BE BOLD

2022 INORGANIC VENTURES WEBINAR SERIES

IS YOUR METHOD FIT FOR PURPOSE – A Dive Into Validation

THURSDAY, OCTOBER 20
9:00–9:30AM EST

PRESENTED BY:
Lesley Owens, PhD
Technical Support Manager

Outline

- Purpose of Validation
- Types of Validations
- Characteristics
  - Definitions
  - Suggestions/Guidelines
  - Examples
- Validation at Inorganic Ventures

<u>Validation Characteristics</u>

1. Specificity
2. Linearity
3. Range
4. Accuracy
5. Precision
6. Limits
   a. Detection
   b. Quantification
7. Robustness

What is Validation?
Why is Validation Necessary?

- Merriam-Webster
  - to confirm the validity of
    - valid = well-grounded or justifiable
  - to support or corroborate on a sound or authoritative basis
- Ensures consistent process (manufacturing, testing, packaging, etc.)
- Demonstrate “fitness” for purpose and intended use
- IV CRM/RM Product Validation
  - Is it what we say it is?
  - Does it do what we say it does?

Types of Validation

- Identity – to positively identify analyte(s) in sample (qualitative)
- Purity – to provide information about everything that isn’t the analyte(s) in a sample (qualitative and/or quantitative)
- Assay – to determine the amount analyte(s) in a sample (quantitative)

Specificity

- Ability to detect analyte(s) of interest in the presence of sample components (matrix, impurities, etc.)
  - Spike sample with analyte(s) and compare with unspiked results
  - Agreement on multiple wavelengths (ratio of 1)

- Confirms line selection from method development activities
  - Line selection is crucial in method development
    - Sensitivity
    - Precision
    - Spectral issues (interferences/background)
    - More than one line is ideal (2-3 are recommended; more are fine, but more it means more data to deal with!)

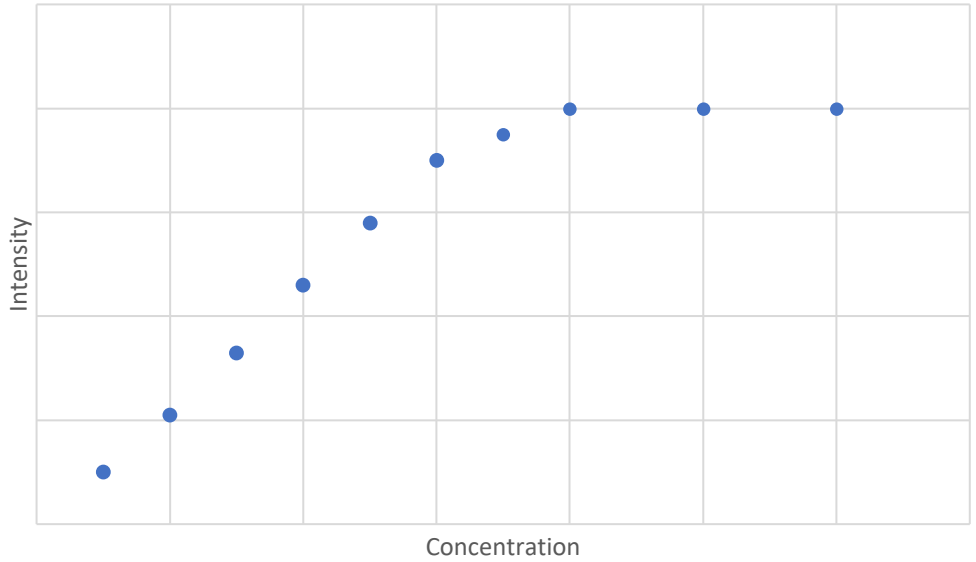
- Qualitative in nature
  - Rule out effects of impurities/interferences
  - Risk assessments are helpful in identifying potential impurities/interferences

Specificity Example

Test Solution Level	Primary Wavelength		Secondary Wavelength		Specificity Ratio
	455.403 nm		585.367 nm		
	Measured Test Solution Conc. µg/g	Mean Test Solution Conc. µg/g	Measured Test Solution Conc. µg/g	Mean Test Solution Conc. µg/g	Acceptance Criteria: 0.8 - 1.2
10.0	10.0	10.0	10.0	10.0	1.00
	10.0		10.0		
	10.0		10.0		
	10.0		10.0		
	10.0		10.0		
	10.0		10.0		

