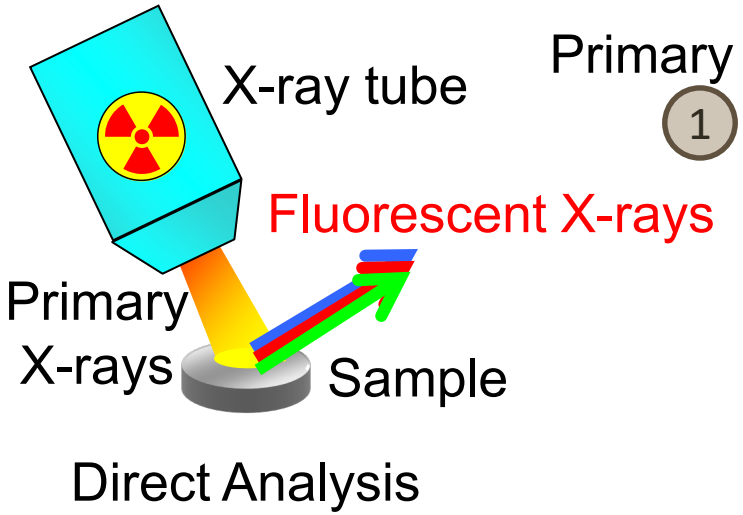
4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements November 9-10, 2020

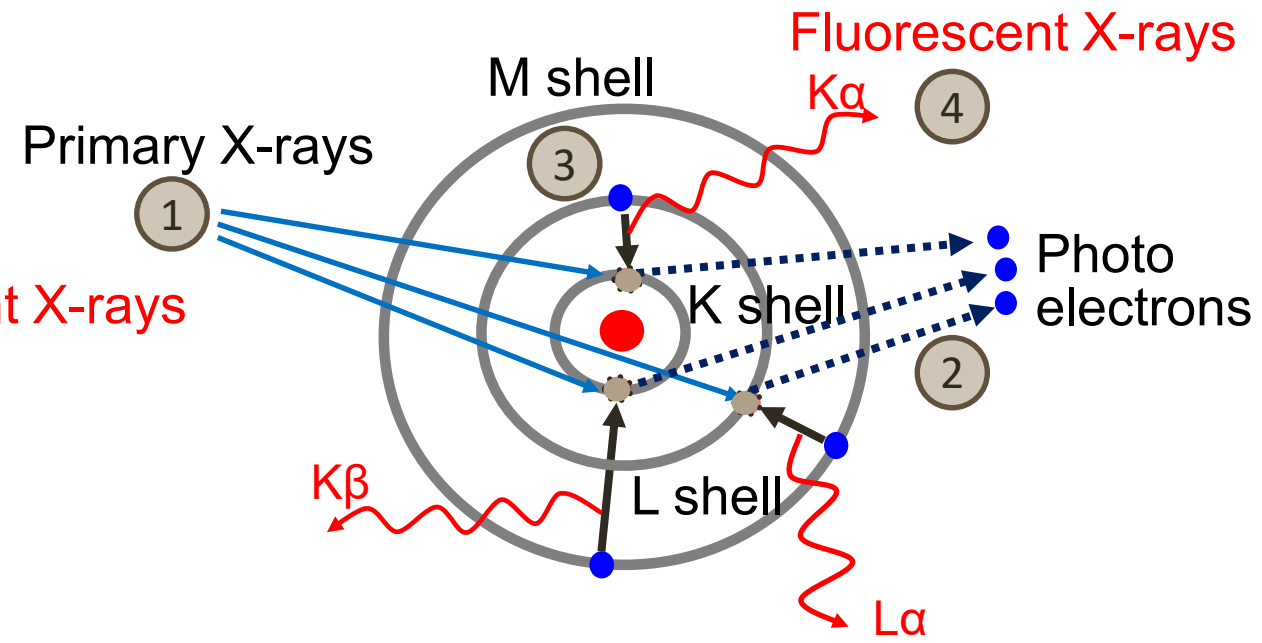
XRF Results of Phase 2 Collaborative Study

Presented by: Glenn Williams, Ph.D., Rigaku
Thanh Nguyen, Ph.D., Rigaku

PQRI
Product Quality Research Institute

What is XRF?





① Primary X-rays strike inner shell electrons.
② An inner shell electron is kicked out as a photo electron.
③ An outer shell electron transfers to fill the vacancy.
④ Fluorescent x-ray is emitted with equivalent energy difference.
Intensity is proportional to concentration

