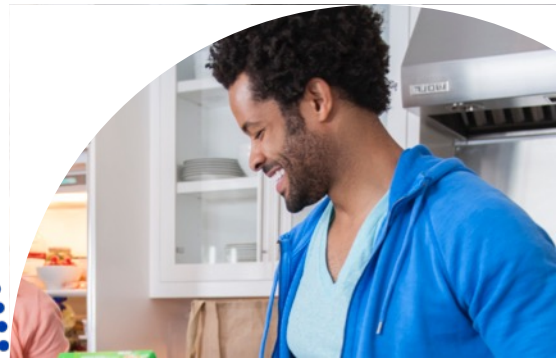
Method Development & Laboratory Participant Perspective

Denise McClenathan

Group Leader, Elemental Analysis Capability



A Tale of Two Labs in One

"Reference Lab"

ICP-MS Method Development and Optimization

Total Digestion & Exhaustive Extraction

Tablet and Raw Material Reference Values

"Participant Lab"

Study Sample Analysis – Phase 2

ICP-MS and XRF

Elemental Impurities at P&G

400+ DRUG PRODUCTS WITH WIDE RANGE OF MATERIALS

Excipients: Salts, Minerals, Botanicals, Organics, Polymers

Actives: Bismuth Subsalicylate, TiO_2, ZnO, SnF_2, NaF, SeS_2, Al/Zr Based Actives

Co-Mingled: Trace Els and Inorganic RMs

Analytical Challenges: Matrix Effects, Specificity, Digestion

ICP-MS Method Development

Uniform Procedures for Phase 2

Approach to Development and Optimization

- Total Digestion → Total Content Assessment
  Achieve Mass Balance
- Exhaustive Extraction (w/o HF/HBF_4)
  Evaluate Relative to Total Digestion
- Applicable to Wide Range of Instrumentation
  Individually-Pressurized Vessels & Single Reaction Chamber

Milestone UP

Milestone
UltraWAVE with ECR
(HCl compatible)

- Leverage ICP-MS/MS (QQQ) for Selectivity

Agilent 8800
QQQ ICP-MS

Andrei Shauchuk

Method Development
for ICP-MS

Kelly Smith

Keys to Total Digestion Approaches

MORE THAN JUST "NUKING" THE MATRIX

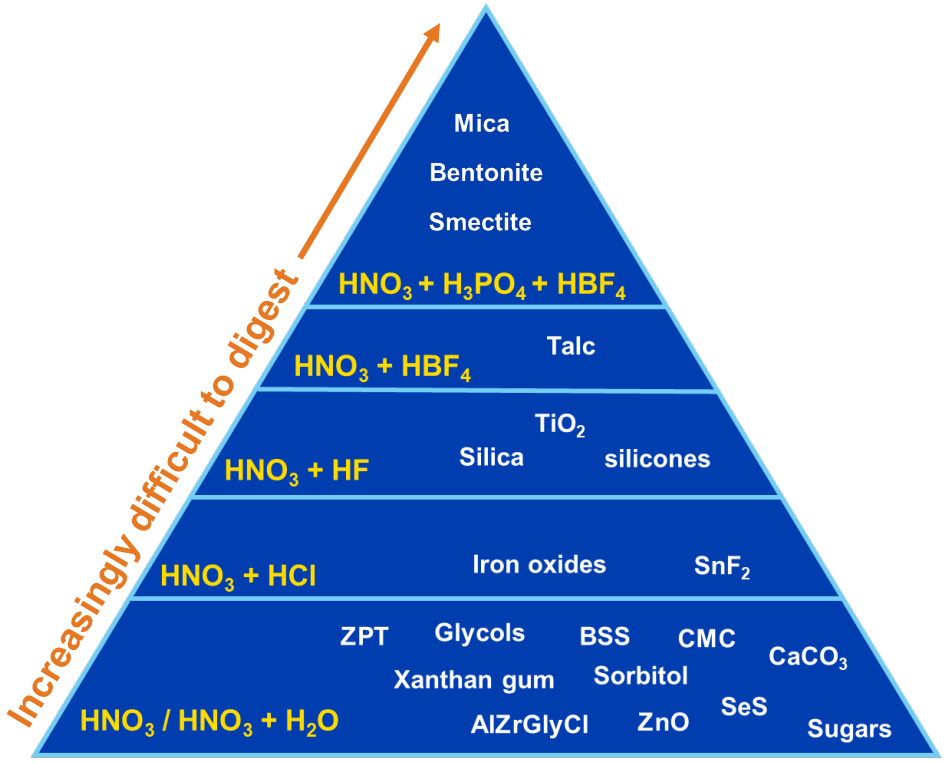
Titrate acid combination to most complex ingredient

Stabilize the analytes (ex. Hg with Au or HCl)

Prevent formation of insoluble fluorides (Mg, Al, Ca, etc.)

- Complex excess fluoride with boric acid (2 step process)
- Prepare ultra-trace HBF_4 from HF & boric acid

Ultra-trace HBF_4 not commercially available



Sample Preparation – Total Digestion

RAW MATERIALS AND TABLETS

(1) Weigh sample
- Tablet (0.25 g)
- Raw material (0.01-0.15 g)

(2) Add reagents
- 0.5 mL of HCl
- 2.5 mL of HNO_3
- 0.5 mL H_3PO_4
- 1.0 mL of HBF_4

(3) Microwave digest

(4) Transfer to 50 mL tube and dilute to volume

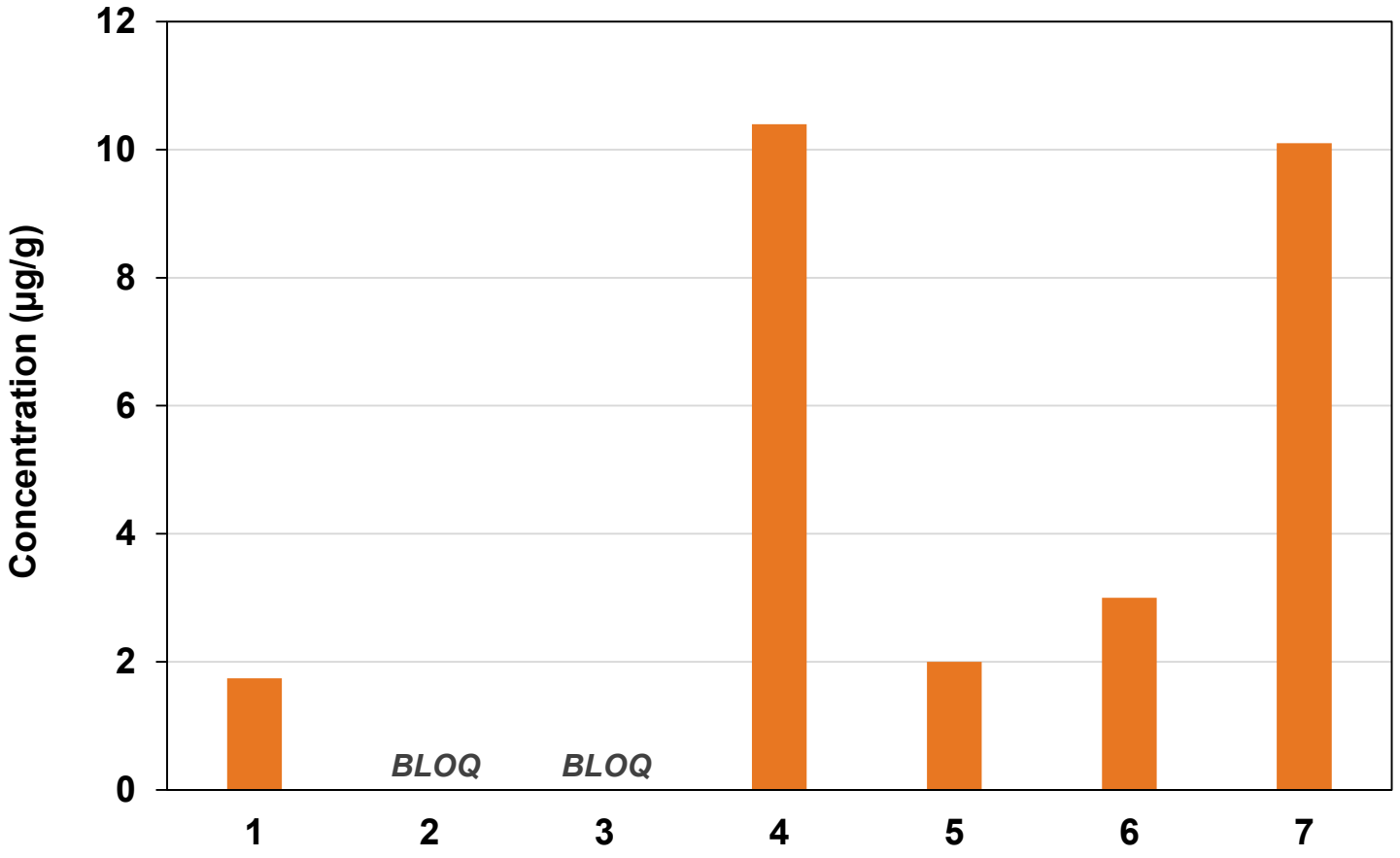
(5) Prepare 50X dilution with internal standard

