Statistical Considerations in Setting Product Specifications

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Manufacturing: Regulatory Impact of Statistics
2014 MBSW, Muncie, Indiana

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2. (Min, Max)
3. Tolerance Interval
4. Confidence Interval of Percentiles

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IV. Sample Size Calculation

V. Concluding Remarks

I. Background

- What are specifications?

  Specifications define quality standard/requirements.

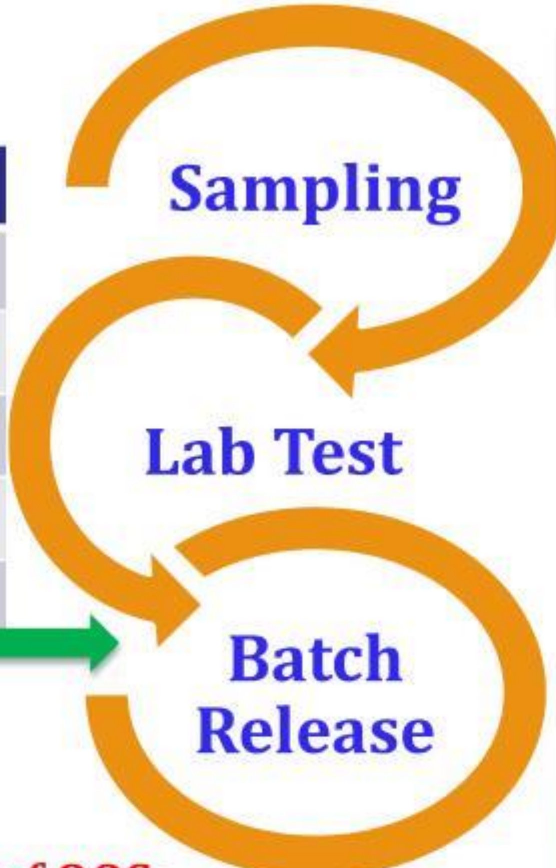
  ICH Q6A/B: a specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.

- It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.
- Specifications are one part of a total control strategy designed to ensure product quality and consistency.

I. Background (2)

- Specifications define quality standard/requirements.

Test	Specification
Assay	90-110%LC
Impurities	≤ 1%
Content Unif.	USP<905>
Dissolution	USP<711>
Microbial	≤ 2 %



Fail

Investigate root cause of OOS:
analytical error, process change, product change

I. Background (3)

- Specifications are important quality standards.
  - Only batches which satisfy specifications can be released to the market;
  - Provide a high degree of assurance that products are of good quality;
  - Assure consistent manufacturing process;
  - Most importantly, directly/indirectly link to product efficacy and safety;
  - Out-of-spec. (OOS) data are informative: analytical error, process change, product change

I. Background (4)

How specifications are determined?

Phase I/II

- May be used as supportive data

Phase III

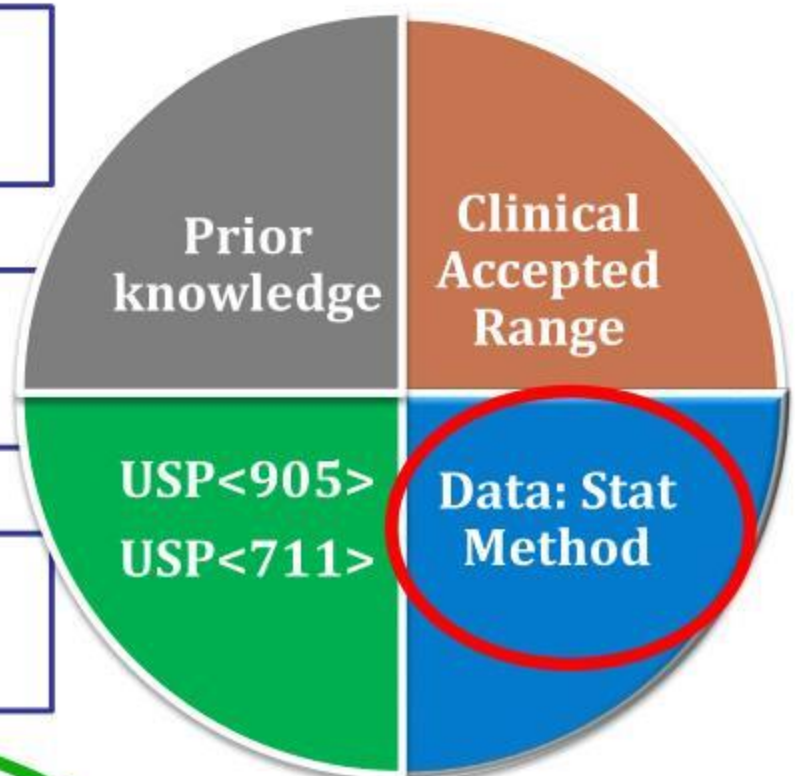
- **Use 3 clinical batches to set spec.**