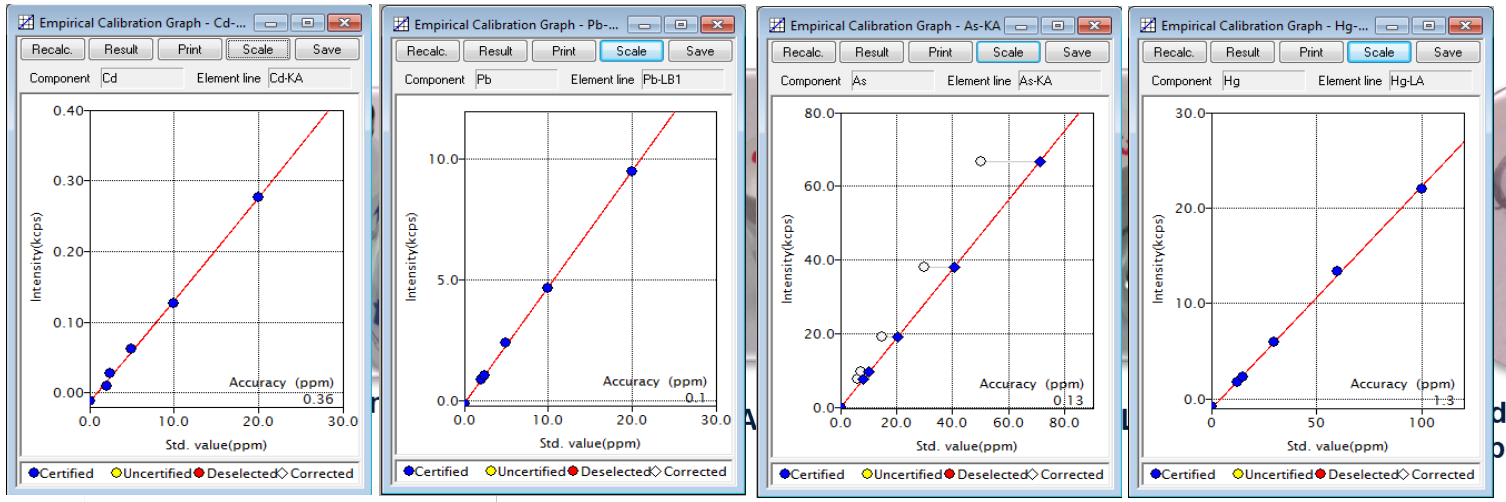
PQRI
Product Quality Research Institute

XRF Methods in One Slide

USP <735> General Chapter on XRF

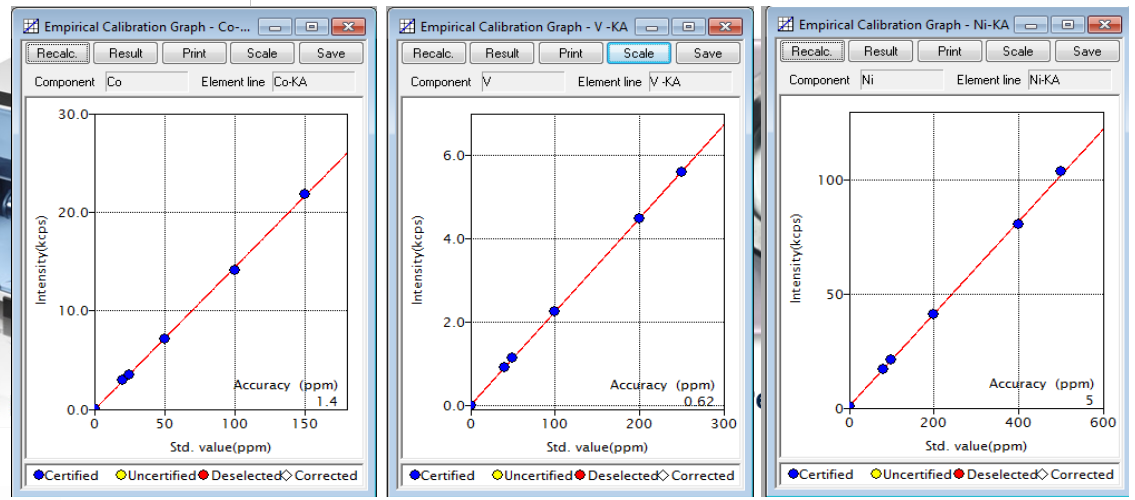
PQRI
Product Quality Research Institute

XRF Methods in One Slide



d to the "*ENTIRE*" 5g blank powders
posable acrylic mix vials - Dried

Samples



STABLE - Recalibrations NOT Necessary

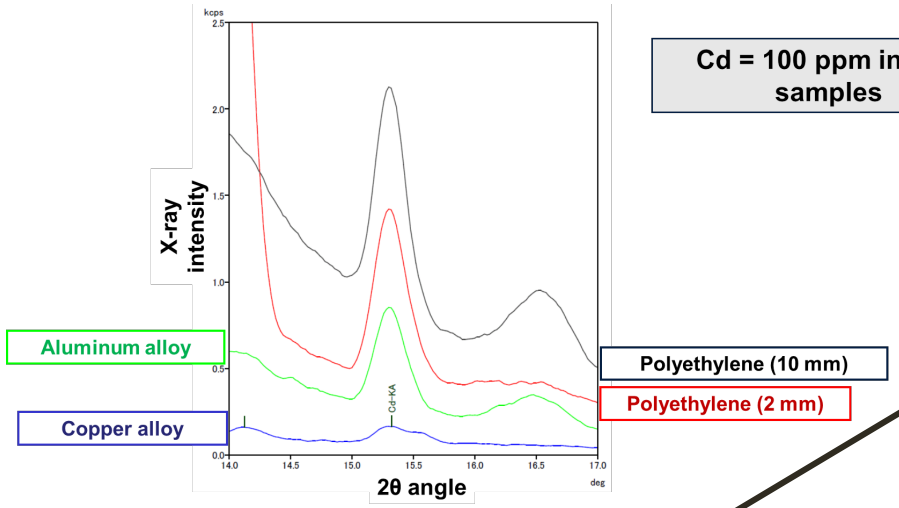
Sample/Cup Ready for Analysis

PQRI
Product Quality Research Institute

Elemental analysis by WD-XRF: A simplified approach

https://tabletscapsules.com/wp-content/uploads/pdf/tc_20170301_0027.pdf

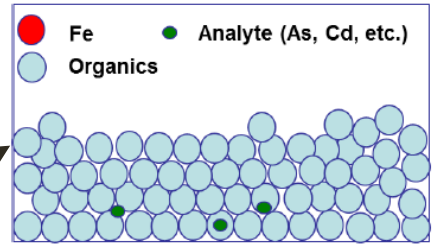
Special Considerations for Phase 2 Study



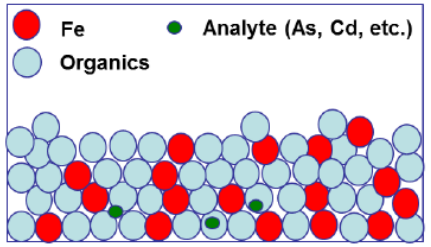
Cd = 100 ppm in all 4 samples

Phase 2 Study Materials

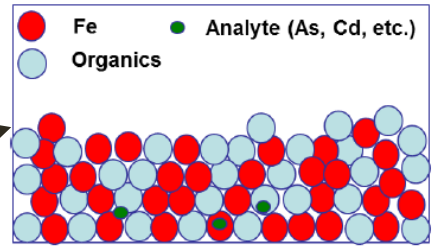
5% Iron Oxide
5% Magnesium Aluminum Silicate



Formulation 1



Formulation 2



Formulation 3

- **Option 1** If these three different formulations are to be analyzed for As, Cd, etc. using an **empirical** quantitative method without analyzing any matrix components (eg. Fe) then **3 separate methods would be required** for best accuracy for each formulation.
- **Option 2** If Fe is analyzed (and the balance organic (ave molecular formula) input) in addition to the As, Cd, etc. (analytes) then as an **FP** quantitative method only **1 method could be developed for ALL** formulations.

PQRI
Product Quality Research Institute

Screening vs Final Product Testing

Screening → Universal Method

Final Product → Unique Empirical Method Calibration

PQRI
Product Quality Research Institute

Calibration Ranges – 1 g Dose Target Level!

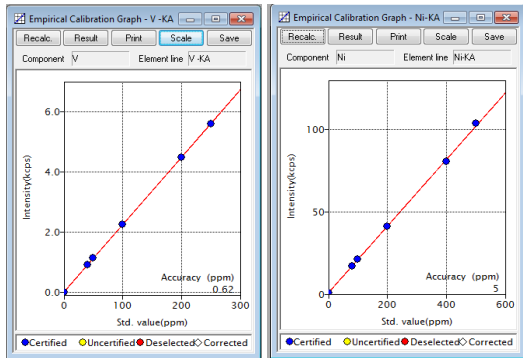
Element	Class	Oral 1 J (µg/g)	Oral 0.3 J (µg/g)	Oral 3 J (µg/g)
Cd	1	5	1.5	15
Pb	1	5	1.5	15
As	1	15	4.5	45
Hg	1	30	9	90
Co	2a	50	15	150
V	2a	100	30	300
Ni	2a	200	60	600

	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5	Formulation 6	Formulation 7	Formulation 8
RECOMMENDED Spiking Levels (ppm)								
Cd	1.5	3	5	10	3	15	1.5	7.5
Pb	1.5	3	5	10	15	7.5	1.5	3
As	4.5	30	15	9	9	45	4.5	22.5
Hg	9	18	30	60	18	90	9	45
Co	15	30	50	100	30	150	15	75
V	30	60	100	200	60	300	30	150
Ni	60	120	200	400	120	600	60	300

