Evaluating Method Equivalency with TOST Introduction and Practical Applications

Gregory O. Noonan, US Food and Drug Administration
Timothy D. Norden, US Department of Agriculture

Why Determine Equivalency

Commonly used in Manufacturing and the Pharmaceutical Industry:

- Compare Processing at Pilot Plant to Manufacturing Plant
- Compare New Diagnostic Test with Approved Tests
- Compare Different Medical Interventions
- Compare Generic Drugs to Brand

Compare 2 methods:

- Rational versus Empirical
- Rapid Method versus Full Instrumental Method
- Different Instrument Platforms

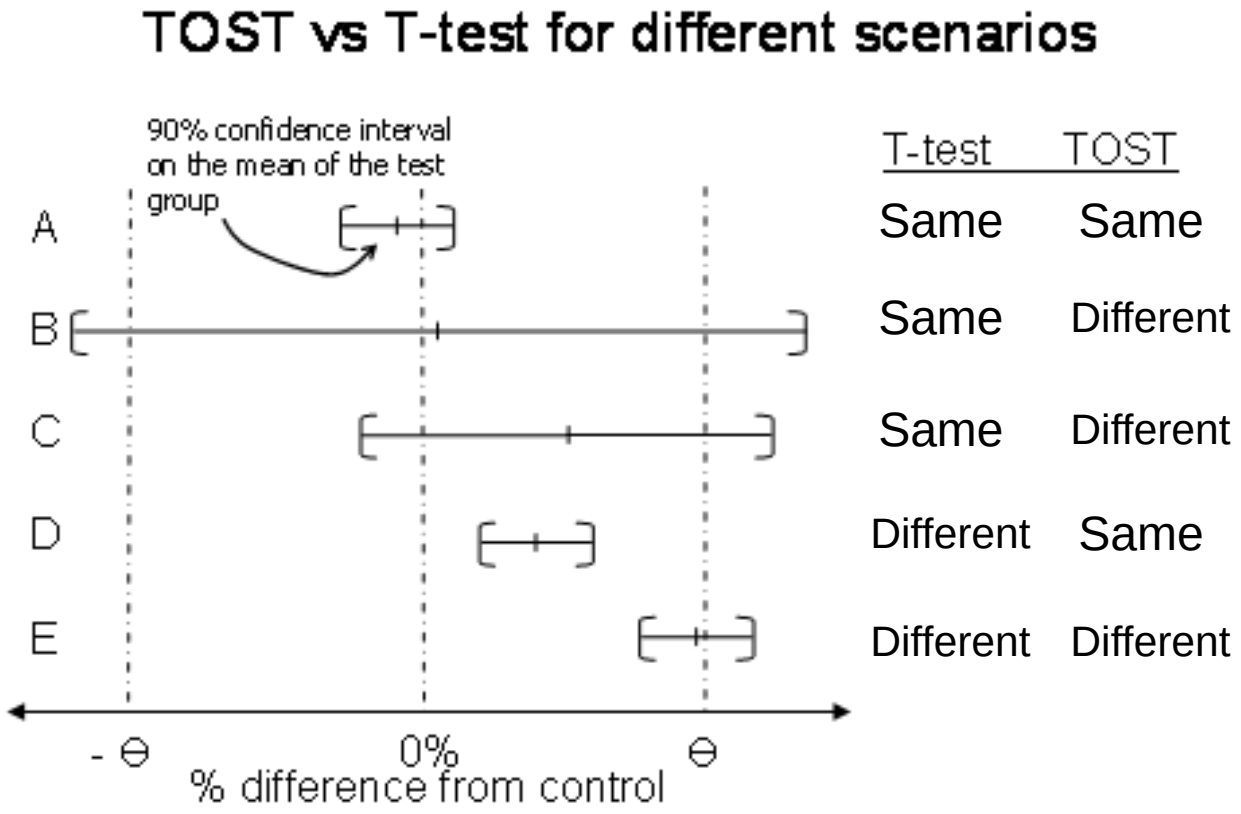
Compare 2 laboratories

More stringent than setting Performance Criteria

Methods for Determining Equivalence

- Two Sample t-test
  - Comparison of Mean Values
  - Assumption is Means are Equal
  - May Reward Poor Precision
- Limits of Agreement
  - Comparison of Means and Confidence Interval
  - Very Simple, Limited Samples
  - No allowance for Bias, little flexibility
- Two one-sided t-test (TOST)
  - Comparison of Mean Values
  - Assumption is Means are Not Equal
  - Allows for Practical Differences