Single Reaction Chamber
Ramp and Hold @ 250 °C

Individually-Pressurized Vessel
Ramp and Hold @ 180 °C

Magnesium Aluminum Silicate Results

TOTAL DIGESTION AND ICP-MS/MS



Confirmation of Specificity

Analyte	Detection Scheme	Concentration (µg/g)
Cobalt	59 → 59 [He]	2.00
	59 → 75 [O_2]	1.83
Vanadium	51 → 51 [NH_3]	10.1
	51 → 135 [NH_3]	11.2

Interferences at m/z 59

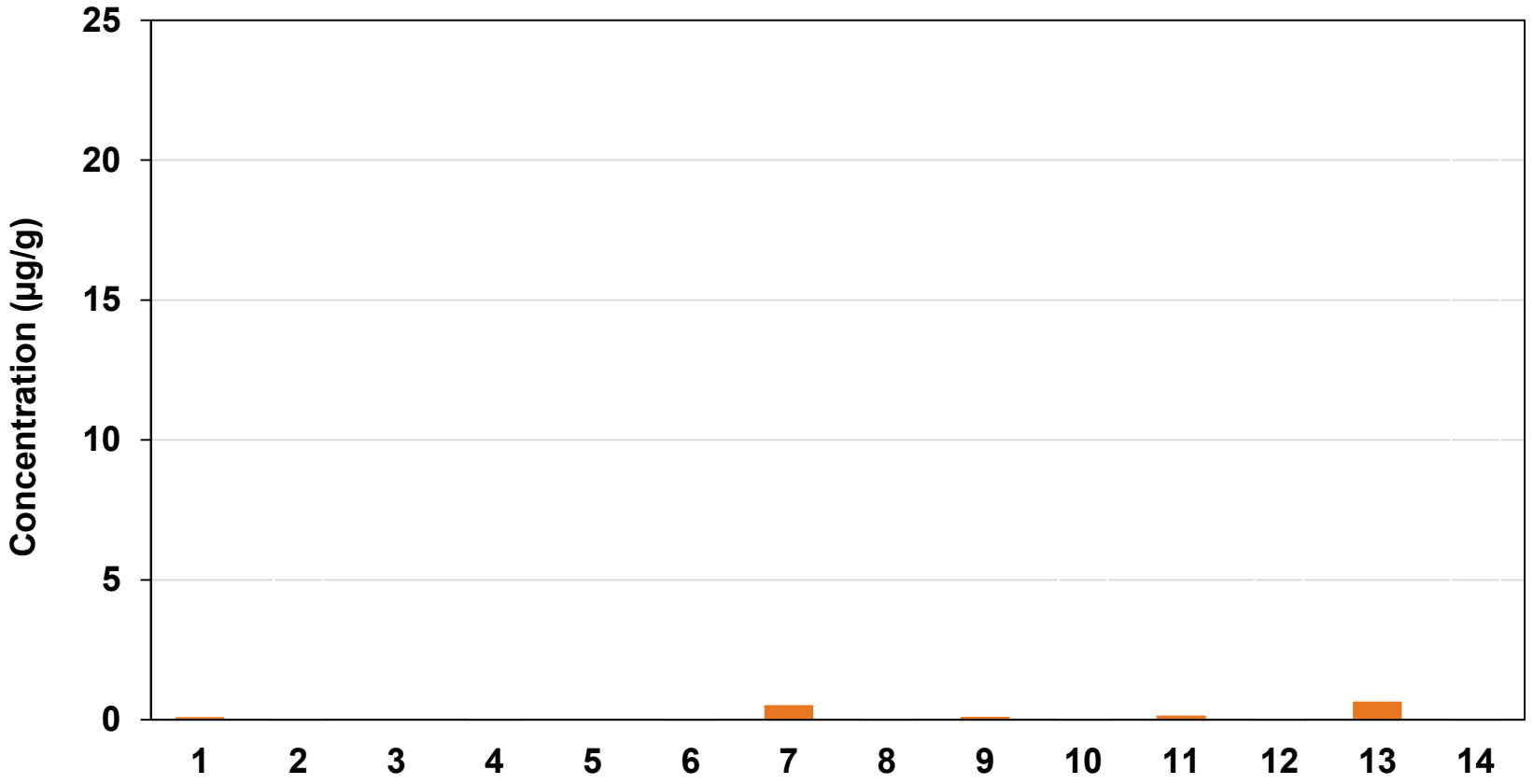
$^{43}Ca^{16}O^+$, $^{42}Ca^{16}O^1H^+$, $^{24}Mg^{35}Cl^+$, $^{36}Ar^{23}Na^+$, $^{40}Ar^{18}O^1H^+$, $^{40}Ar^{19}F^+$

Interferences at m/z 51

$^{34}S^{16}O^1H^+$, $^{35}Cl^{16}O^+$, $^{38}Ar^{13}C^+$, $^{36}Ar^{15}N^+$, $^{36}Ar^{14}N^1H^+$, $^{37}Cl^{14}N^+$, $^{36}S^{15}N^+$, $^{33}S^{18}O^+$, $^{34}S^{17}O^+$

Summation Approach

LEVEL 1 TABLET – TOTAL DIGESTION



Raw Materials

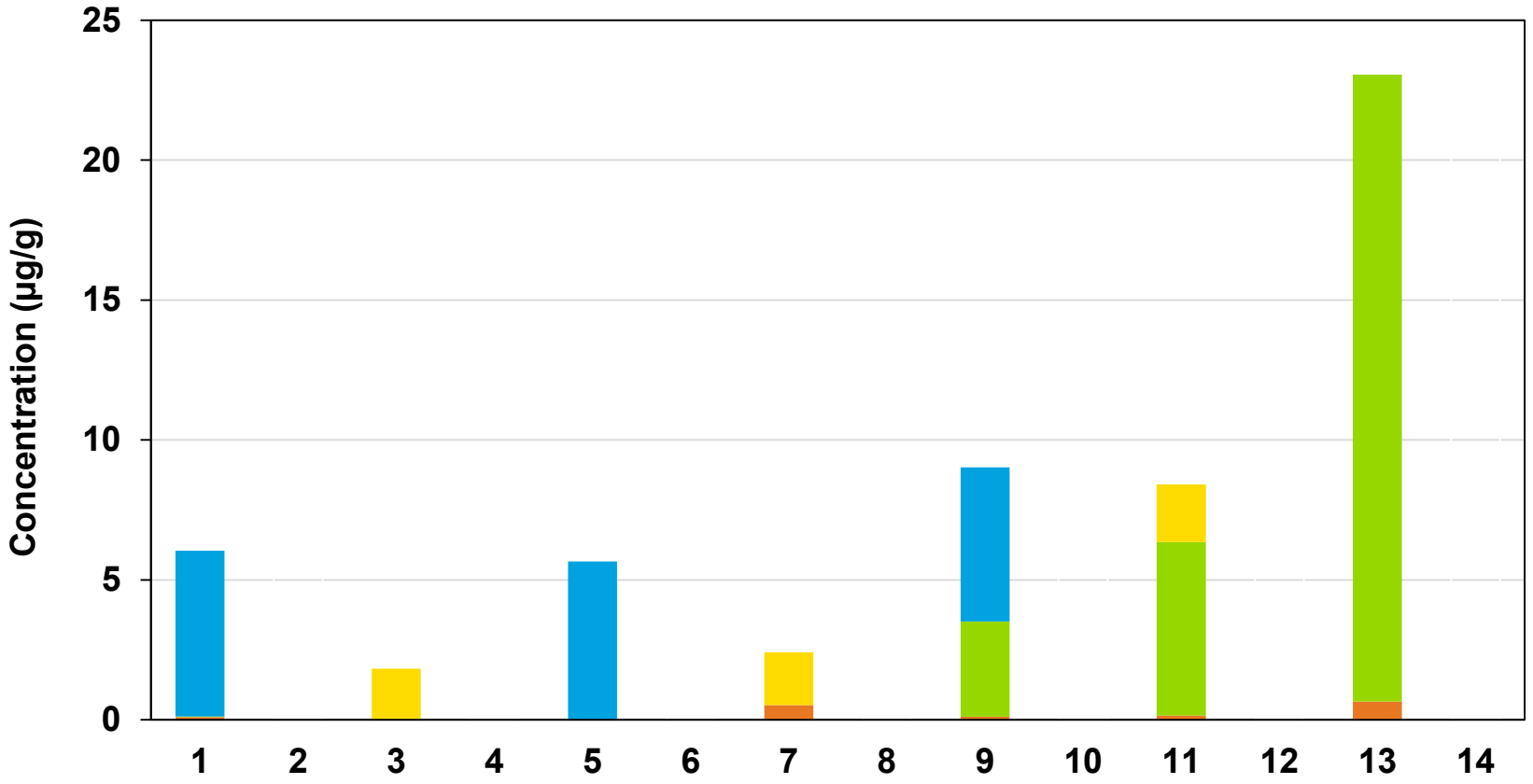
Magnesium Aluminum Silicate
Ferric Oxide Red
Silicon Dioxide, As Co Hg
Silicon Dioxide, Cd Pb Ni
Microcrystalline Cellulose
Pregelatinized Starch
Stearic Acid
Lactose

