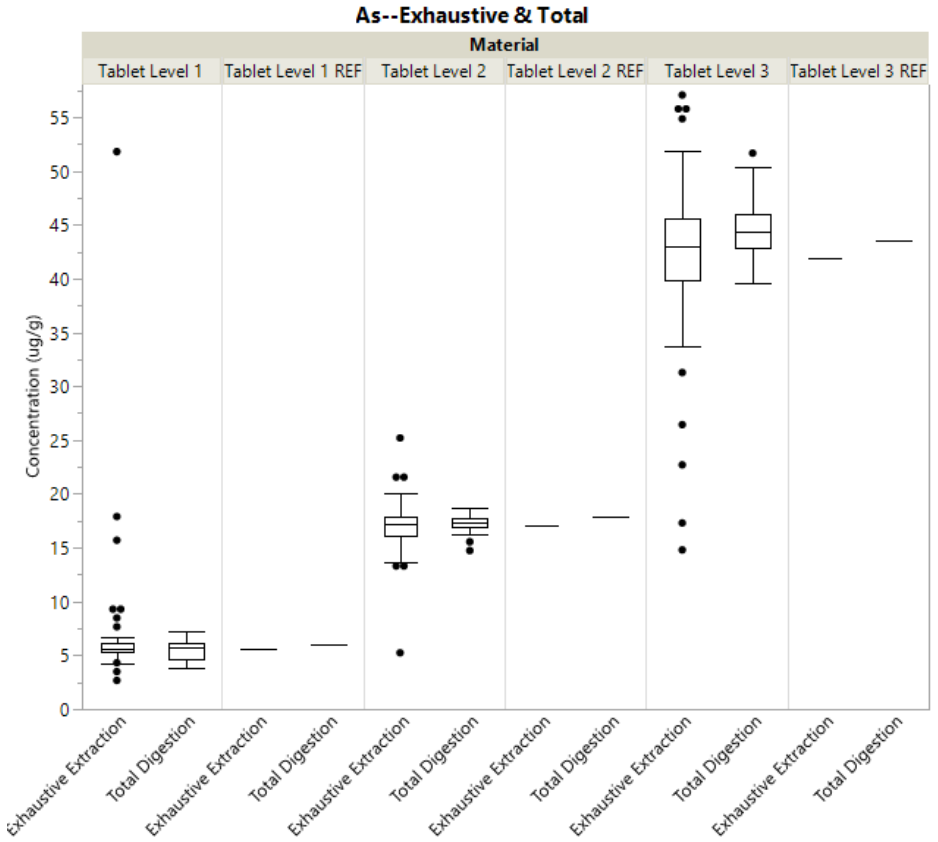


Key takeaways: Digestion method

Exhaustive extraction vs Total Digestion

- No significant difference for tablets
  - P values: 0.064 – 0.739
- Variability was different between methods
  - Total digestion < exhaustive extraction
  - Both within and between labs