Differences Between Tests



Comparison Between Development and Processing Lab

Dissolution of Tablets (n=12)

	Development	Processing	
Mean	89.3%	87.7%	← Δ = 1.6%
Std Dev	1.9	1.3	
%RSD	2.1	1.5	

Two sample t-test p-value = 0.02 Evidence that the Means are not equal

TOST

Θ is set at 3.7% based on std dev, number of samples etc.
Confidence interval of 2 means is 0.5 to 2.7%.
Since the CI falls within ±Θ, methods are equivalent.

WHICH IS CORRECT?

Comparison Between Development and Processing Lab

Dissolution of Tablets (n=6)

	Development	Processing	
Mean	82%	79%	← Δ = 3%
Std Dev	5.6	7.3	
%RSD	6.9	9.2	

TOST

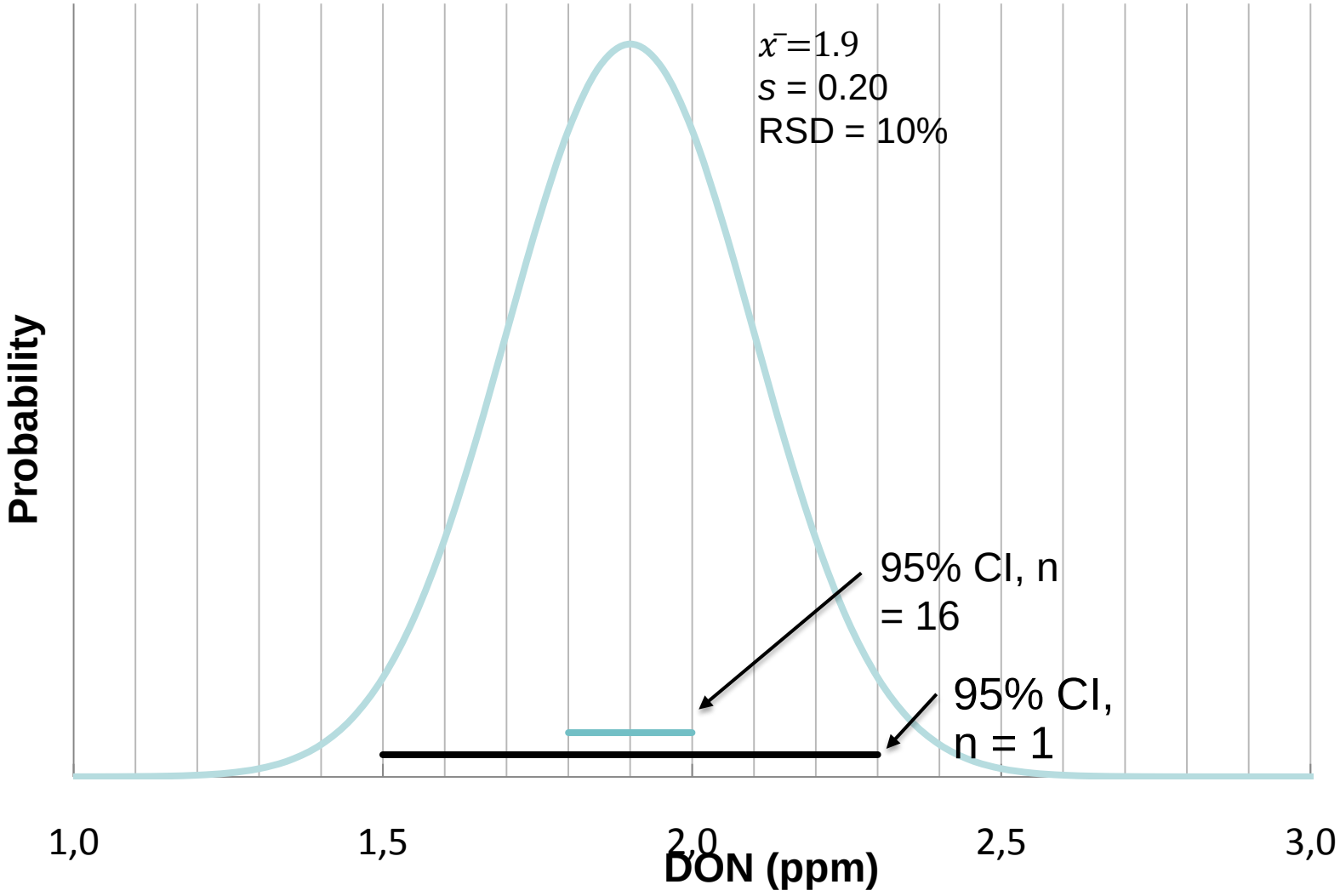
If Θ is set at 3.5% based on previous data, Methods are not equivalent