Finished Product

Level 1 Tablet

Summation Approach

LEVEL 1 TABLET – TOTAL DIGESTION



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Microcrystalline Cellulose
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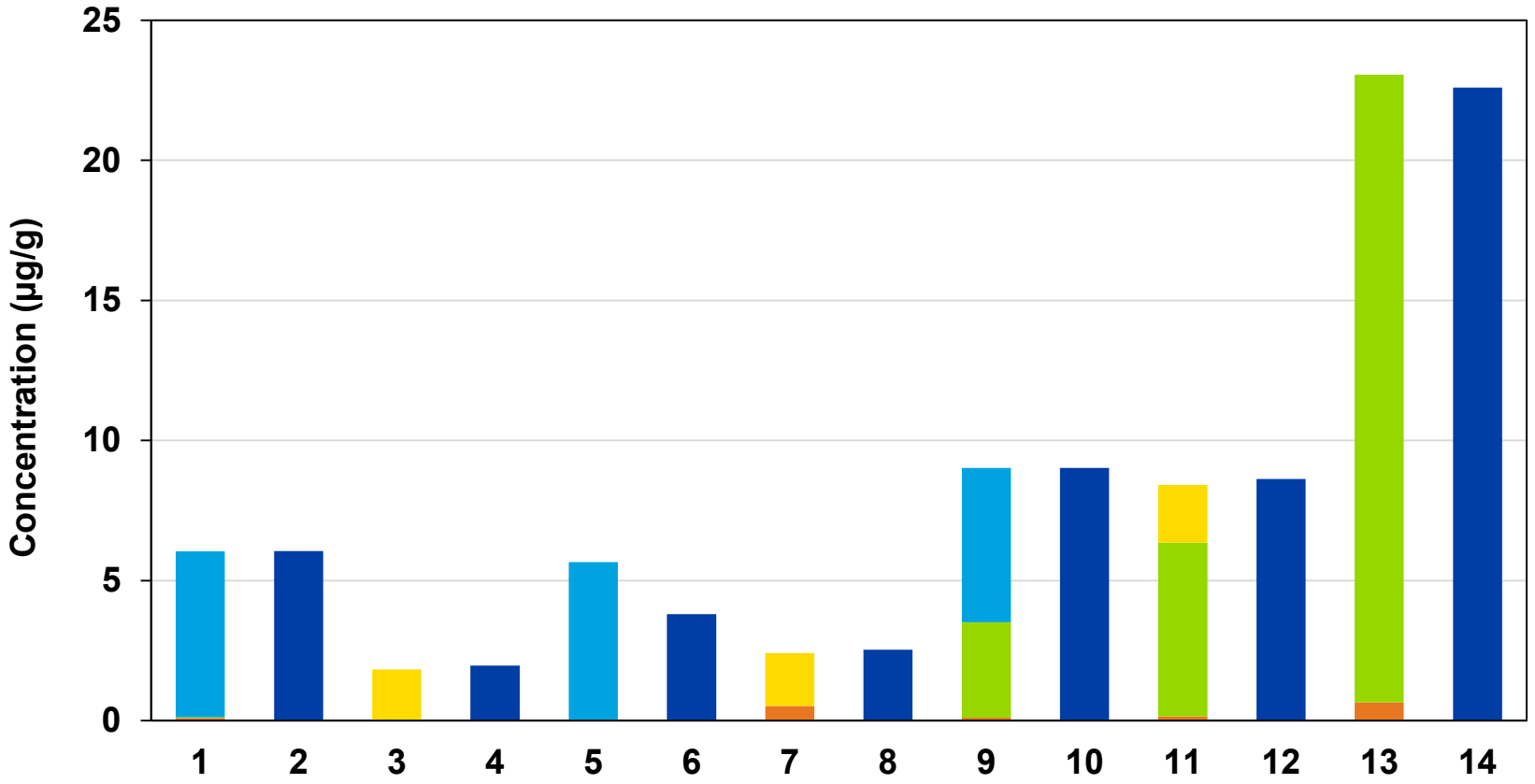
Stearic Acid
Lactose

Finished Product

Level 1 Tablet

Mass Balance Assessment

LEVEL 1 TABLET – TOTAL DIGESTION



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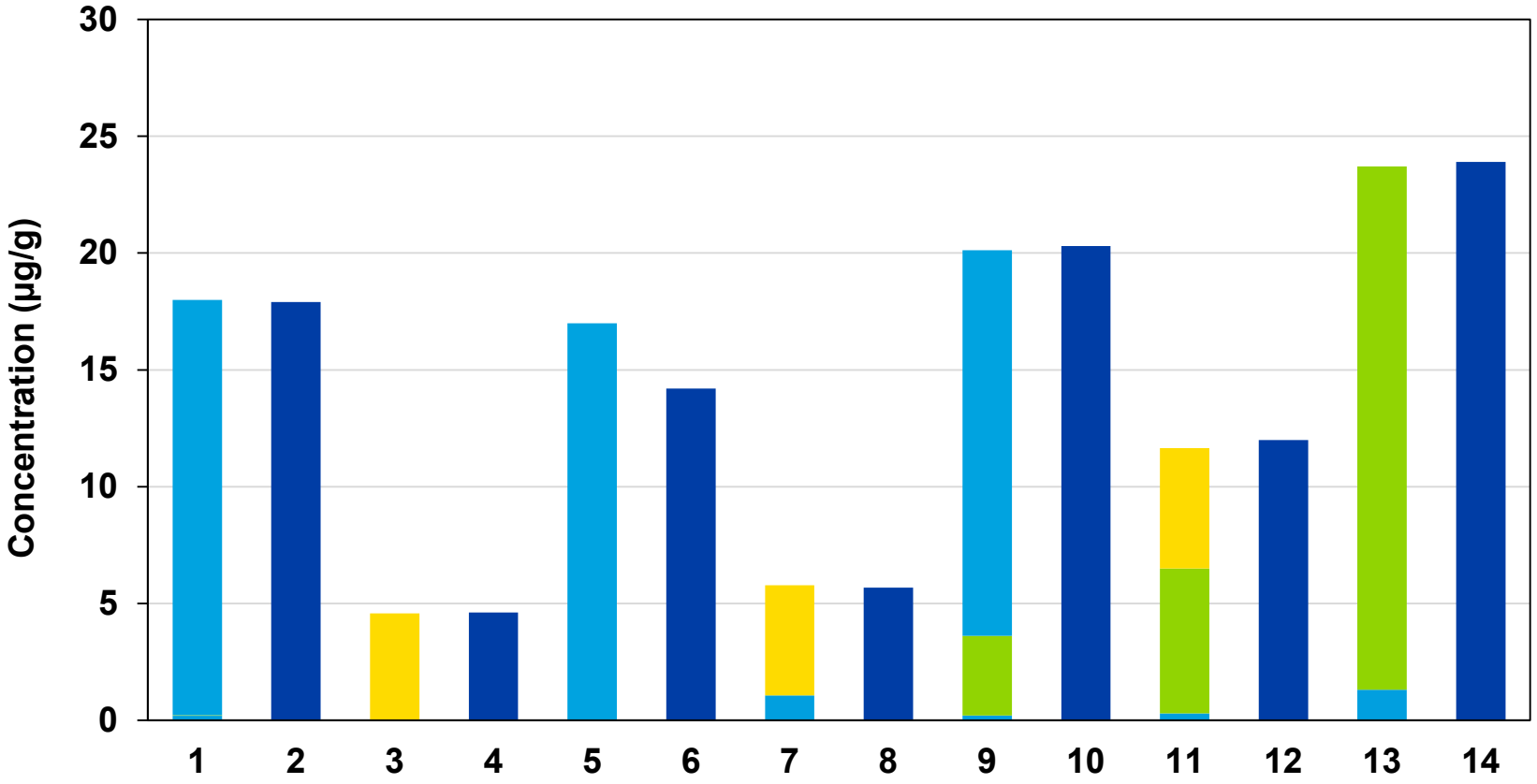
Silicon Dioxide, As Co Hg
Silicon Dioxide, Cd Pb Ni
Microcrystalline Cellulose
Pregelatinized Starch
Stearic Acid
Lactose

