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# 2009 USP Annual Scientific Meeting Sheraton Centre Toronto Hotel Toronto, Ontario Canada

Session I, Track IV

Quality of Manufactured Medicines New Compendial Initiatives  
Performance Based Monographs

September 23, 2009

10:30 AM – 12:30 PM

*Quality Standards for Medicines, Supplements, and Food Ingredients throughout the World*



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# Performance-Based Monographs: Statistical Considerations in Implementation

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Presentation to USP Annual Scientific  
Meeting  
September 23, 2009

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# Outline

- ◆ Equivalent or better
- ◆ Accuracy-precision tradeoff
- ◆ Operating characteristics curves (OCC's)
- ◆ Setting acceptance limits
- ◆ Issues and questions



## USP Regarding Alternative Procedures

- ◆ USP General Notices -- "Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in General Chapter *Validation of Compendial Procedures* <1225> and must be shown to give **equivalent or better** [emphasis added] results."
- ◆ Became official May 1, 2009



# Four Options for Demonstrating “Equivalent or Better”

Option	Name	Demonstrating	Comparison To Official Procedure?	Based on Numerical Results or Conclusion?	Number of Characteristics Considered
1	Acceptable Procedures	Acceptable	No	Results	Many
2	Performance Equivalence	Equivalent or Better	Yes	Results	Many
3	Results Equivalence	Equivalent	Yes	Results	One
4	Decision Equivalence	Equivalent	Yes	Conclusions	One

- ◆ PBM’s are taking the approach of Option 1; i.e., no comparison to an official procedure
- ◆ How? Set minimum requirements for validation criteria
- ◆ Advantages –
  - Difficult to show equivalent or better if already very good
  - There need not be an official method



# Why Looking at Accuracy-Precision Tradeoff?

- ◆ Tradeoff – Acceptable level of bias depends on the precision and vice versa
- ◆ Validation perspective --
  - An option for setting validation acceptance criteria for accuracy and precision
  - Validation is intended to show “that the performance characteristics of the procedure meet the requirements **for the intended analytical applications**” (<1225>)
  - Desirable property of tradeoff -- directly related to monograph limits and thus ties the acceptance criteria to the procedures intended use