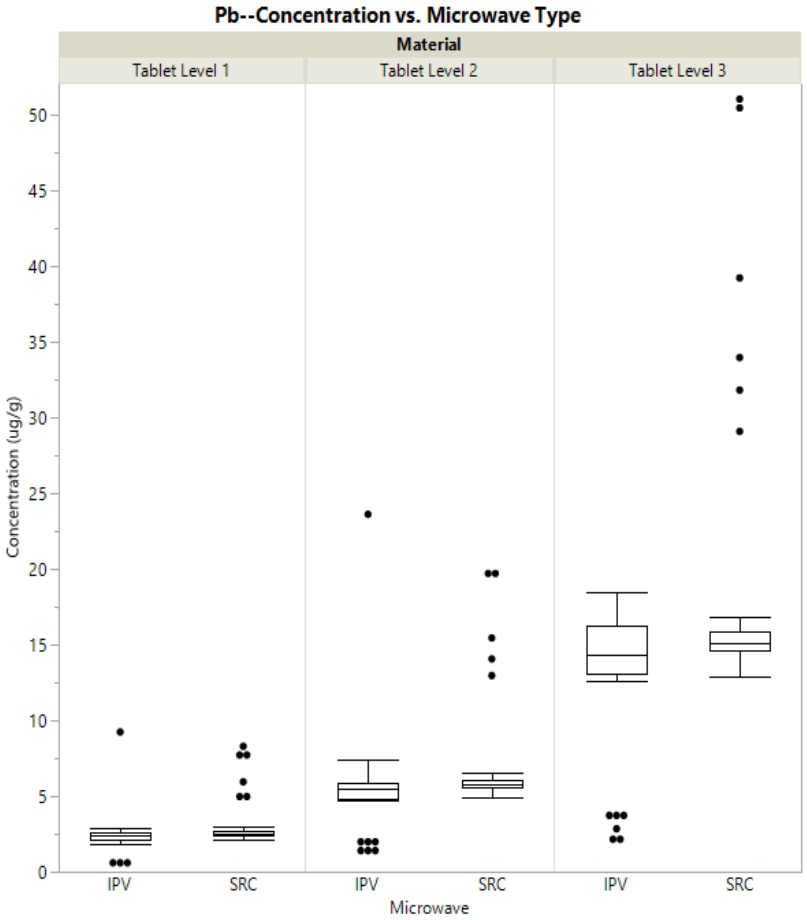


Key takeaways:

SRC vs IPV

- Most elements in Raw Materials >LOQ were consistent
- Exceptions: Hg, Pb
  - Concentrations by SRC > IPV
  - IPV more variable
  - Potential volatility of Hg?

Analyte	Material	P-value
Hg	Tablet Level 1	0.013
	Tablet Level 2	0.004
	Tablet Level 3	< 0.001
Pb	Tablet Level 1	0.080
	Tablet Level 2	0.017
	Tablet Level 3	0.002



Key takeaways: Raw Material analysis

Raw material analysis (all labs)

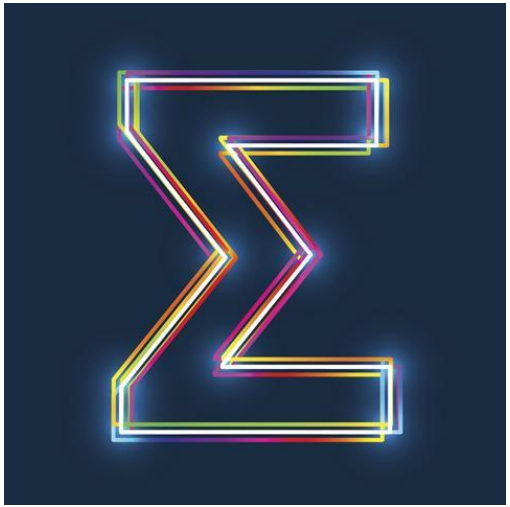
Material	Elements with false positive rate >10%*	Elemental recoveries vs Reference	Elements 90-110% recovery vs Reference	Highly reproducible elements (s_R:s_r < 6)	Elements of Concern
Lactose	Ni, V	NA	NA	Ni, Pb	Ni, V
Magnesium Aluminum Silicate		99.4 – 362%	Pb, V	Co, Ni, Pb, V	As, Cd, Ni
Microcrystalline Cellulose	As, Cd, Co, Hg, Ni, V	NA	NA	Hg, Ni, Pb	As, Cd, Co, Hg, Ni, V
Red Ferric Oxide	Cd	83.0 – 248%	Ni	As, Co, Hg, Ni, Pb	Cd
Silicon Dioxide Standard (As, Co, Hg)	Cd, Ni, Pb, V	88.7 – 91.8%	As	As, Co, Hg	V
Silicon Dioxide Standard (Cd, Ni, Pb)	Co, Hg, V	33.0 – 98.1%	Cd, Ni, Pb	As, Cd, Ni, Pb	V
Starch	Ni, Pb, V	NA	NA		V
Stearic Acid	Cd, Pb, V	NA	NA		V

Within-lab variability was better than between-lab variability, greater variability for RM's than tablets
High false positive rate for V
Similar analysis was performed for Exhaustive only, Total only

Key takeaways:

Raw material analysis - Summation Analysis vs Direct Analysis

Material	Elements w/ Avg conc p < 0.05	Within lab st dev p < 0.05	Between lab std dev p < 0.05	Elements of Concern
Tablet Level 1	Hg, Pb	Cd, Co, Hg, V	Cd, Co, Hg, Pb, V	Hg
Tablet Level 2	Cd, Hg	As, Cd, Ni, V	As, Cd, Co, Pb	Cd
Tablet Level 3	As, Cd, Hg, V	Cd, Co, Hg, Pb, V	Co, Hg, Ni, Pb, V	Hg, V

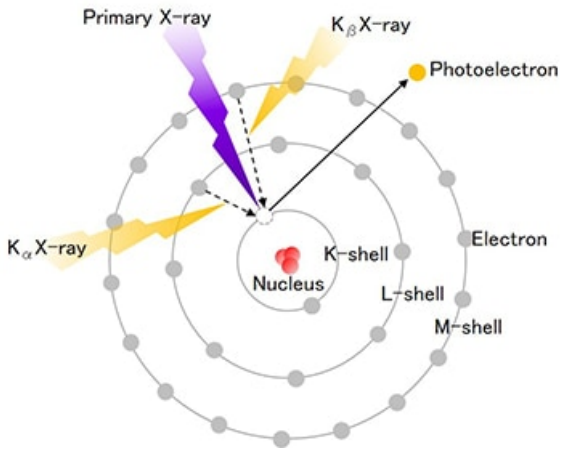


- Mixed agreement between the summation approach and the direct analysis of tablets.
- As, Co, Ni, and V – best agreement between measured and summed concentrations
- Variability of the summation approach was higher than direct analysis
  - Summation could impact the analysis of low level impurities.

XRF results summary - reproducibility

- **Quality control reproducible within labs except Cd**; good reproducibility for most elements across labs

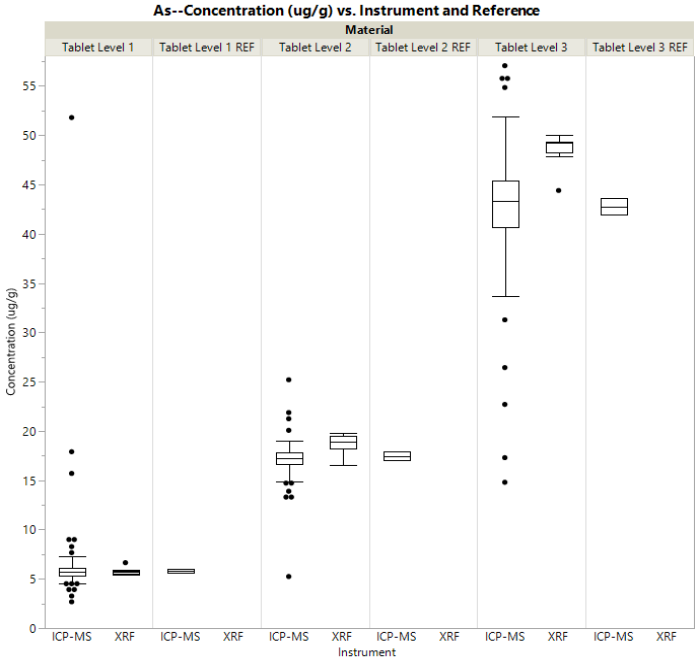
Material	Analyte	Mean $\log_{10}$(concentration+1) (µg/g)	Within lab RSD (%)	Across lab RSD (%)
Formulation 1 Readback	As	0.680	1.7	10.2
	Cd	0.316	14.4	65.7
	Co	1.227	0.9	12.4
	Hg	1.008	1.2	5.1
	Ni	1.775	0.3	4.5
	Pb	0.439	3.3	7.3
	V	1.629	0.4	7.0
Formulation 7 Readback	As	0.724	1.2	5.7
	Cd	0.303	12.9	37.9
	Co	1.113	1.0	7.1
	Hg	0.976	3.5	4.4
	Ni	1.769	0.5	1.7
	Pb	0.491	4.0	9.0
	V	1.474	0.7	0.8



Key takeaways: XRF analysis

Vs reference

- Most elements agreed with reference
- Consistent within-lab variability, higher between-lab variability
- As, Cd: ICP-MS < XRF



Vs participant ICP-MS

- Cd consistently higher by XRF
- Within-lab variability
  - Better for XRF, likely an artifact
- Between-lab variability: XRF < ICP-MS
- Similar for Total and Exhaustive