Finished Product

Level 1 Tablet

Mass Balance Assessment

LEVEL 2 TABLET – TOTAL DIGESTION



Raw Materials

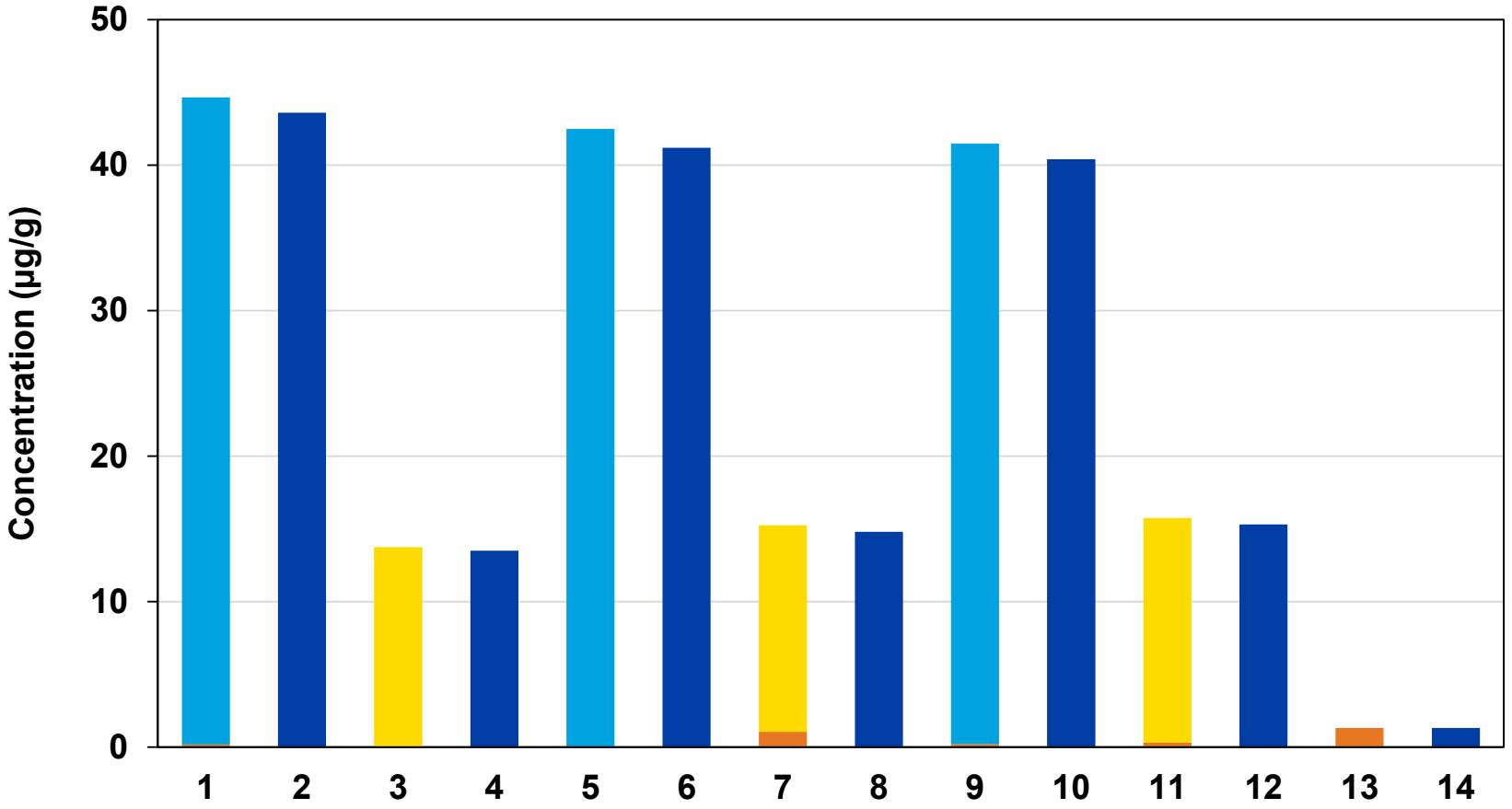
Magnesium Aluminum Silicate
Ferric Oxide Red
Silicon Dioxide, As Co Hg
Silicon Dioxide, Cd Pb Ni
Microcrystalline Cellulose
Pregelatinized Starch
Stearic Acid
Lactose

Finished Product

Level 2 Tablet

Mass Balance Assessment

LEVEL 3 TABLET – TOTAL DIGESTION



Raw Materials

Magnesium Aluminum Silicate
Ferric Oxide Red
Silicon Dioxide, As Co Hg
Silicon Dioxide, Cd Pb Ni
Microcrystalline Cellulose
Pregelatinized Starch
Stearic Acid
Lactose

Finished Product

Level 3 Tablet

Mass Balance Assessment

ALL TABLET LEVELS – TOTAL DIGESTION

Percent of the Predicted Value

(Measured Tablet / RM Summation)

Sample	Arsenic	Cadmium	Mercury	Lead	Cobalt	Nickel	Vanadium
Tablet 1	100%	108%	67%	105%	100%	103%	98%
Tablet 2	99%	101%	84%	98%	101%	103%	101%
Tablet 3	98%	98%	97%	97%	97%	97%	100%

Sample Preparation – Exhaustive Extraction

RAW MATERIALS AND TABLETS

(1) Weigh sample
    Tablet (0.25 g)
    Raw material (0.01-0.15 g)

(2) Add reagents
    10 mL of HNO_3
    50 µL of 1000 ppm Au

(3) Microwave digest

(4) Transfer to 50 mL tube and dilute to volume

(5) Prepare 50X dilution with internal standard

Single Reaction Chamber
Ramp and Hold @ 175 °C

Individually-Pressurized Vessel
Ramp and Hold @ 175 °C

Exhaustive Extraction – Tablets and Raw Materials

COMPARISON TO TOTAL DIGESTION

Percent of Total Digestion

(Exhaustive Extraction vs RM Summation)

	Arsenic	Cadmium	Mercury	Lead	Cobalt	Nickel	Vanadium
Tablet 1	98%	98%	93%	94%	99%	101%	99%
Tablet 2	106%	103%	95%	102%	97%	100%	99%
Tablet 3	111%	103%	96%	99%	98%	93%	100%
Magnesium Aluminum Silicate	92%	N/A	N/A	98%	95%	100%	77%
Ferric Oxide	93%	N/A	N/A	N/A	N/A	N/A	105%
SiO_2 (As, Hg, Co)	110%	N/A	118%	N/A	113%	N/A	N/A
SiO_2 (Cd, Pb, Ni)	N/A	106%	N/A	105%	N/A	107%	N/A

N/A – Results BLOQ

Reference Lab Learnings

Exhaustive extraction can be equivalent to total digestion when the procedure is appropriately optimized for the matrix.