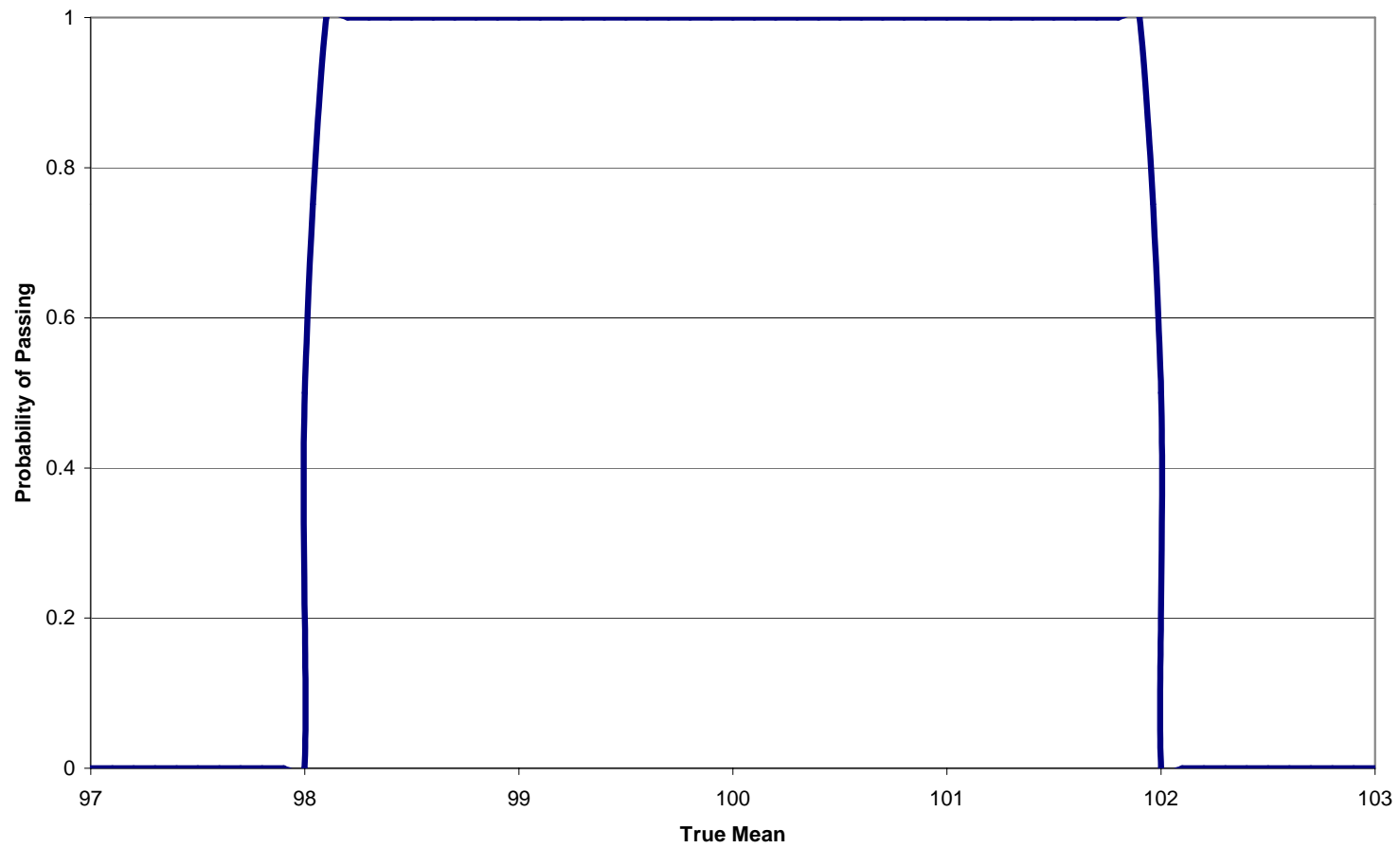
## Starting Point – OCC's

- ◆ Operating Characteristic Curves characterize the method in terms of its ability to make correct decisions  
i.e., if actually outside 98-102, does it fail?;  
if actually inside, does it pass?
- ◆ Look at probability of meeting the acceptance limits as a function of the actual value of the material and the properties of the method (accuracy and precision)



# Ideal OCC

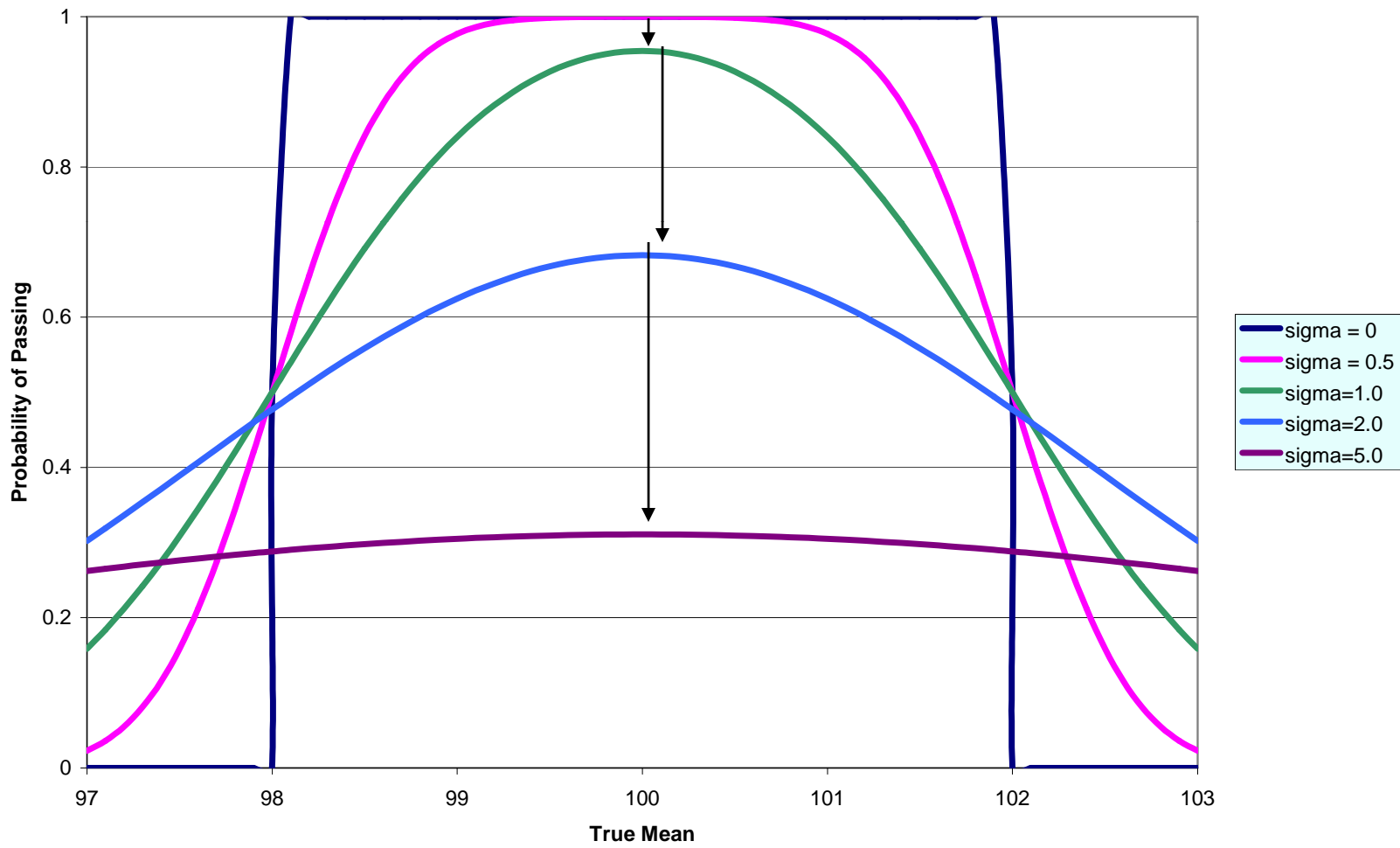
Ideal OCC, No Bias, No Variance, 98%-102% Limits