If Θ is set using the Std Dev of 5.6%, the CI becomes 19.

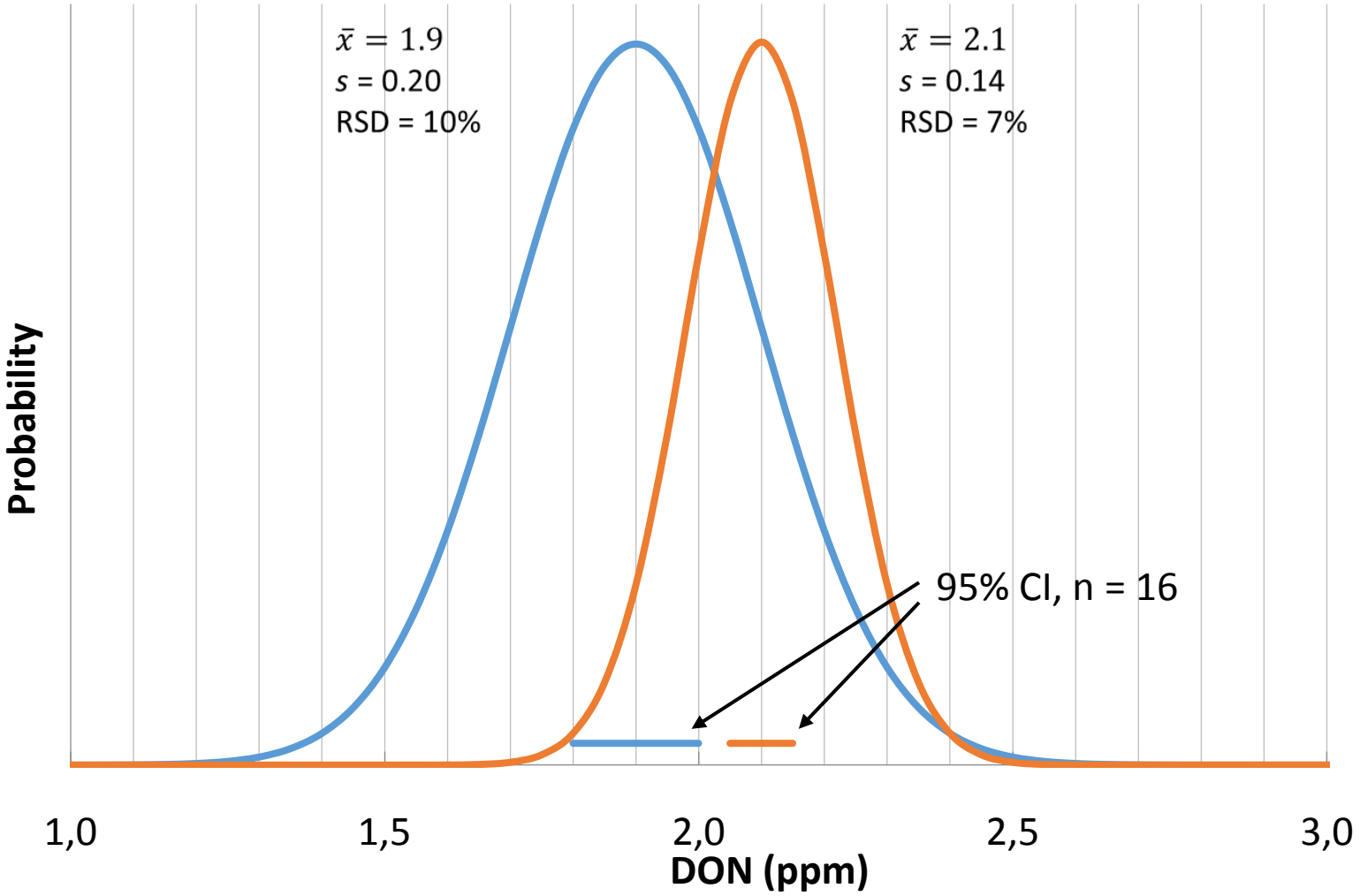
Two sample t-test p-value = 0.36 No Evidence that the Means are not equal