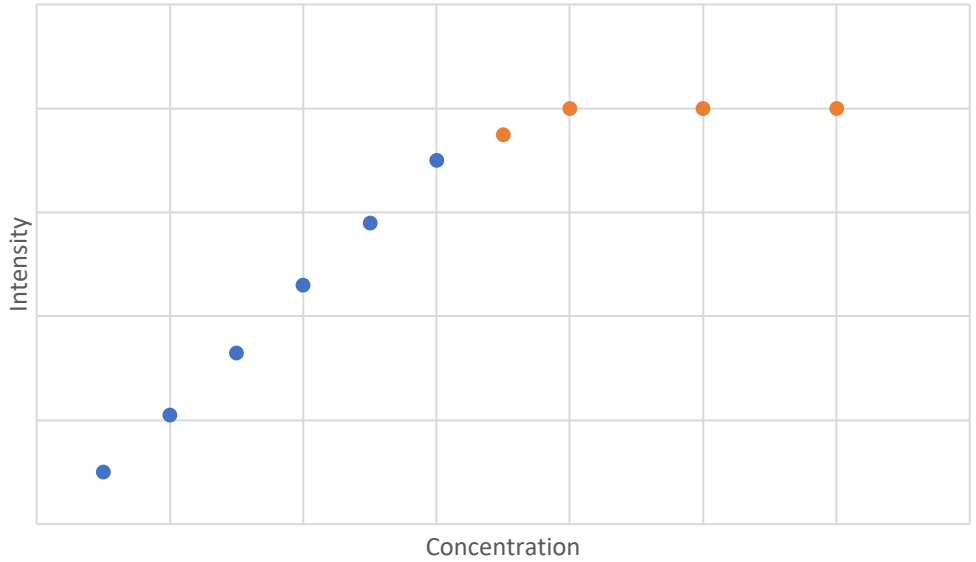
Linearity

- Range in which results are directly proportional to analyte concentration
- Multi-point analysis
- Minimize sources?



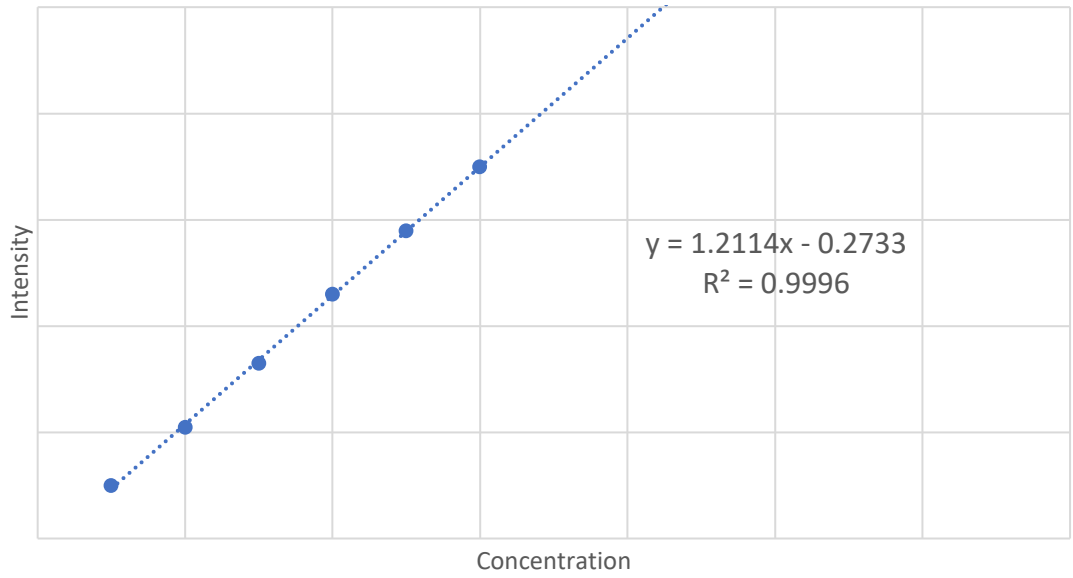
Linearity

- Range in which results are directly proportional to analyte concentration
- Multi-point analysis
- Minimize sources?