PQRI
Product Quality Research Institute

Results – Summary

Element	Class	Oral 1 J (µg/g)	Oral 0.3 J (µg/g)	Oral 3 J (µg/g)
Cd	1	5	1.5	15
Pb	1	5	1.5	15
As	1	15	4.5	45
Hg	1	30	9	90
Co	2a	50	15	150
V	2a	100	30	300
Ni	2a	200	60	600



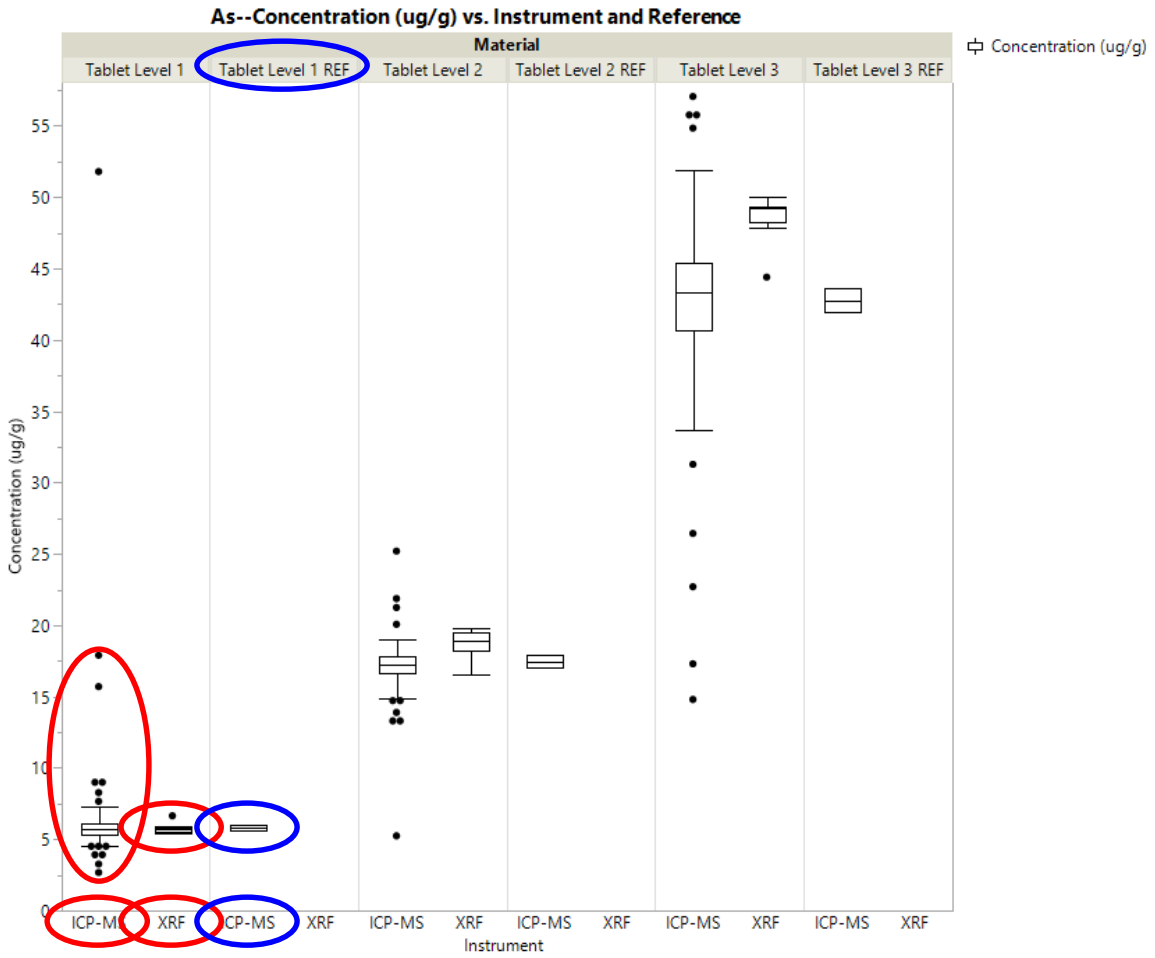
Comparison of XRF Values to Reference Values

Analyte	Material	Total Measurements (n)	Measurements >LOQ (n)	Reference concentration (ug/g)	Mean concentration (ug/g)	Geometric standard deviation (ug/g)	95% confidence Interval	P value
As	Tablet Level 1	9	9	6.05	5.6	1.0	(5.5, 5.7)	< 0.001
	Tablet Level 2	9	9	17.9	19	1	(18, 19)	0.078
	Tablet Level 3	9	9	43.6	48	1	(47, 50)	< 0.001
Cd	Tablet Level 1	9	9	1.97	2.5	1.2	(2.2, 2.9)	0.007
	Tablet Level 2	9	9	4.61	7.2	1.3	(6.1, 8.5)	< 0.001
	Tablet Level 3	9	9	13.5	18	1	(15, 22)	0.019
Co	Tablet Level 1	9	9	9.02	8.1	1.7	(5.8, 11.4)	0.568
	Tablet Level 2	9	9	20.3	22	1	(18, 27)	0.545
	Tablet Level 3	9	9	40.4	41	1	(38, 45)	0.534
Hg	Tablet Level 1	7	4	3.80	2.6	1.2	(2.2, 3.1)	0.026
	Tablet Level 2	7	4	14.2	3.4	1.2	(2.8, 4.2)	< 0.001
	Tablet Level 3	7	7	41.2	3.6	2.2	(2.1, 6.4)	< 0.001
Ni	Tablet Level 1	9	9	8.63	7.3	1.8	(5.0, 10.8)	0.435
	Tablet Level 2	9	9	12.0	11	2	(8, 15)	0.641
	Tablet Level 3	9	9	15.3	18	1	(16, 20)	0.025
Pb	Tablet Level 1	9	9	2.53	2.3	1.2	(2.0, 2.6)	0.175
	Tablet Level 2	9	9	5.68	5.2	1.6	(3.9, 7.0)	0.598
	Tablet Level 3	9	9	14.8	15	1	(12, 19)	0.985
V	Tablet Level 1	9	9	22.6	17	2	(10, 29)	0.343
	Tablet Level 2	9	9	23.9	20	2	(12, 31)	0.426
	Tablet Level 3	9	9	1.31	1.9	2.3	(1.1, 3.3)	0.224