Material	Elements Average concentration p < 0.05	Within lab standard deviation p < 0.05	Between lab standard deviation p < 0.05
Level 1	Cd, Hg	As, Co, Ni, V	As, Co, Ni, V
Level 2	As, Cd, Hg	As, Co, Ni, Pb, V	Co
Level 3	As, Cd, Ni	As, Cd, Co, Ni,	As

Summary of ICP-MS results by analyte

	Strong Equivalence	Moderate Equivalence	Weak Equivalence
Reproducibility How variable is an element between labs and within labs (Strong = low variability; weak = higher variability)	As, Co, Ni	Cd, Hg, Pb	V
Exhaustive vs Total Compares exhaustive vs total	Cd	As, Co, Hg, Ni, Pb	V
Microwave types (SRC vs IPV) Compares SRC vs IPV	Cd, Ni	As, Co, V	Hg, Pb
Summation Approach Compares summation of RM's vs finished product analysis	Ni	As, Co, Pb	Cd, Hg, V
Comparison to Reference Compares all lab results to Reference lab results	Pb	As, Cd, Co, Ni	Hg, V
Overall ICP-MS Summarizes overall element performance	Ni	As, Cd, Co, Pb	Hg, V

Note: Similar analysis performed for raw materials.

Summary of XRF results by analyte

	Strong Equivalence	Moderate Equivalence	Weak Equivalence
Reproducibility How variable is an element between labs and within labs (Strong = low variability; weak = higher variability)	As	Hg	Cd, Co, Ni, Pb, V
XRF vs ICP-MS (all) Compares XRF lab results to all ICP-MS laboratory results	Pb, V	Co, Hg, Ni	As, Cd
XRF vs ICP-MS (exhaustive) Compares XRF lab results to ICP-MS laboratory results for exhaustive extraction		Co, Hg, Ni, Pb, V	As, Cd
XRF vs ICP-MS (total) Compares XRF lab results to ICP-MS laboratory results for total digestion	Co, Pb	Hg, V	As, Cd, Ni
Comparison to Reference Compares XRF lab results to ICP-MS reference laboratory results for total digestion	Co, Ni, Pb, V		As, Cd, Hg
Overall XRF Summarizes overall element performance	Pb	Co, Ni, V, Hg	As, Cd

Note: XRF analysis only performed for Tablet materials.

Points for thought

Comparable results for Ni, As, Cd, Co, Pb

Hg loss

only in formulation, not in raw material

V interferences

NH_3 recommended for trace analysis

Cd challenges

MoO, Sn

Exhaustive vs Total digestion

Not all methods are created equal!

Conclusions

- Several elements were comparable between participants, reference laboratory. Exceptions: Cd, Hg, V.
- Reproducibility was good for high conc elements. Reproducibility was better for total digestion than for exhaustive extraction.
- Comparable concentrations were reported for exhaustive vs total; total digestion was less variable than exhaustive extraction.
- SRC and IPV systems comparable high conc elements, except mercury and lead. Greater variability for IPV systems.
- Summation approach was comparable to direct analysis of tablets for most analytes except Hg and Cd, but summation demonstrated greater variability for most analytes.
- XRF was comparable to ICP-MS, both participant labs and reference values, for most analytes except As, Cd, and Hg. Variability was greater for ICP-MS than XRF. Only As and Hg demonstrated strong reproducibility.

Key questions – Breakout session coming up!

- What level of error or uncertainty would represent a compelling indicator for adjusting analytical methods?
- What strategies are labs taking with respect to total digestion/ exhaustive extraction considering the extensive infrastructure and safety considerations for total digestion?
  - How are you demonstrating equivalence between exhaustive extraction and total digestion methods?
- How do analytical labs design internal SOP's for validation to account for variability and address regulatory requirements for method development?
- When approaching a control limit or PDE, how do you account for variability? Are any additional steps included to account for this?
- Are comparable levels of analytical uncertainty and variability of results acceptable for risk assessment purposes as for routine release testing of products?
- What role do statisticians and analytical experts play in the development of risk assessments to account for potential uncertainties?
- Are the observations regarding mercury recovery in tablets (i.e. loss over time) consistent with real-world products, and if so, what can be done to account for hold time?

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