Linearity

- Range in which results are directly proportional to analyte concentration
- Multi-point analysis
- Minimize sources?

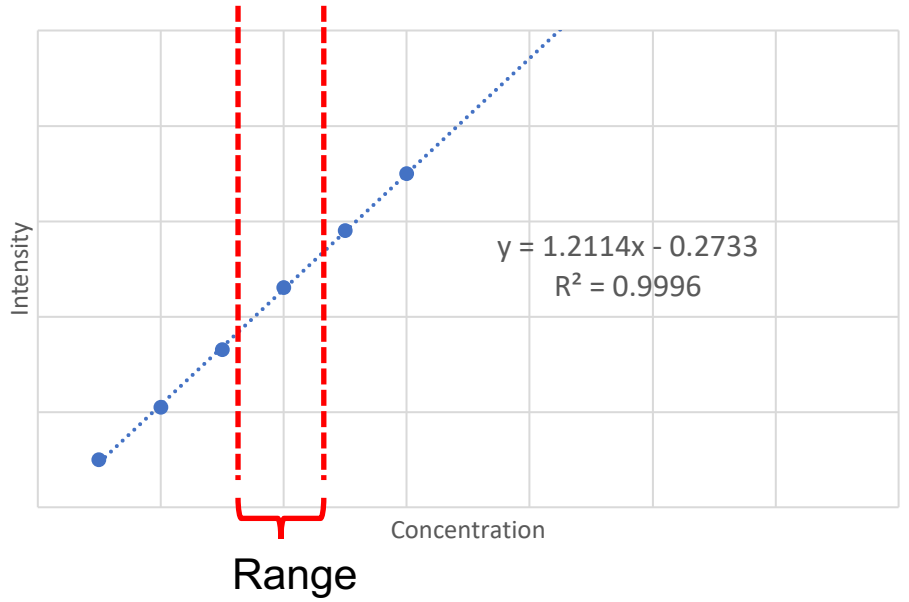


Linearity Example

Element	Correlation Coefficient (r) Acceptance Criteria: ≥ 0.9950	Slope	y-intercept
Ba	0.9997	2133618.8186	1042736.3831

Range

- Interval between upper and lower concentrations of analyte in sample
- ± 20% of target value



Range Example

Element	Correlation Coefficient (r) **Acceptance Criteria: ≥ 0.9950**	Slope	y-intercept	Range (ug/g)
Ba	0.9999	2160458.7930	736447.8205	8.0 – 12.0

Accuracy

- Agreement with accepted reference value and value found during analysis
- “Trueness”
- Best Practices:
  - Comparison to reference materials (CRMs or SRMs)
  - Use of a second validated method if no RMs exist
  - Standard Additions
  - Spike recovery

Accuracy Example

Test Solution Level	Theoretical Test Solution Conc. µg/g	Measured Test Solution Conc. µg/g	Mean Test Solution Conc. µg/g	% Recovery	Mean % Recovery
				Acceptance Criteria: 95 - 105%	Acceptance Criteria: 95 - 105%
Test Solution Level 1	8.0	8.0	8.0	99.9	100.0
		8.0		99.7	
		8.0		100.5	
Test Solution Level 2	9.0	9.0	9.0	99.9	99.9
		9.0		99.7	
		9.0		100.0	
Test Solution Level 3	10.0	10.0	10.0	100.0	99.9
		10.0		99.7	
		10.0		99.7	
		10.0		99.8	
		10.0		100.0	
		10.0		100.0	
Test Solution Level 4	11.0	11.0	11.0	100.1	100.3
		11.0		100.3	
		11.1		100.5	
Test Solution Level 5	12.0	11.9	12.0	99.3	99.7
		12.0		99.9	
		12.0		99.8	
QC	10.0	10.0	10.0	100.0	99.9
		10.0		99.9	