ICP-MS **XRF**

PQRI
Product Quality Research Institute

Results - Arsenic



PQRI
Product Quality Research Institute

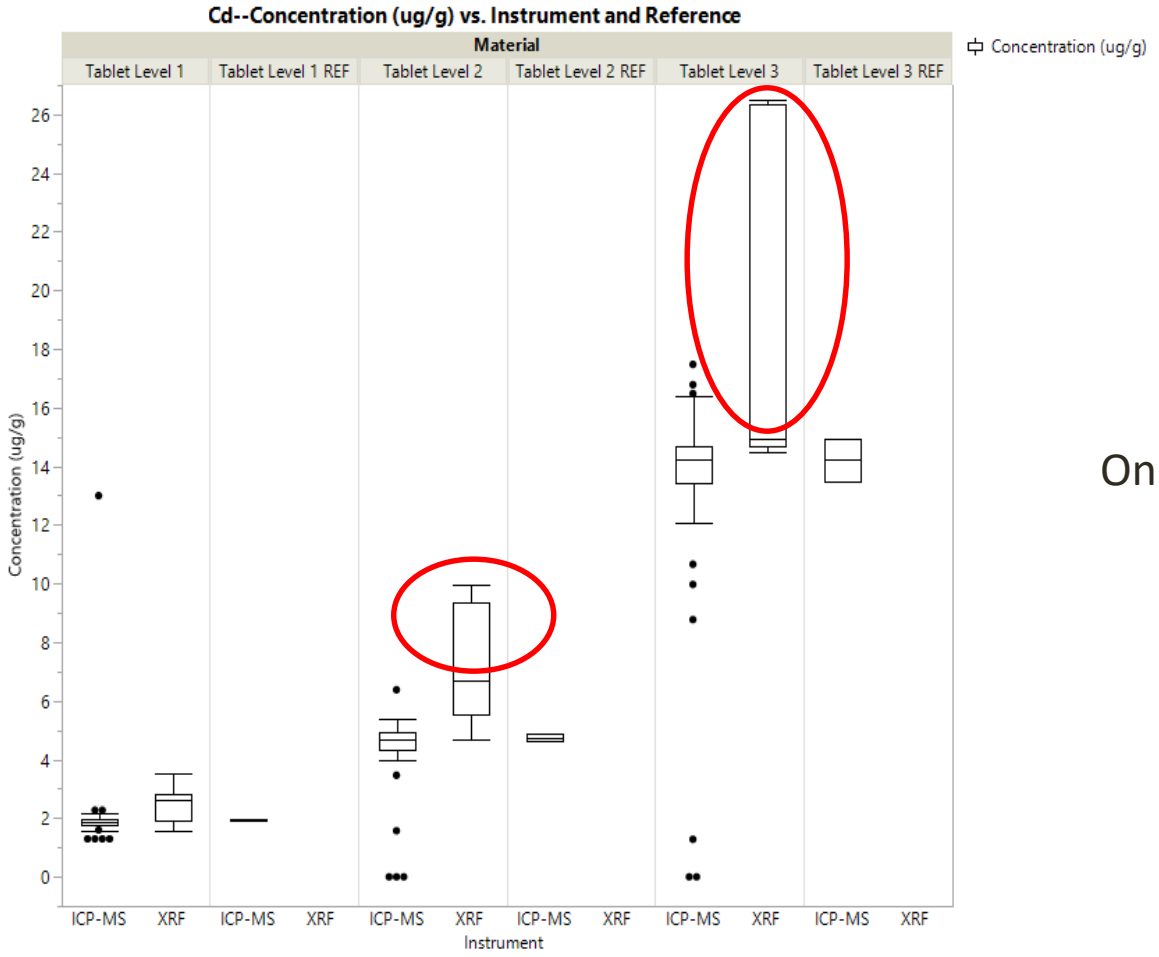
Results – Summary – Reference vs Expected Values

Analyte	Material	Expected concentration (ug/g)	Reference Concentration (ug/g)	% Recovery Reference vs Expected	XRF Concentration (ug/g)
As	Magnesium Aluminum Silicate	1.5	1.90	127	
	Red Ferric Oxide	0	0.473	NA	
	Silicon Dioxide Standard (As, Co, Hg)	1090	988	90.6	
	Tablet Level 1	**6.65**	6.05	91.0	**5.6**
	Tablet Level 2	**19.8**	17.9	90.4	**19**
	Tablet Level 3	**49.2**	43.6	88.6	**48**

Direct Analysis Technique – No Digestion (or potential volatile loss? during digestion)