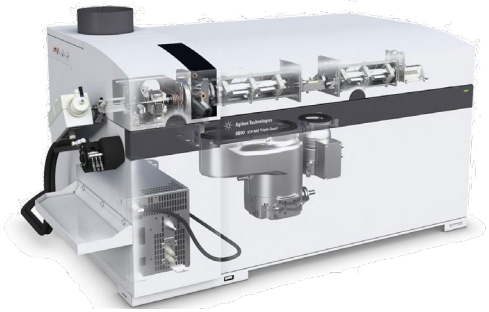
ICP-MS Participant Results

Instrumentation / Approach

RAW MATERIALS AND TABLETS

Milestone
UltraWAVE

Agilent 7900 ICP-MS



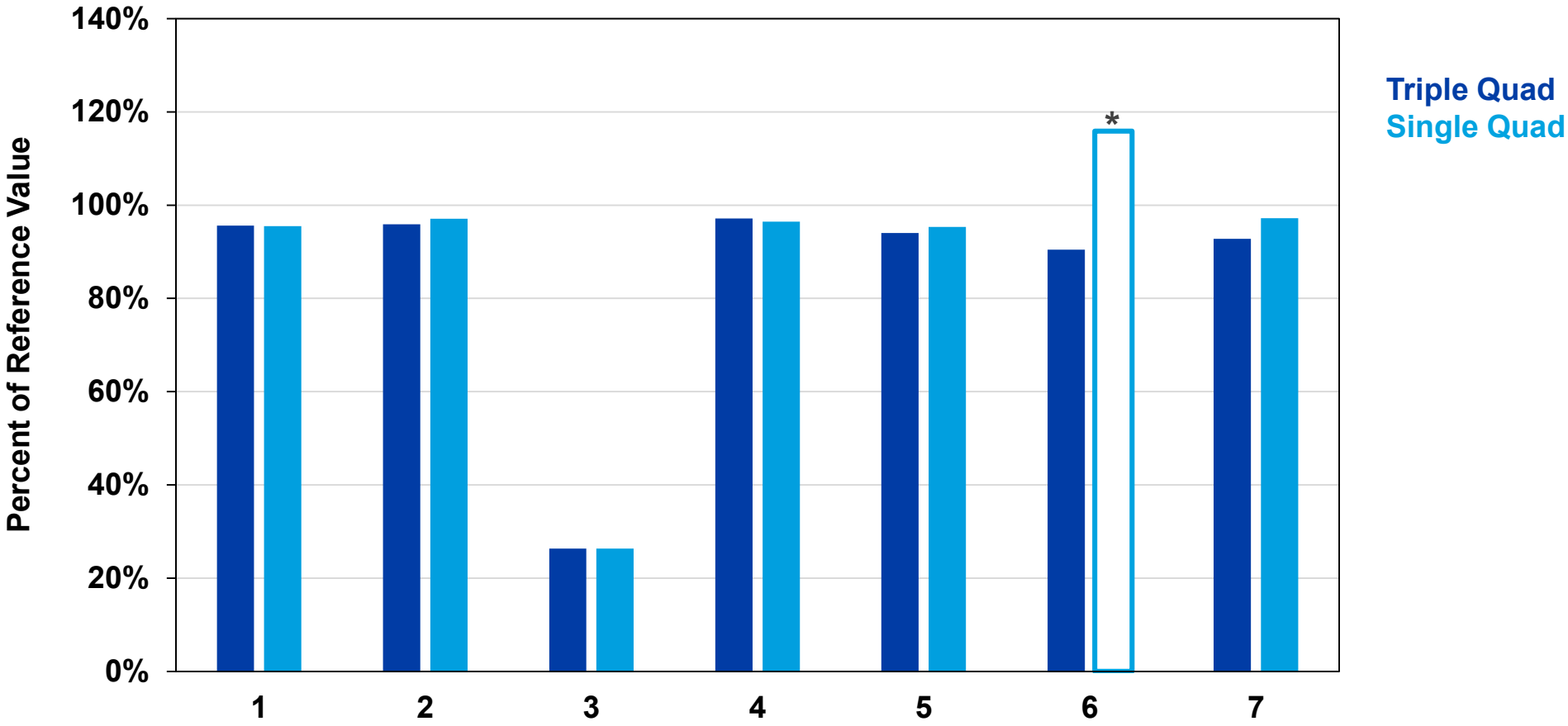
Agilent 8800 QQQ ICP-MS

Total Digestion
Exhaustive Extraction
ICP-MS & ICP-MS/MS

Usa Rattanaudompol

Total Digestion Results for Example Tablet

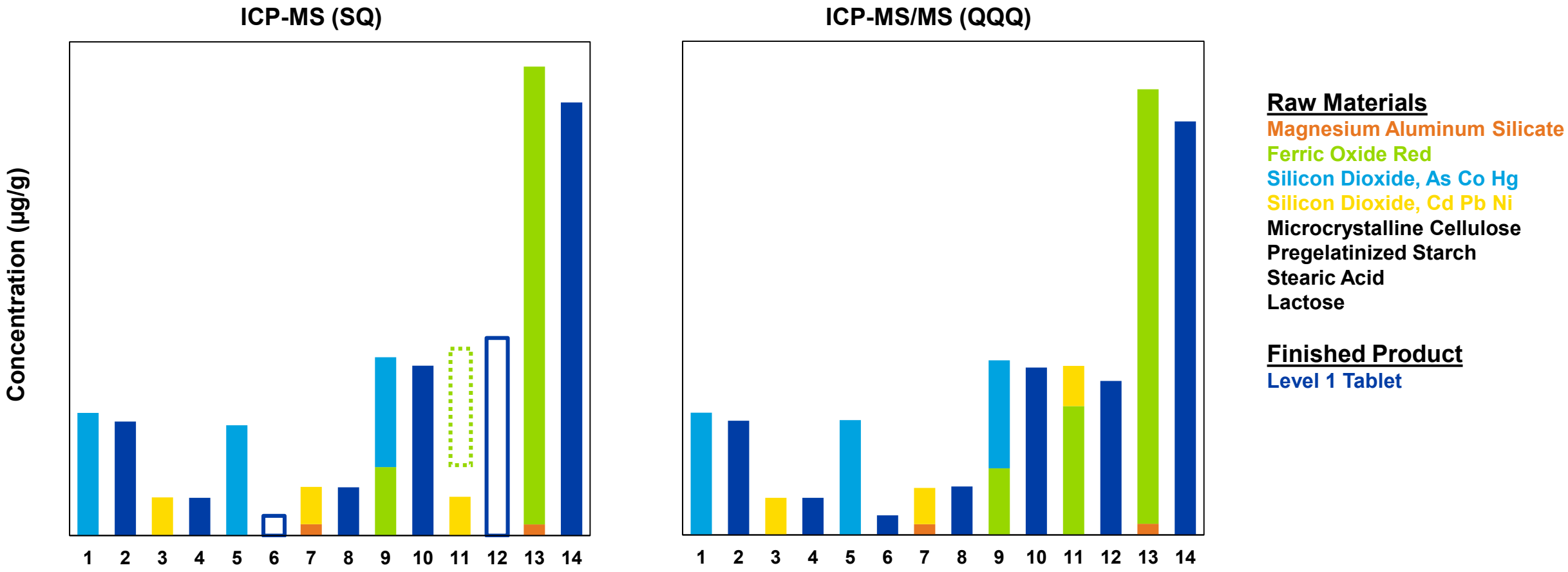
COMPARISON TO REFERENCE VALUE



*Represents LOQ Value

Summation Approach & Mass Balance Assessment

EXAMPLE TABLET – TOTAL DIGESTION



Raw Materials

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Ferric Oxide Red
Silicon Dioxide, As Co Hg
Silicon Dioxide, Cd Pb Ni
Microcrystalline Cellulose
Pregelatinized Starch
Stearic Acid
Lactose

Finished Product

Level 1 Tablet

Summary of ICP-MS Results for Tablets

COMPARISON TO REFERENCE VALUES

Percent Recovery vs Reference

Sample	Preparation	ICP-MS	Arsenic	Cadmium	Mercury	Lead	Cobalt	Nickel	Vanadium
Tablet 1	Total	QQQ							
		SQ						BLOQ	
	Extract	QQQ							
		SQ						BLOQ	
Tablet 2	Total	QQQ							
		SQ							
	Extract	QQQ							
		SQ							
Tablet 3	Total	QQQ							
		SQ							BLOQ
	Extract	QQQ							
		SQ							BLOQ

Scale ± 15% ± 15% to 30% > 30%

Summary of ICP-MS Results for RM Summation

COMPARISON TO REFERENCE VALUES

Percent Recovery vs Reference

Sample	Preparation	ICP-MS	Arsenic	Cadmium	Mercury	Lead	Cobalt	Nickel	Vanadium
Tablet 1	Total	QQQ							
		SQ						*	
	Extract	QQQ							
		SQ						*	
Tablet 2	Total	QQQ							
		SQ						*	
	Extract	QQQ							
		SQ						*	
Tablet 3	Total	QQQ							
		SQ							*
	Extract	QQQ							*
		SQ							*