Precision

- Agreement of multiple measurements
- Expressed as variance or (relative) standard deviation, and confidence interval
- 3 levels:
  1. Repeatability – 3 replicates at 3 concentrations (cover range) OR 6 replicates at 100%
  2. Intermediate precision – different days, technicians, instruments, etc.
  3. Reproducibility – multi-laboratory studies

- ICP issues that can impact precision:
  - Spectrally rich/complex regions
  - Sample introduction system (tubing, torch, etc.)
  - High salt content (salting out)
  - Instrument warmup time

Precision Example

Test Solution Level	Theoretical Test Solution Conc. µg/g	Measured Test Solution Conc. µg/g	Mean Test Solution Conc. µg/g	Test Solution Level % RSD	% RSD of % Recovery
				Acceptance Criteria: ≤5%	Acceptance Criteria: ≤5%
Test Solution Level 1	8.0	8.0	8.0	0.42	0.42
		8.0			
		8.0			
Test Solution Level 2	9.0	9.0	9.0	0.12	0.12
		9.0			
		9.0			
Test Solution Level 3	10.0	10.0	10.0	0.17	0.17
		10.0			
		10.0			
		10.0			
		10.0			
		10.0			
Test Solution Level 4	11.0	11.0	11.0	0.22	0.22
		11.0			
		11.1			
Test Solution Level 5	12.0	11.9	12.0	0.34	0.34
		12.0			
		12.0			
QC	10.0	10.0	10.0	0.13	0.13
		10.0			