PQRI
Product Quality Research Institute

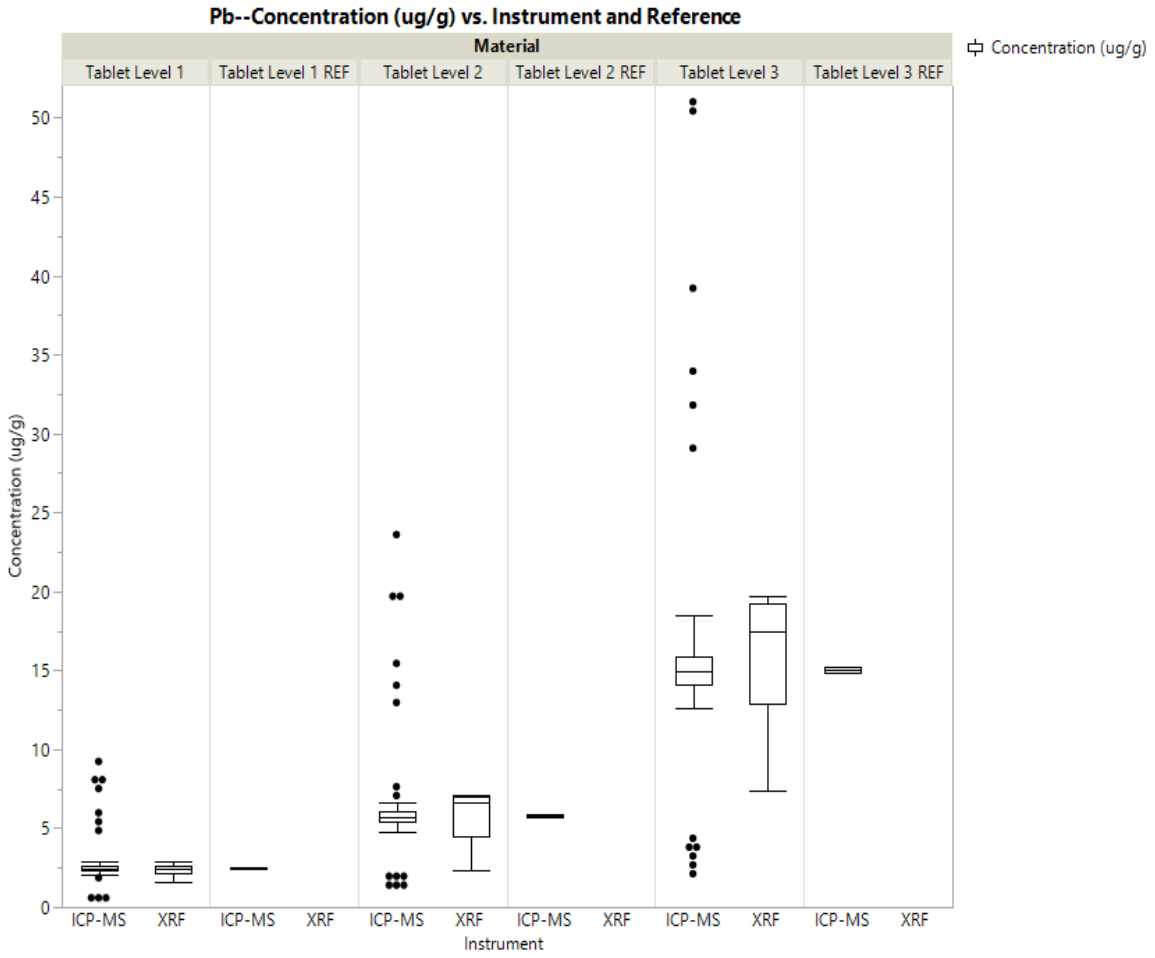
Results - Cadmium



Only 4 XRF Labs – 1 Lab with potential repeatable high bias

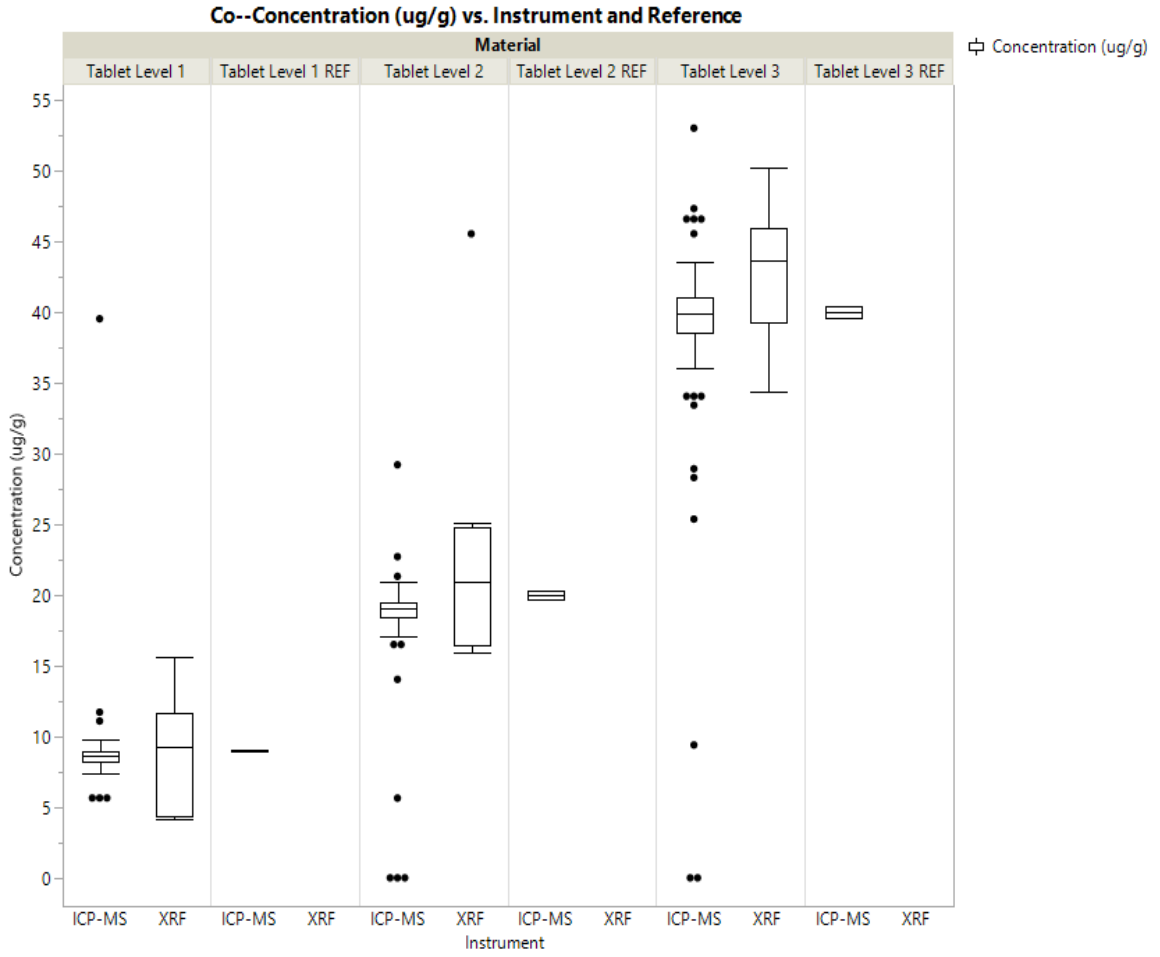
PQRI
Product Quality Research Institute

Results - Lead



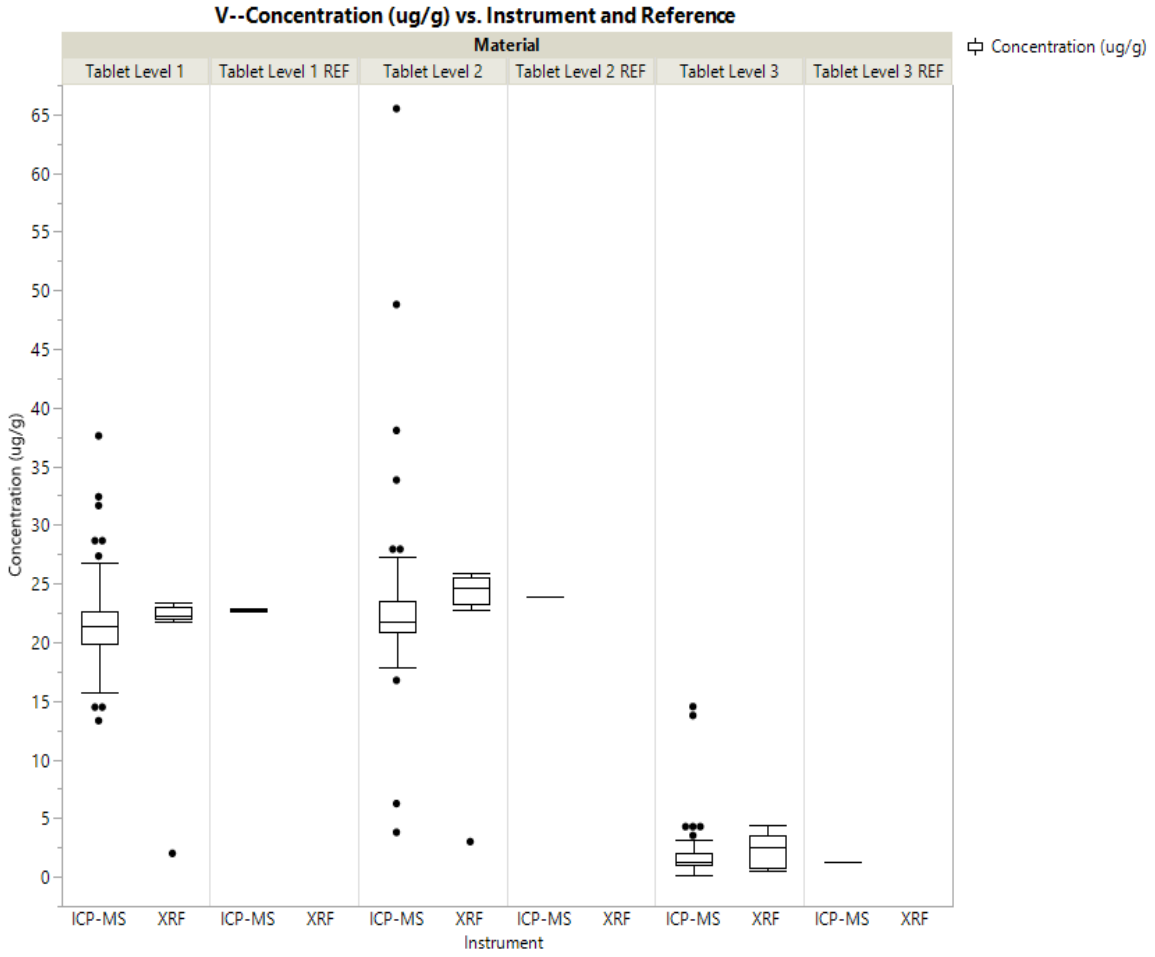
PQRI
Product Quality Research Institute