Scale ± 15% | ± 15% to 30% | > 30%

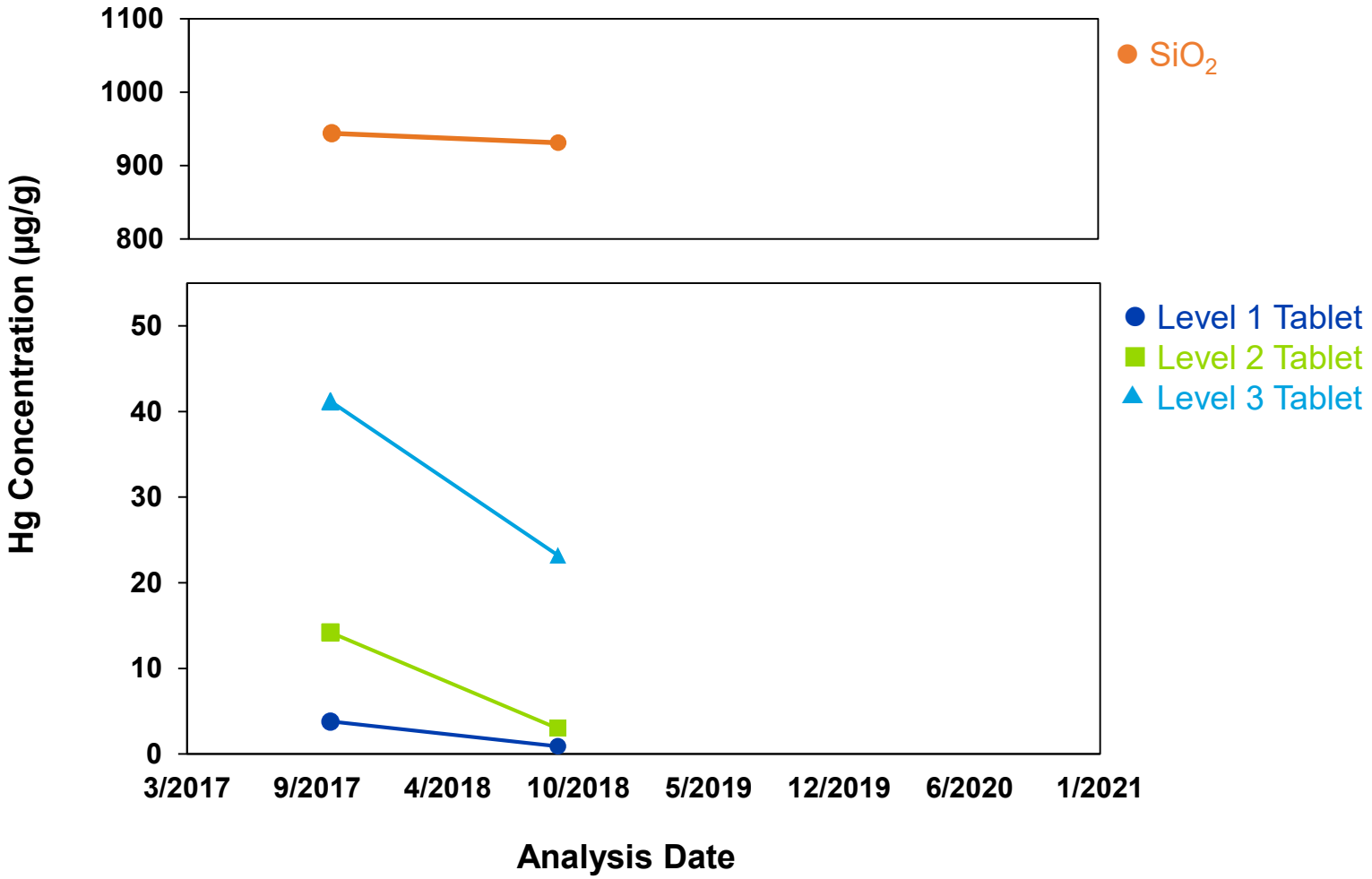
**BLOQ values*

Difference in Mercury Results

INVESTIGATING UNEXPECTED DATA

Lab error?

Stability?

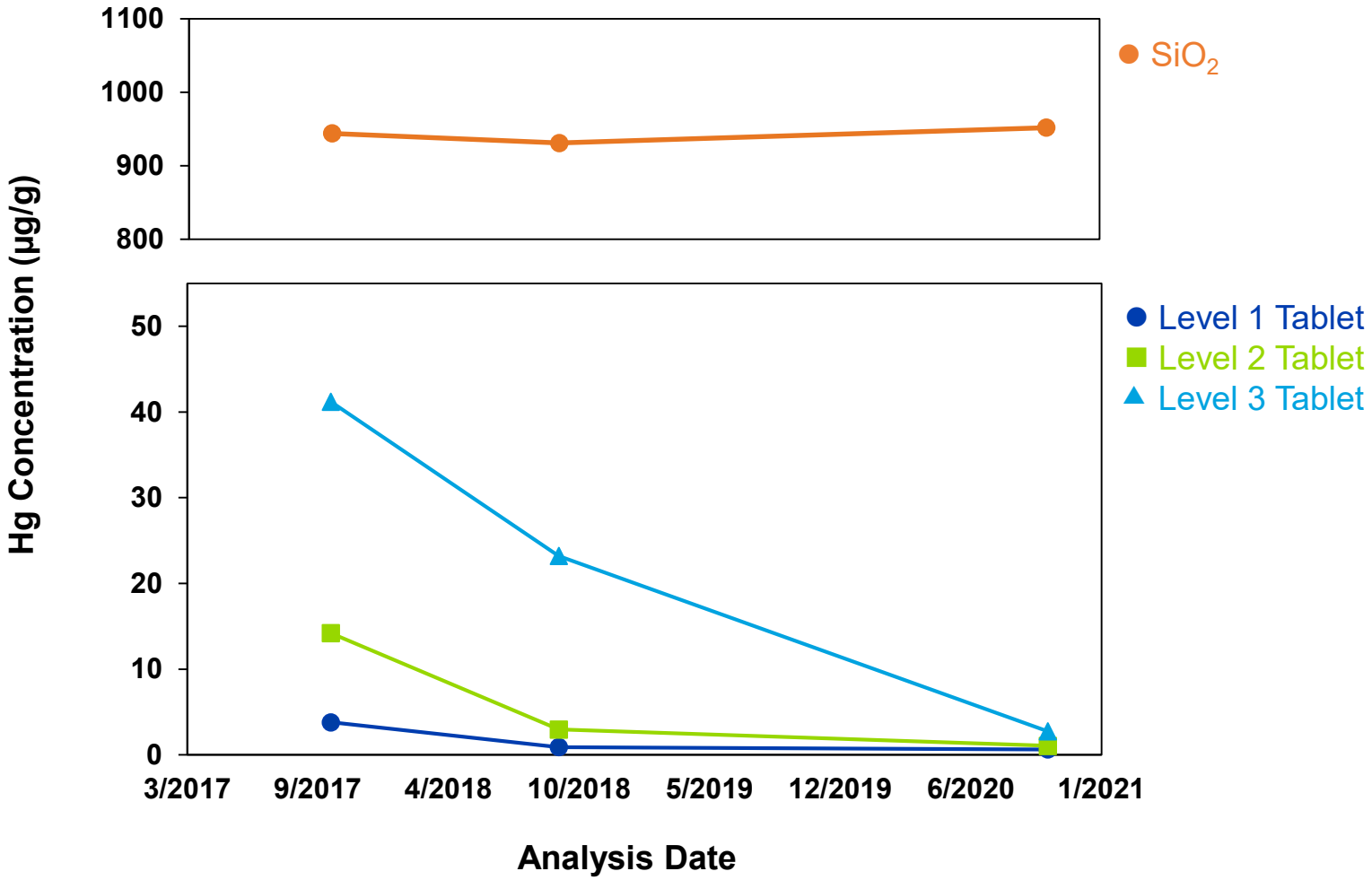


Difference in Mercury Results

INVESTIGATING UNEXPECTED DATA

Lab error?

Stability?