# Add Variability

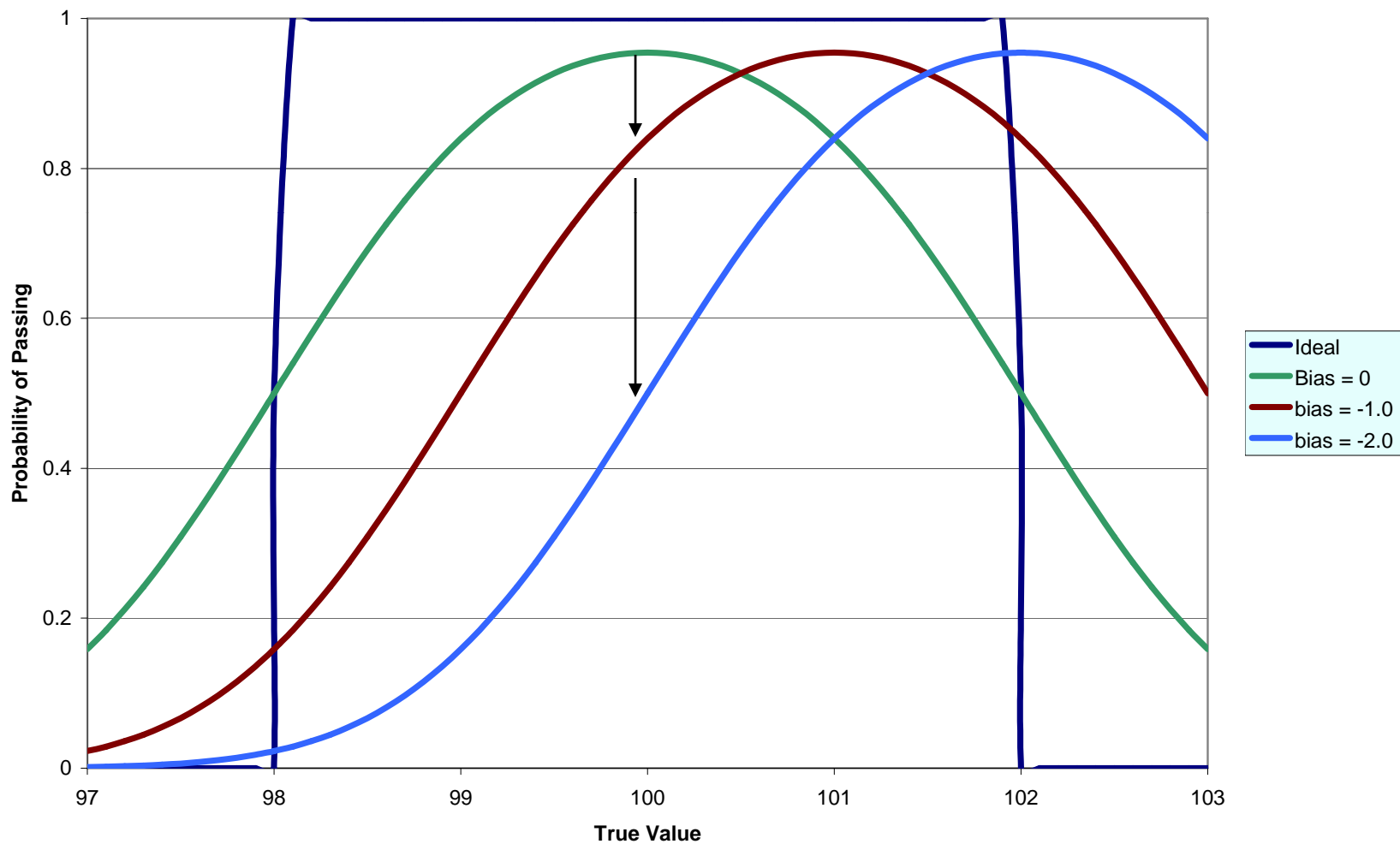
OCC, No Bias, 98%-102% Limits





# Add Bias with Some Variance

OCC, Sigma = 1.0, 98%-102% Limits

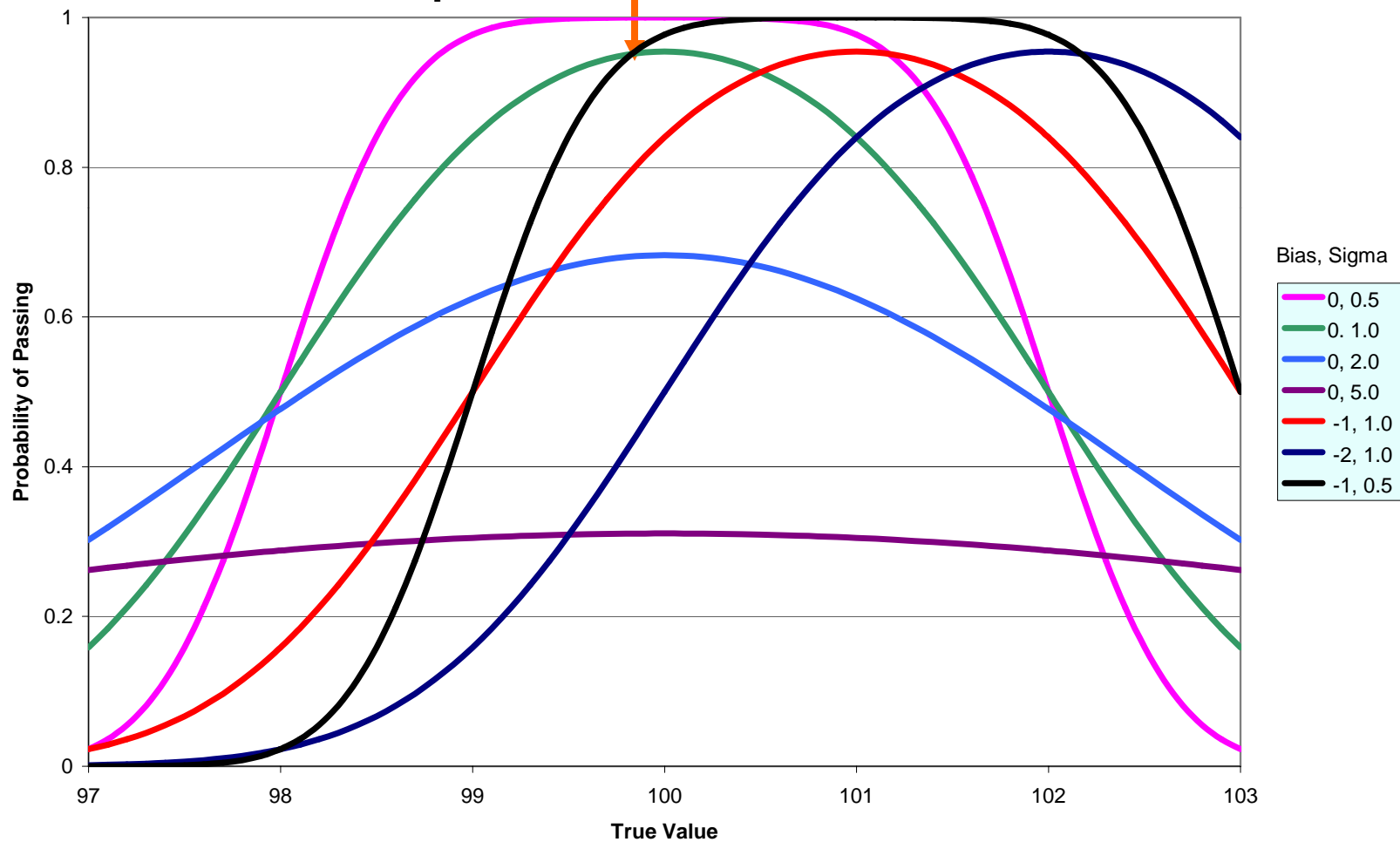




# A Stake in the Ground

**Acceptable: Curve cannot fall below this point**

OCC, 98%-102% limits





## Next Step

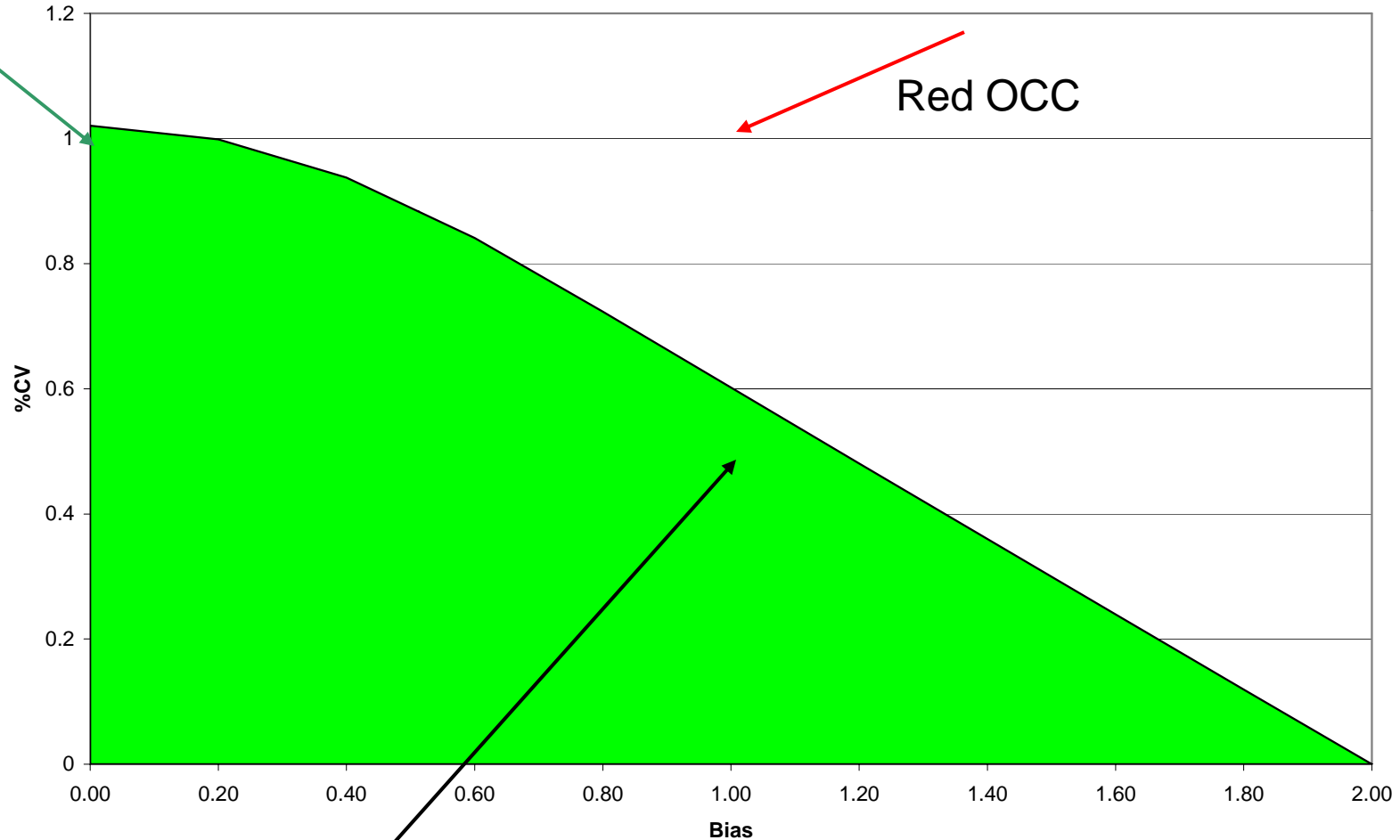