Results - Cobalt



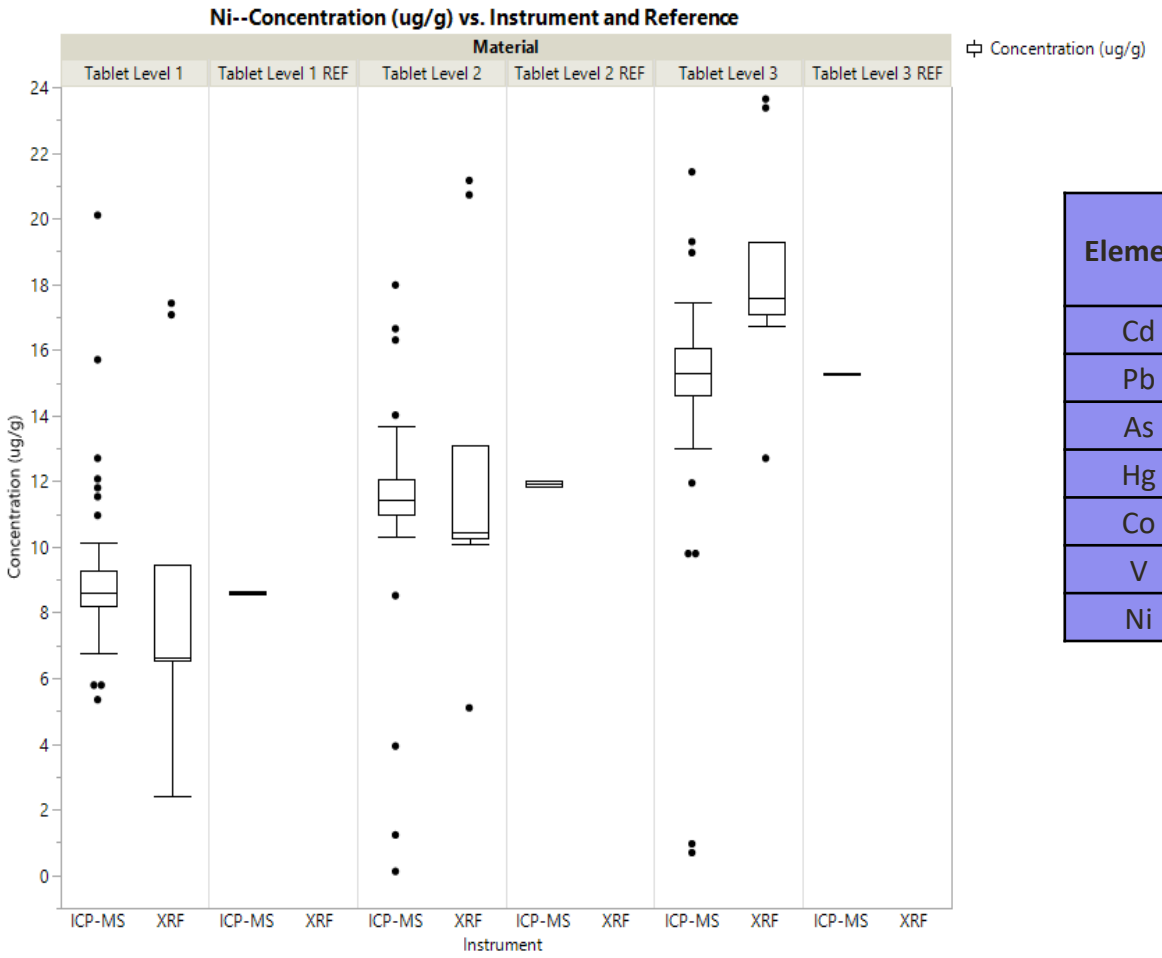
PQRI
Product Quality Research Institute

Results - Vanadium



PQRI
Product Quality Research Institute

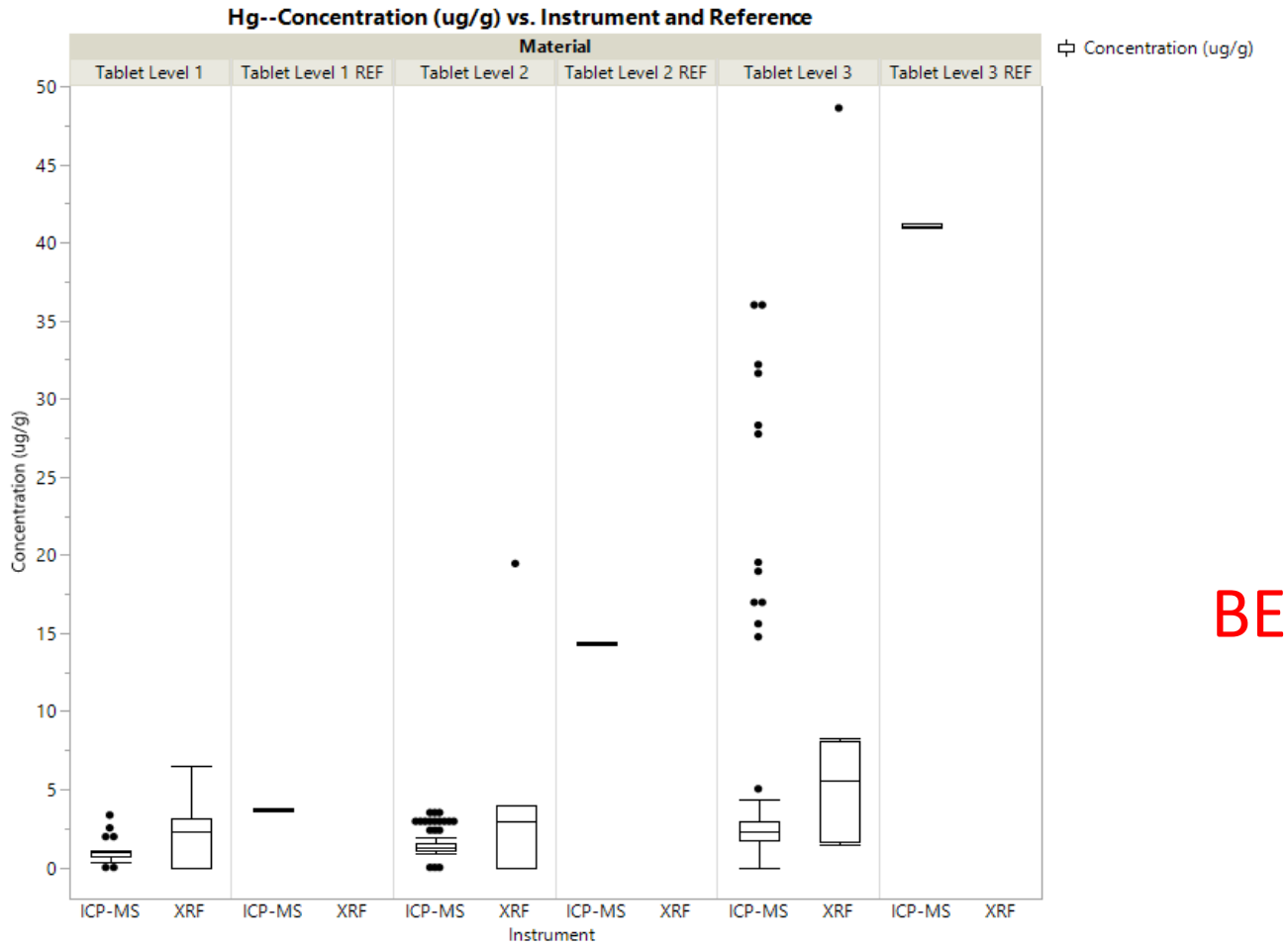
Results - Nickel



Element	Class	Oral 1 J (µg/g)	Oral 0.3 J (µg/g)	Oral 3 J (µg/g)
Cd	1	5	1.5	15
Pb	1	5	1.5	15