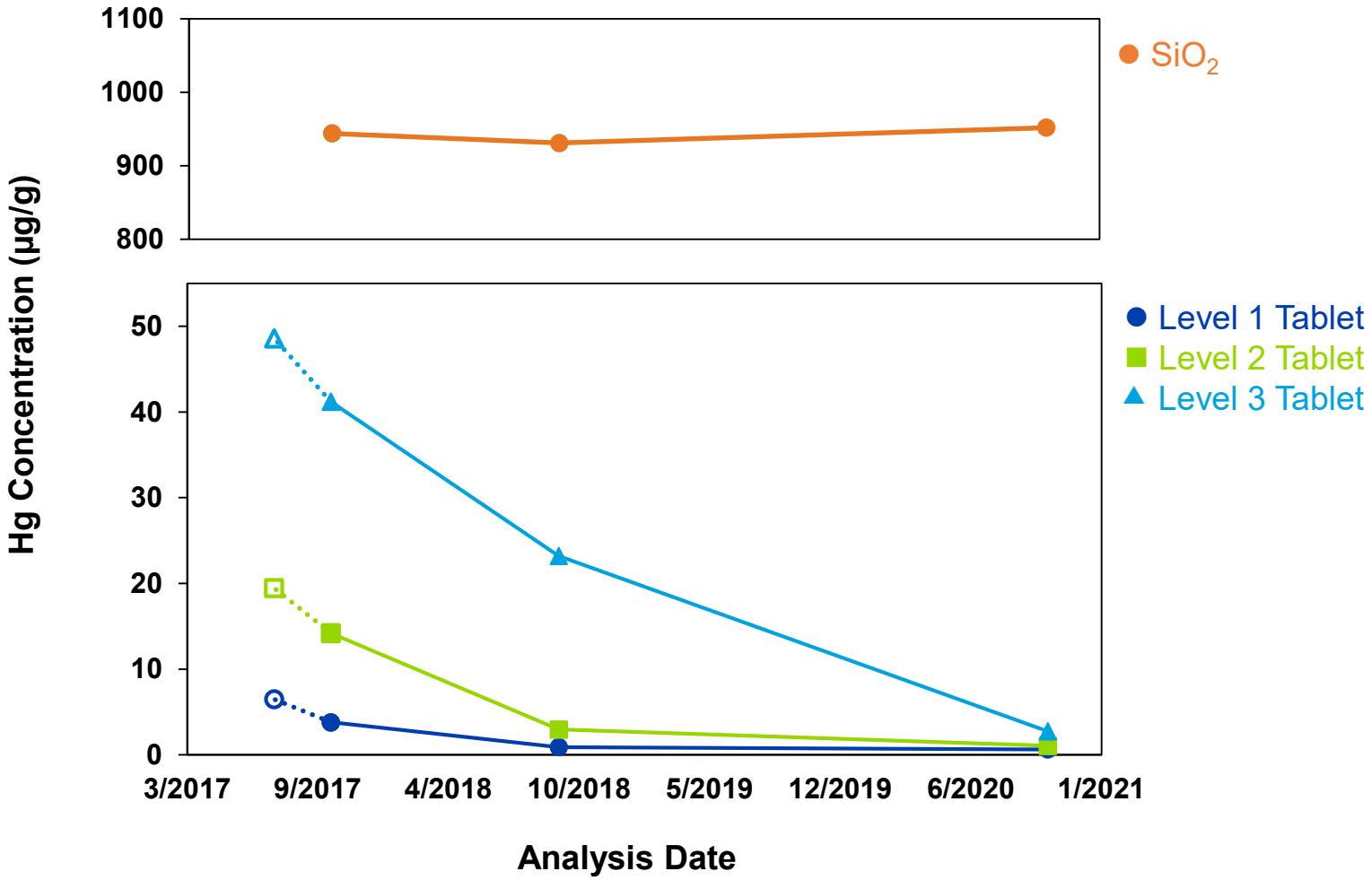
Difference in Mercury Results

INVESTIGATING UNEXPECTED DATA

Lab error?

Stability?

Use RM result to extrapolate back to formulation date



ICP-MS Learnings

Good agreement across digestion approaches and ICP-MS systems, with a few exceptions.

Mercury was unstable in the tablets AGAIN.

XRF Participant Results

Instrumentation / Approach

TABLET ANALYSIS

Standard Preparation

Blend Raw Materials
Add Liquid Standard
Dry in Furnace
Grind & Press

Sample Preparation

Grind & Press

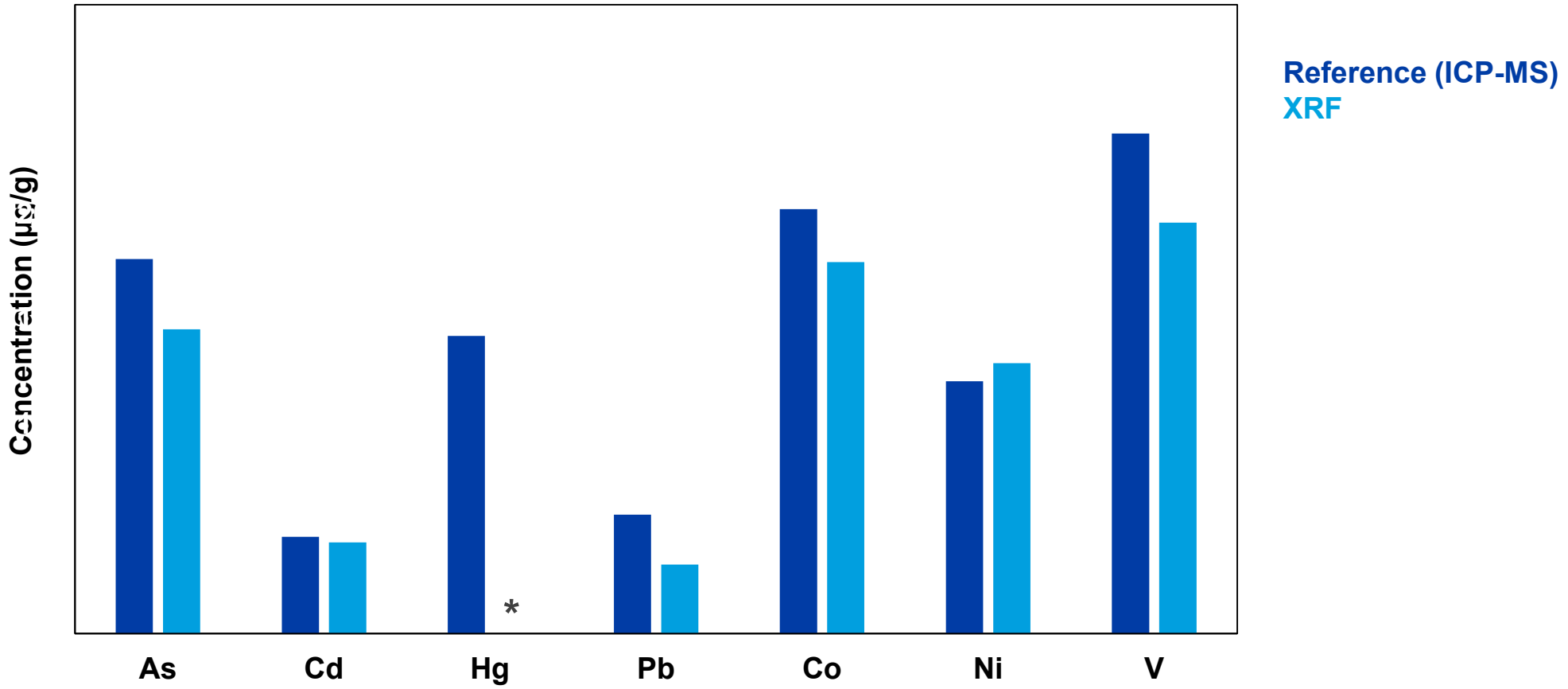
Bruker Tiger S8
WD-XRF

Wavelength Dispersive XRF

Christina Haven

Example XRF Results

COMPARISON TO REFERENCE VALUE



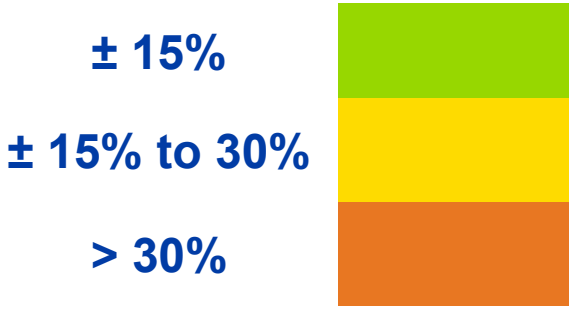
*Not measured

XRF Results – All Tablets

COMPARISON TO REFERENCE VALUE

Percent of Reference Value

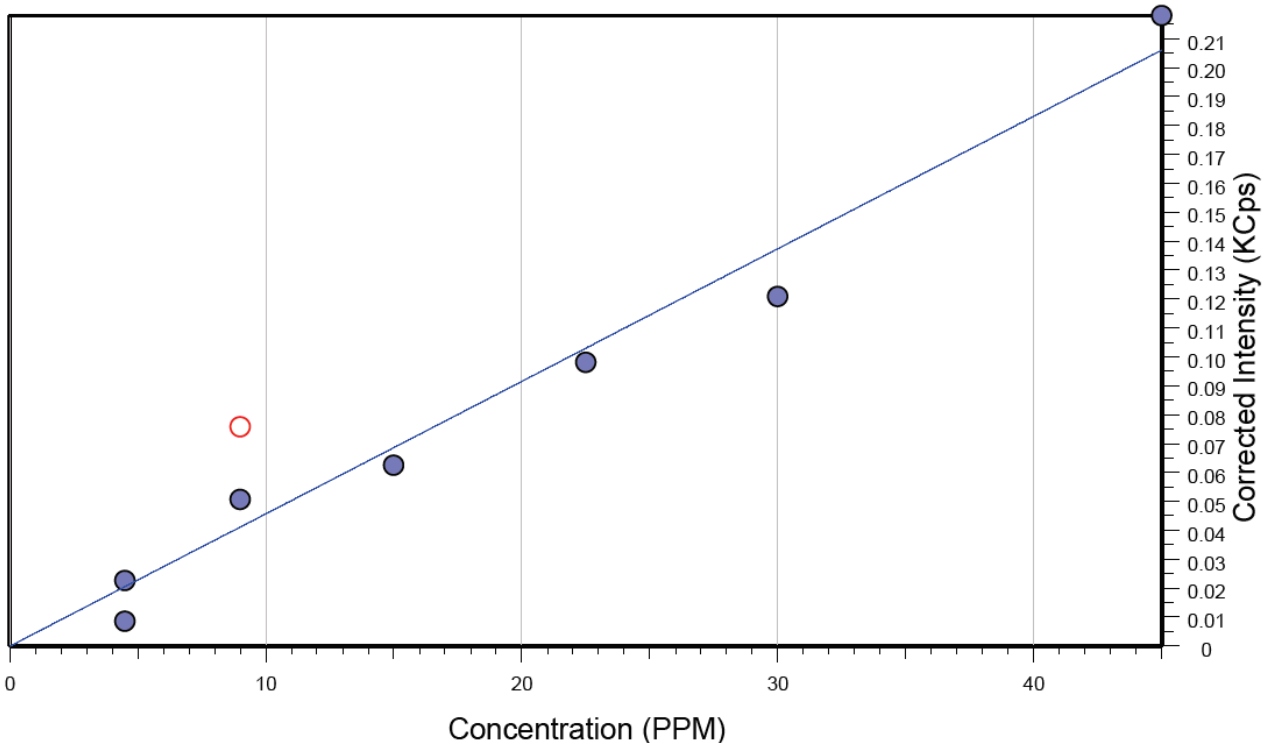
	Arsenic	Cadmium	Mercury	Lead	Cobalt	Nickel	Vanadium
Tablet 1							
Tablet 2							
Tablet 3							