- ◆ What are the combinations of bias and precision that meet the requirement set by the “stake”?
- ◆ Leads to the following graphs



# Accuracy – Precision Tradeoff, 98%-102%

Bias-%CV Tradeoff, 98%-102% limits, True Value = 100, Prob'y Passing 0.95

Green OCC



Black OCC



## Acceptance Criteria

- ◆ Want to be within the green area of the appropriate “tradeoff” graph
- ◆ BUT, don’t actually know bias and precision, only have estimates
- ◆ Therefore, cannot necessarily have confidence that one is actually in the green
- ◆ Solution: Use confidence interval for bias and upper confidence bound for %CV



# Example

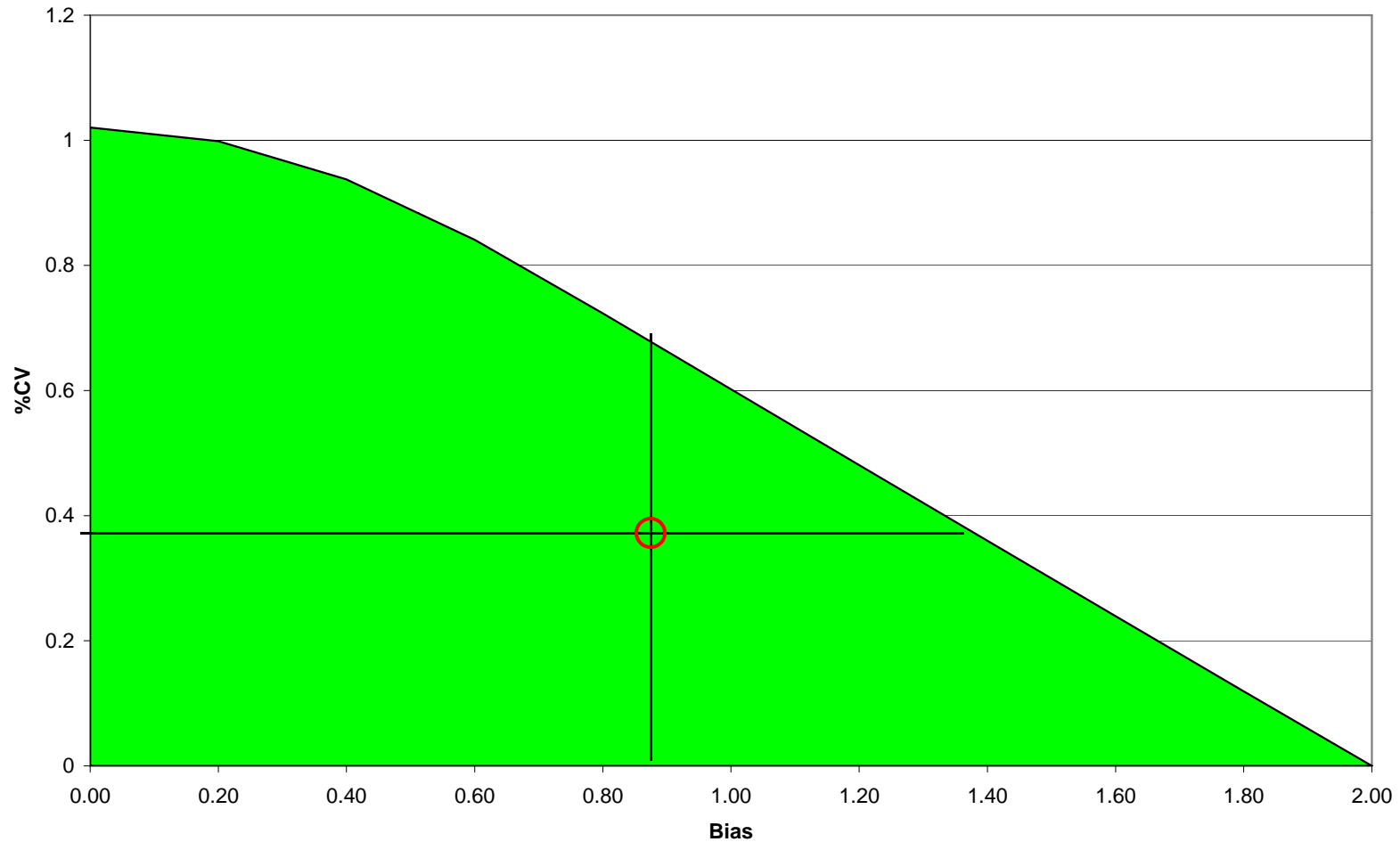
$$\% \text{ Assay} = (\text{Sample area} / \text{Standard area}) * (\text{Standard weight} / \text{Sample weight}) * \text{potency}$$