As	1	15	4.5	45
Hg	1	30	9	90
Co	2a	50	15	150
V	2a	100	30	300
Ni	2a	200	60	600

PQRI
Product Quality Research Institute

Results - Mercury

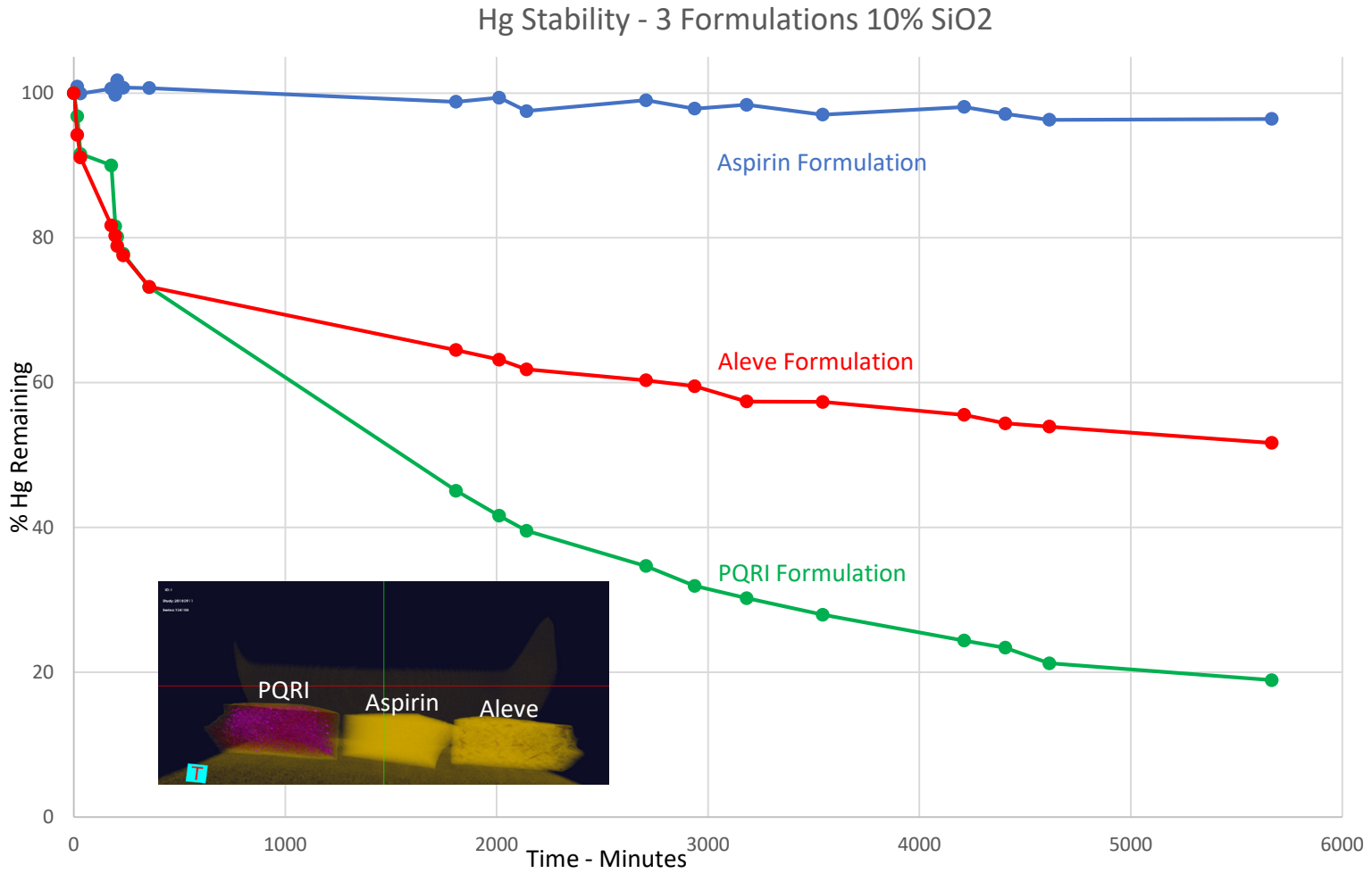


ALL LABS

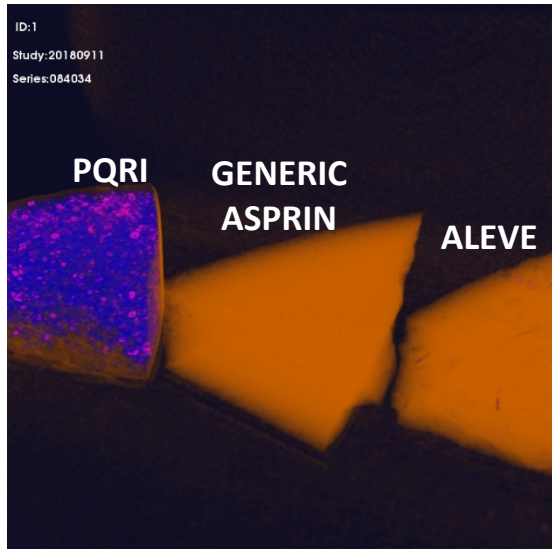
BELOW EXPECTED

PQRI
Product Quality Research Institute

Mercury Stability Study – Formulation Porosity !!