N/A – Not Measured

Calibration and Drift – Arsenic

DIGGING DEEPER INTO THE XRF RESULTS



Standard	Concentration (µg/g)	Residual Error	QC Recovery
1	4.5		
2	30		N/A
3	15		N/A
4	9.0		N/A
5	9.0		N/A
6	45		N/A
7	4.5		
8	23		N/A

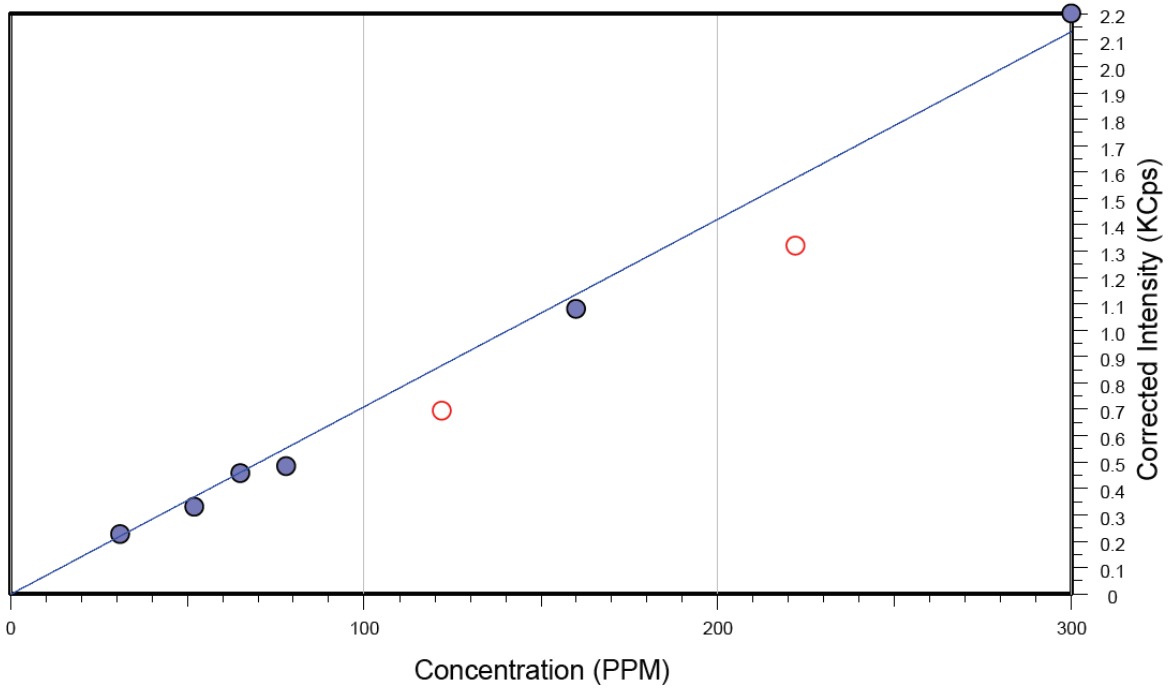
± 15%

± 15% to 30%

> 30%

Calibration and Drift – Vanadium

DIGGING DEEPER INTO THE XRF RESULTS



Standard	Concentration (µg/g)	Residual Error	QC Recovery
1	52		
2	78		N/A
3	122		N/A
4	222		N/A
5	65		N/A
6	300		N/A
7	31		
8	160		N/A

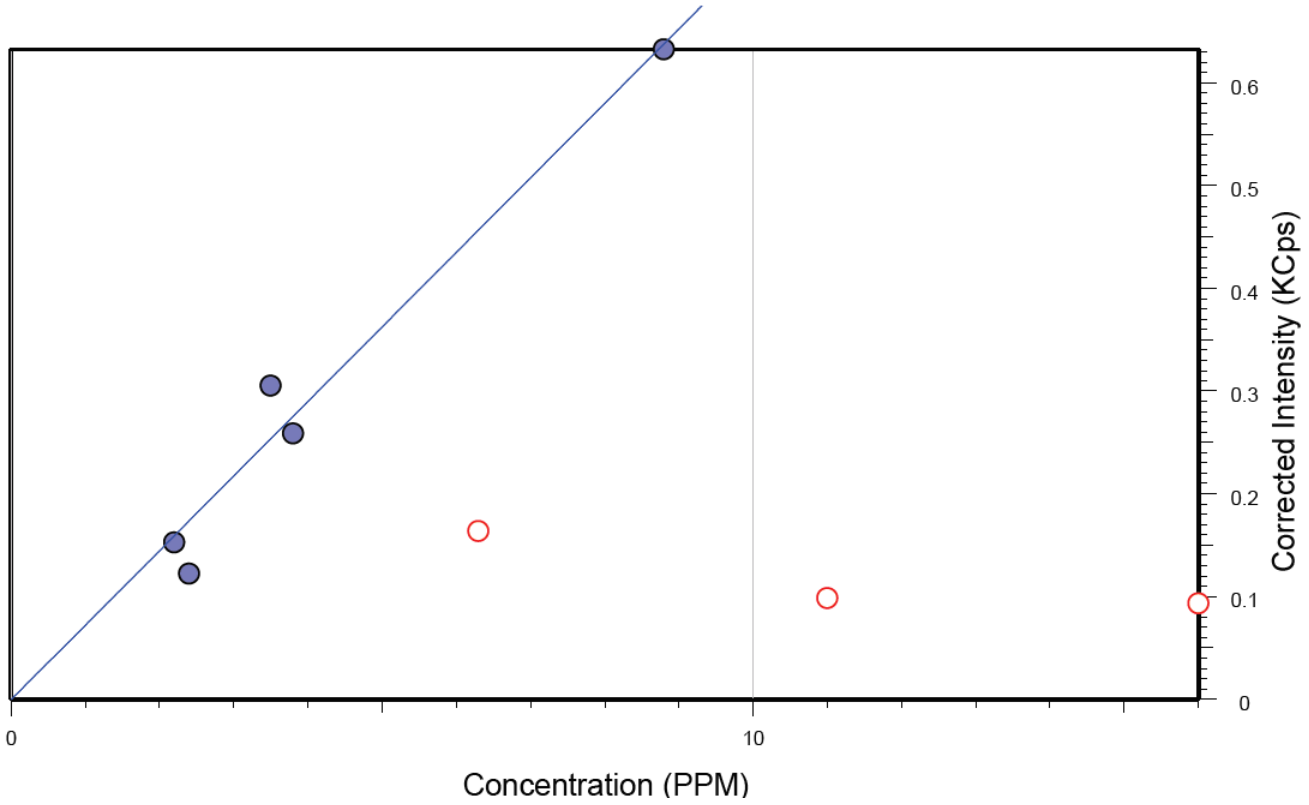
± 15%

± 15% to 30%

> 30%

Calibration and Drift – Lead

DIGGING DEEPER INTO THE XRF RESULTS



Standard	Concentration (µg/g)	Residual Error	QC Recovery
1	2.2		
2	3.8		N/A
3	6.3		N/A
4	11		N/A
5	16		N/A
6	8.8		N/A
7	2.4		
8	3.5		N/A

± 15%

± 15% to 30%

> 30%

XRF Learnings

XRF performed better than expectations

Not practical for EI screening on ever-changing number of products and materials

MIGHT consider for control method for a formulation

Broader Learnings

WHAT WE ARE DOING DIFFERENT

- **Investing in alternate approaches / instrumentation for flexibility, robustness, business continuity**
- **Digging into “WHY” for method training/transfers**
- **Balancing familiarity of the method and matrices with embracing the “fresh perspectives”**

Acknowledgements

Procter & Gamble

Kelly Smith

Andrei Shauchuk

Usa Rattanaudompol

Christina Haven

Roy Dobson

Trace Analytical Challenges Sub-Team

Donna Seibert, Perrigo

James Harrington, RTI International

Improving everyday life.