WHICH IS CORRECT?

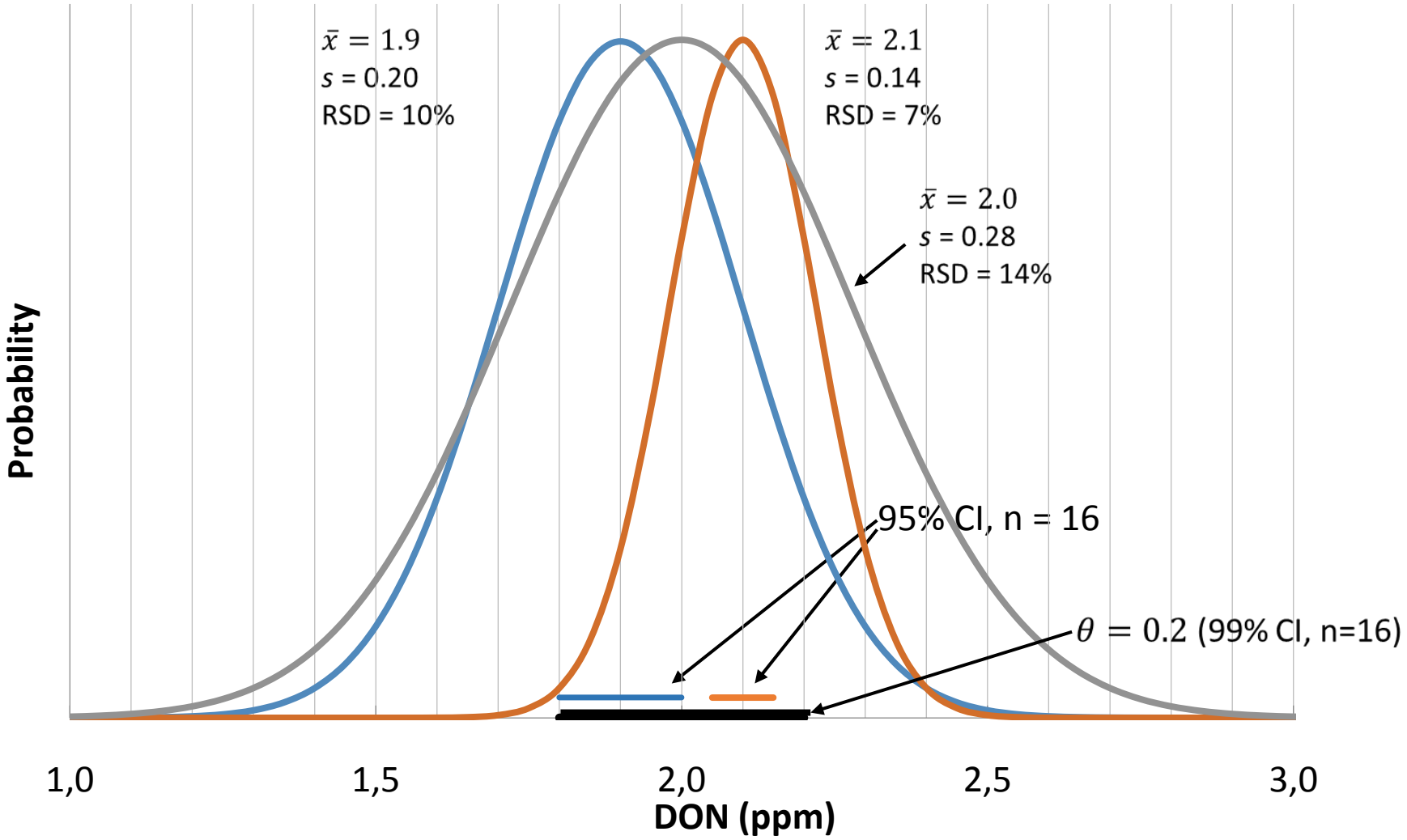
Deoxynivalenol Method 1



Method 1 and 2 – *t*-test

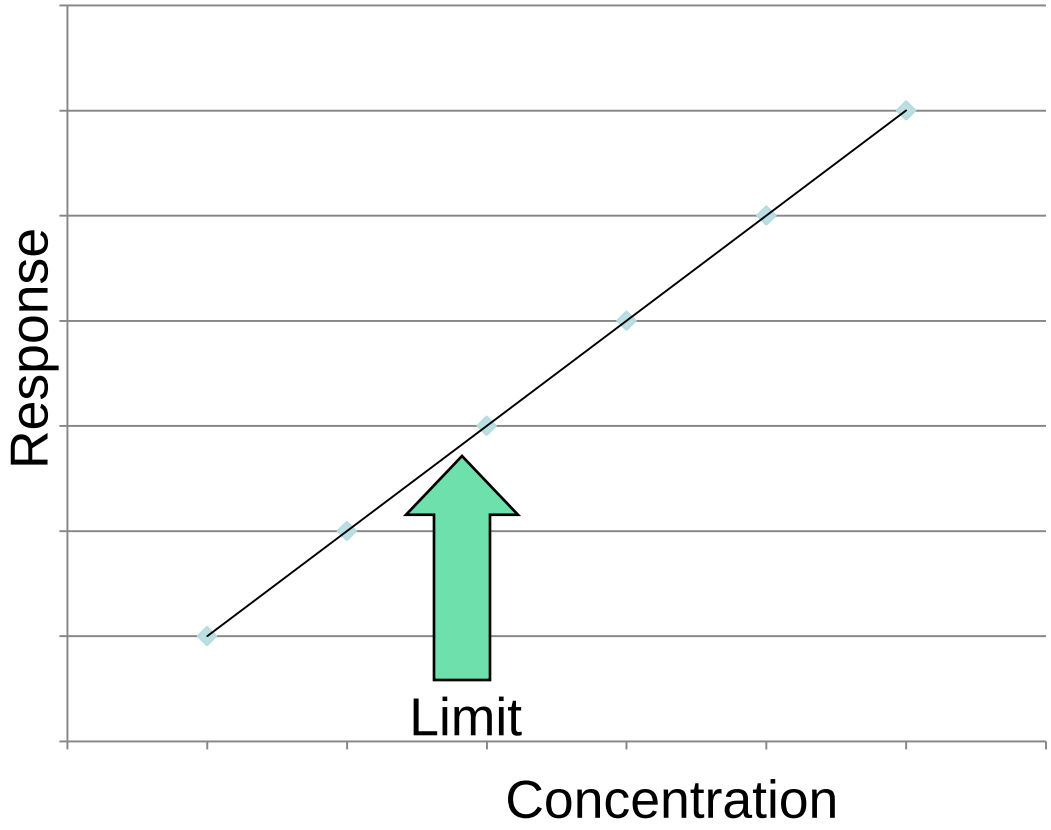


Method 1 and 2 – TOST versus *t*-test



Other Considerations for Equivalence

What Range is Necessary for Equivalence?



Different Matrices?

Use Multi-lab Data?

Conclusions

There are a number of Statistical Approaches for establishing equivalency between methods.

The TOST Approach is a Useful Balance of Practicality and Statistical Rigor.

Choosing the Statistical Approach is a very small part of Determining Equivalence.