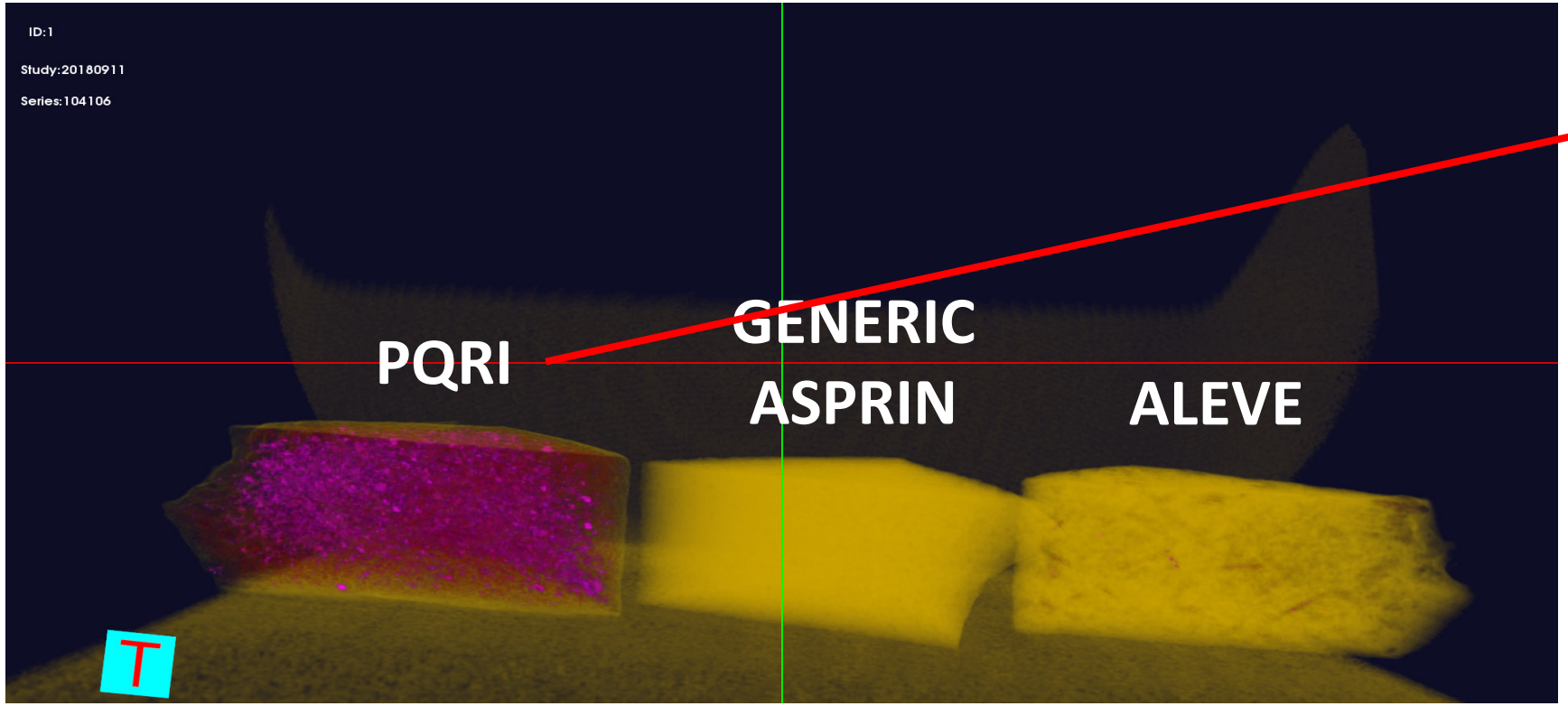
Excipients	Formulation 1 (g)
Microcrystalline Cellulose (grams)	0.75
Magnesium Aluminum Silicate (grams)	0.25
Lactose (grams)	2.65
Starch (grams)	1
Stearic Acid (grams)	0.05
Red Ferric Oxide (grams)	0.25
Silicon Dioxide (grams)	0.04
Total (grams)	4.99



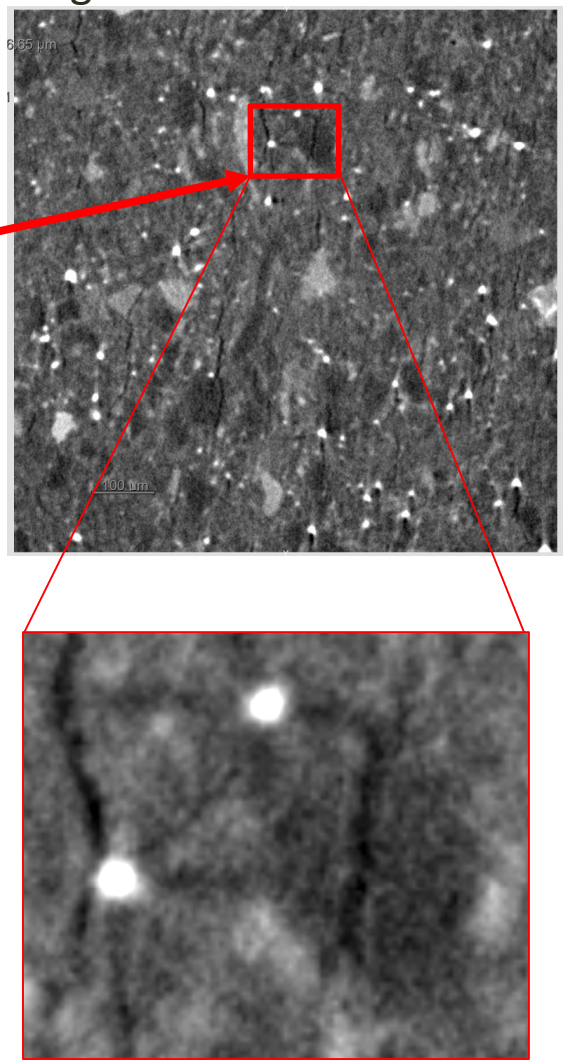
PQRI
Product Quality Research Institute

Mercury Stability Study – Formulation Porosity !!

CT LAB Scan – W Source



High Res Nano3D CT Scan



PQRI
Product Quality Research Institute

Mercury Stability Study – Formulation Porosity !!

Study materials (tablets) not stable with respect to Hg levels

SiO_2 input (spiked with Hg) stable as bulk in closed bottle

SiO_2 input unstable when exposed open and diluted in loose medium

SiO_2 input unstable when prepared in low concentration and in porous medium

Preparing materials with binders that reduce porosity can stabilize Hg

PQRI
Product Quality Research Institute

Questions

Thanks for the opportunity to participate, discuss XRF, and share our passion!

PQRI
Product Quality Research Institute

Thanks for the opportunity to participate, discuss XRF, and share our passion!

PQRI
Product Quality Research Institute