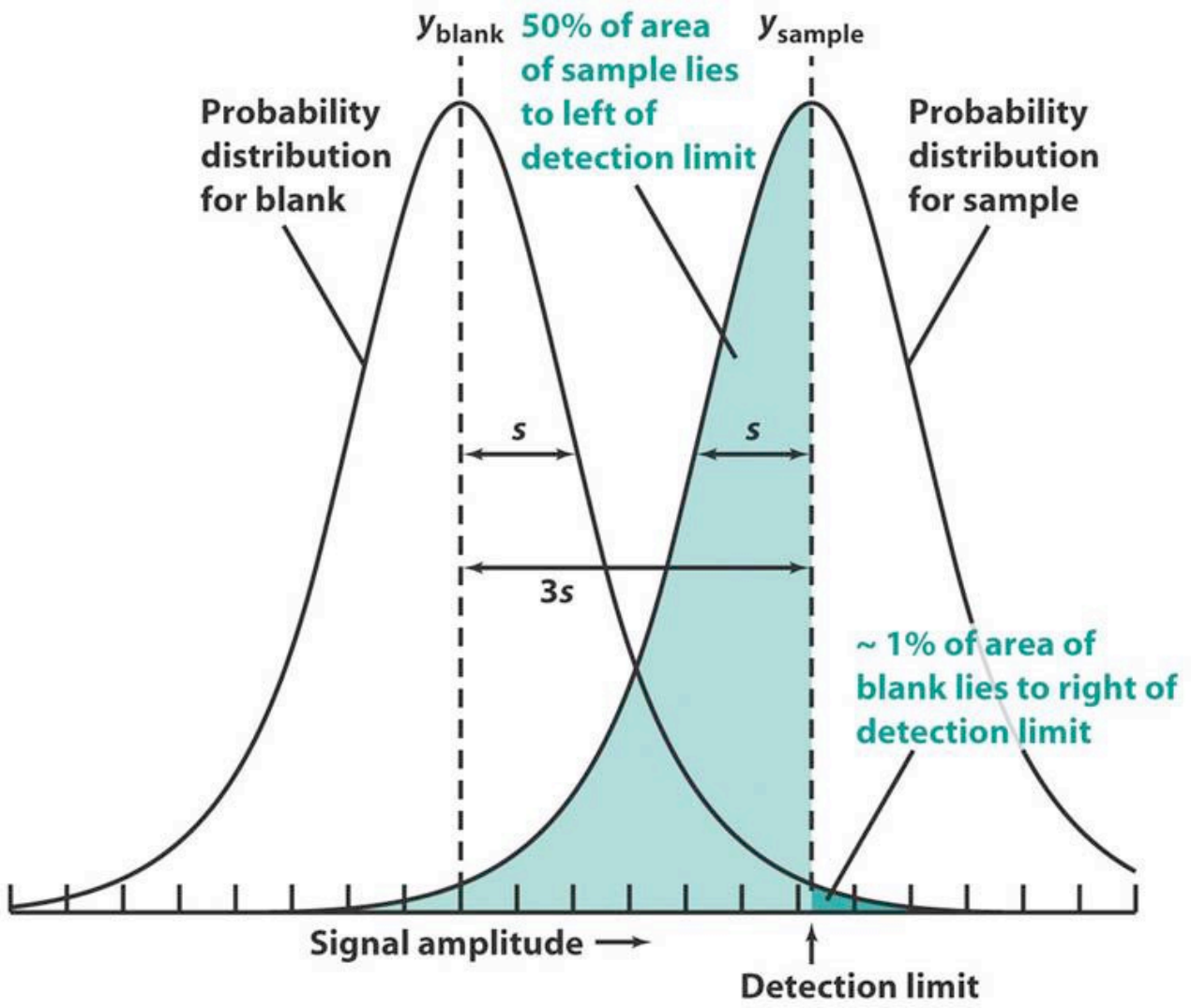
Limits

Detection

- Smallest amount of analyte that can be detected
- 3 x [(S/N) or noise peak-to-peak]
- Validate by analyzing samples near this value

Quantification

- Smallest amount of analyte that can be quantified
- 10 x [(S/N) or noise peak-to-peak]
- Validate by analyzing samples near this value



Taken from Harris “Exploring Chemical Analysis”

Robustness

- Ability to withstand small changes
- Ensures reliability during use
  - Unaffected by variations lab-to-lab, user-to-user, etc.
- Considerations for ICP Measurements
  - Reagents (purity, concentration, etc.)
  - Introduction system components
    - Nebulizer
    - Torch
    - Spray Chamber

Robustness Example

Test Solution Level (µg/g)	Analysis	Measured Test Solution Conc. (µg/g)	Mean Test Solution Conc. (µg/g)	
10.0	t_1 (repeatability)	10.0	10.0	**% RSD n = 6**
		10.0		
		10.0		**Acceptance Criteria: ≤ 5%**
		10.0		0.17
		10.0		
		10.0		
	t_2 (repeatability)	10.0	10.0	**% RSD n = 6**
		10.0		
		10.0		**Acceptance Criteria: ≤ 5%**
		10.0		0.21
		10.0		
		10.0		

Validation at Inorganic Ventures

- “Fit for Purpose"

- How will instrument be used?
  - Certification of Singles lots
  - Check of custom products

- What data is required?
  - Linearity – prove concentration range is linear (instrument qualification)
  - Singles – validate existing singles method of new instrument (method transfer)
  - Customs – verify that calibration/performance is same as old instrument (method transfer); confirm by running solutions on both and comparing results

Life Cycle

- Unfortunately, validation is not a “one-and-done” activity
- Monitor and track trends throughout method
  - Use of control samples and control charting
- Helps determine what type of revalidation should be done, if any

Revalidation

- When?
  - Any time there is a change in process
    - Need to have periodic reviews of SOPs, equipment, sample types, etc.
    - Internal audits can help find process deviations

- More robust methods tend to mitigate revalidation

Summary

- Method validation ensures reliability of results
- Can be done concurrently with method development
- Procedural changes warrant revalidation
  - Method development activities need to be comprehensive and thorough

Resources

- ICH
  - Validation of Analytical Procedures: Text and Methodology Q2(R1)
- EPA
  - Validation and Peer Review of U.S. Environmental Protection Agency Chemical Methods of Analysis
- A Practical Guide to Method Validation
  - DOI: 10.1021/ac961912f
- Analytical Method Development and Validation
  - ISBN 9780824701154

Technical Support & Online Resources

Interactive Periodic Table

Technical Videos

Technical Questions Forum

TCT Information

Guides

- ICP Operations Guide
- Sample Preparations Guide
- Trace Analysis Guide
- Periodic Table Guide
- Instrument Cross reference guide

Visit **inorganicventures.com** to access free educational resources for chemists!