Preparations	Wt. taken (mg)	Average of 2 injections	% Assay content		
1	10.02	5735741	99.31		
2	10	5727796.5	99.38		
3	10.04	5752345	99.40		
4	10	5725816.5	99.34		
5	10.05	5758804.5	99.42		
6	10	5703348	98.95		
			99.30 Average	95% CI	
			-0.70 %Bias	99.12 99.48	
				-0.88	-0.52
			0.1752 SD		
			0.18% %RSD	-	0.37%



# Accuracy – Precision Tradeoff, 98%-102%

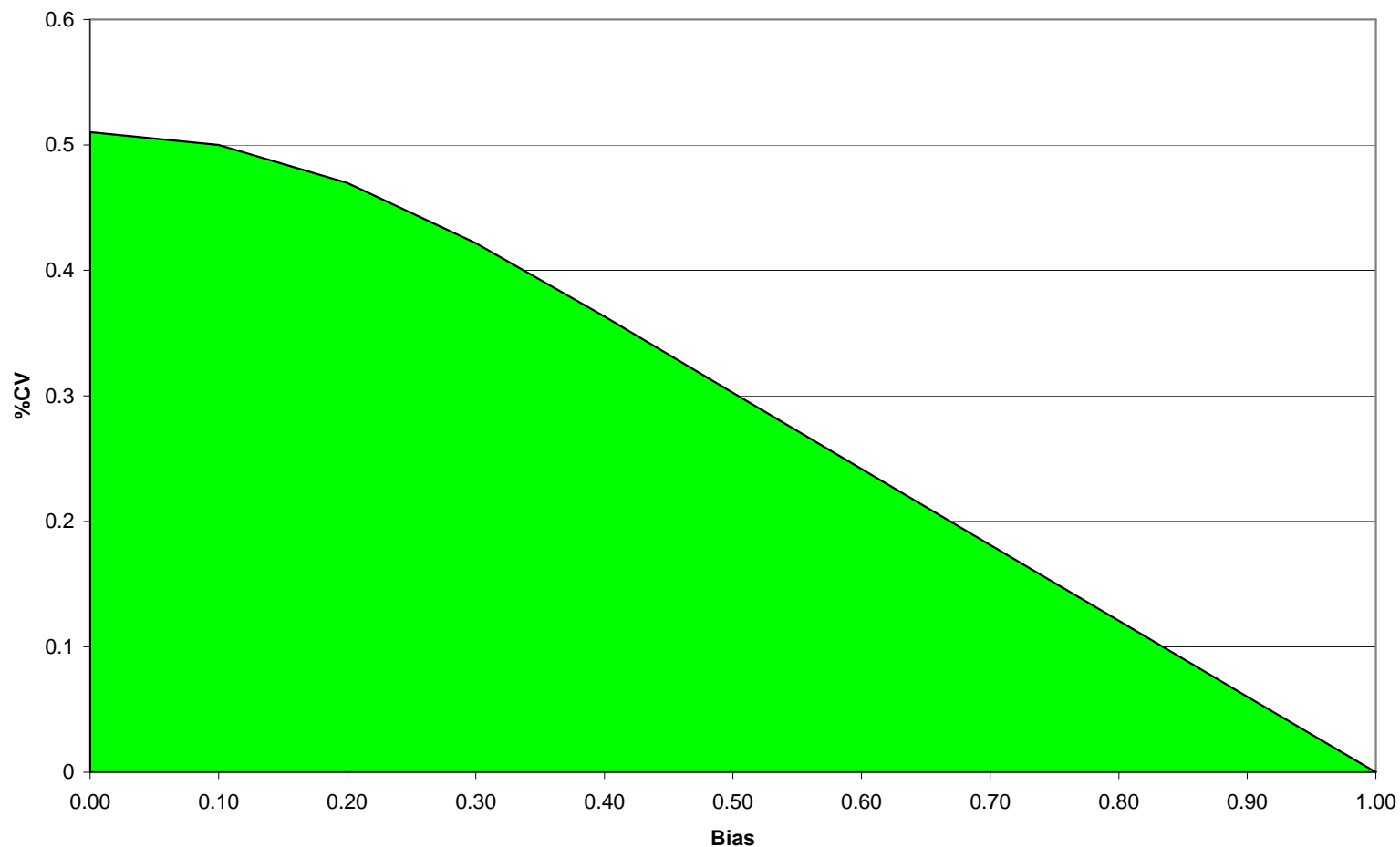
Bias-%CV Tradeoff, 98%-102% limits, True Value = 100, Prob'y Passing 0.95





# Accuracy – Precision Tradeoff, 99%-101%

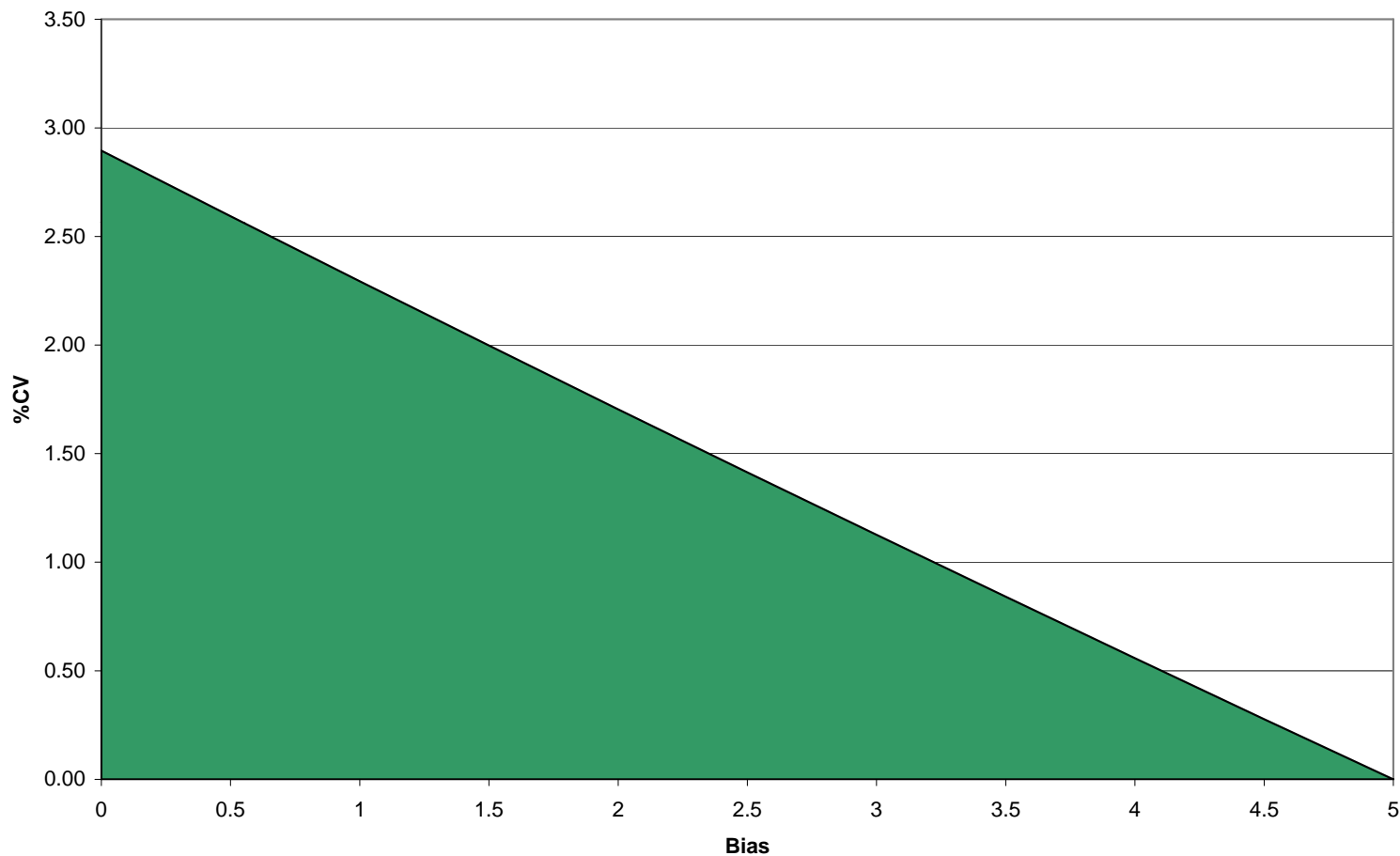
Mean-%CV TRadefoff, 99%-101% limits, True Value = 100, Prob'y Passing 0.95





# Accuracy – Precision Tradeoff, 90%-110%

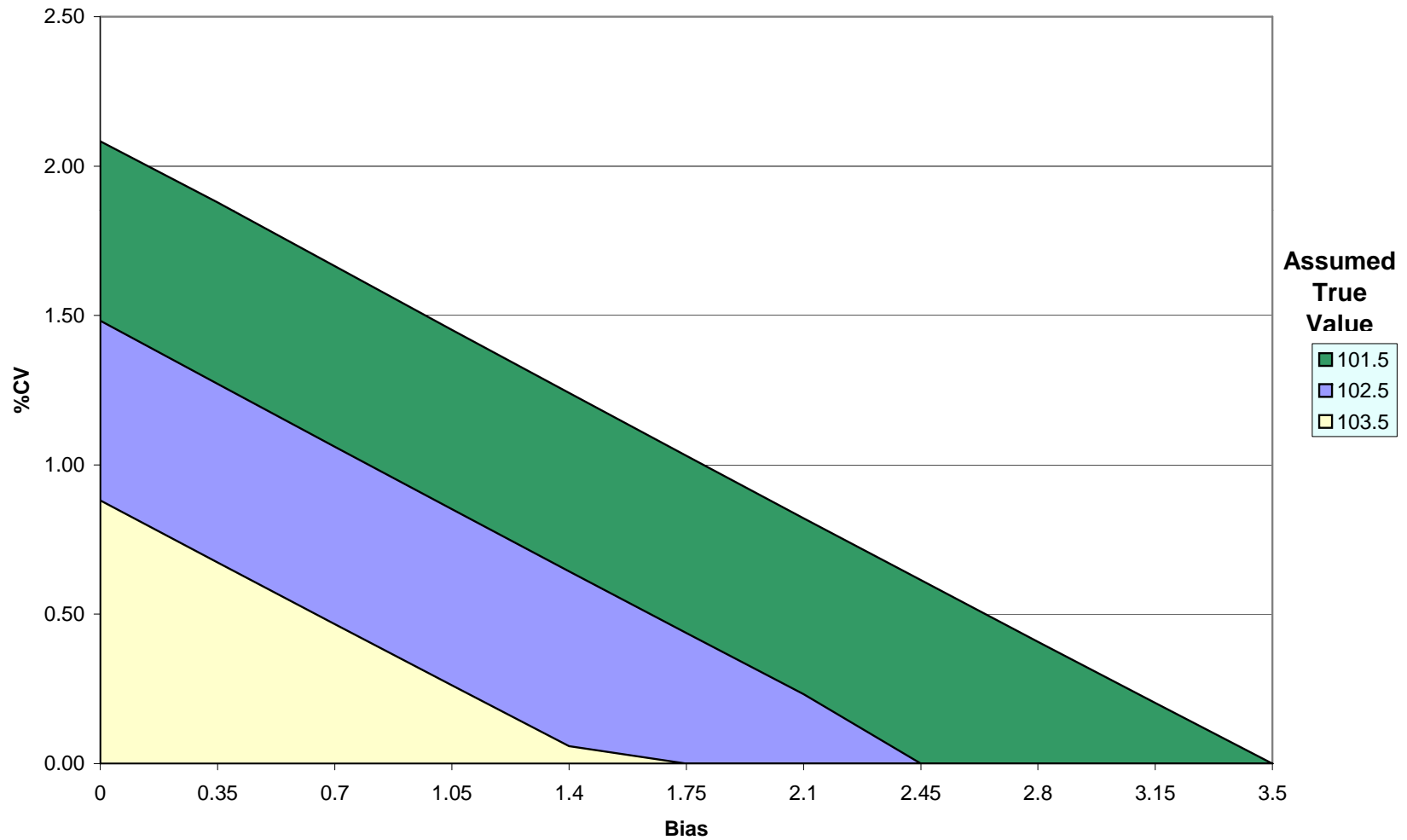
**Bias - %CV Tradeoff, 90%-110% Limits, True Value = 105% (or 95%), Prob'y Passing 0.95**





# Accuracy – Precision Tradeoff, 95%-105%

Mean - %CV Tradeoff, 95%-105% Limits, Prob'y Passing 0.95





## Issues/Questions?

- ◆ How should asymmetric monograph limits be handled?
- ◆ What proportion of the variability can be taken up by manufacturing variability; i.e., Where does the stake go if not at 100?
- ◆ Should we have a stake outside the limits instead of or in addition to one inside the limits? i.e., consider consumer risk as well as producer risk
- ◆ How does the acceptable procedures approach apply to impurity procedures and limit tests generally?



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# Questions?

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**Thank You!**

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