NDA Submission

- Regulatory Approval

Post-marketing Changes

- Accumulated Data: release/stability



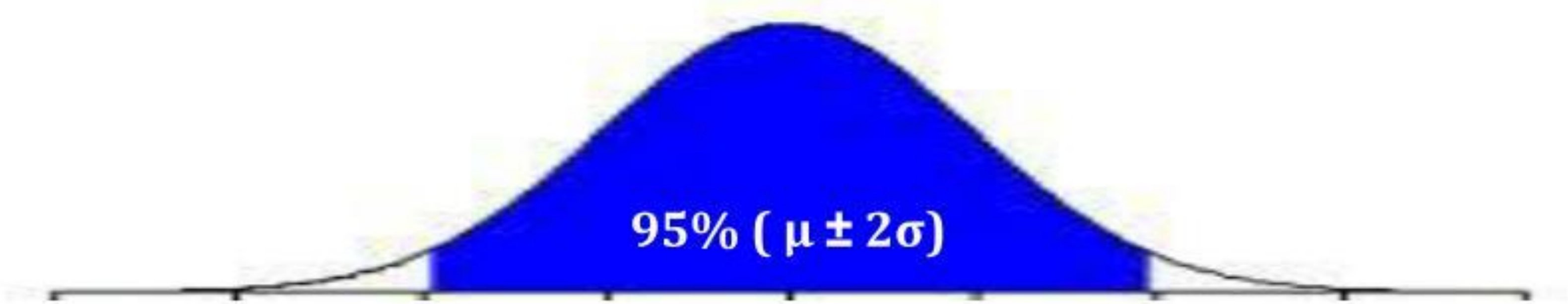
I. Background (5)

What are the impacts of setting inappropriate spec. ?

- **Too wide:**
  - Increase consumer's risk (release poor quality batches)
  - Product recalled or withdrawn from the market
  - Insensitive to detect process drifting/changes
  - Adverse impacts on patients
- **Too narrow:**
  - Increase manufacturer's risk (waste good quality batches)
- Thus, it is important to choose proper stat. method to set **meaningful, reasonable**, and **scientifically justified** specifications.

II. Statistical Methods to Set Spec.

- Assume test data $X \sim \mathrm{N}(\mu, \sigma^2)$
- σ^2:(Analytical + Sampling Plan + Manufacturing) Var
- True Spec. = Interval covering central p% of the population, say 95%.



- Use **limited data** from random samples/stability studies to **estimate** the underlying unknown interval.

II. Statistical Methods to Set Spec. (2)

- Commonly used methods in NDA submissions:
  - Reference Interval: $\bar{X} \pm 2SD$
  - (Min, Max)
  - Tolerance Interval: $\bar{X} \pm kSD$, k is (p%, 1-α%) tolerance factor
- Our proposal under study:
  - Confidence limits of Percentiles
- Compare: Coverage and Interval Width

II.1 Reference Interval

- Reference Interval (RI) = $\bar{X} \pm 2SD$
  - Most common method
  - Used in control chart to monitor process changes
- RI is not a reliable estimate for ($\mu \pm 2\sigma$) at small samples
  - Variability
  - Actual Coverage vs. Intended Coverage (95%)

II.1 Reference Interval (2)

- Variability of RI Limits:

$$Var(\bar{X} + Z_{1-p/2} \times S) = \frac{\sigma^2}{n} + Z_{1-p/2}{}^2 \sigma^2 (1 - C^{-2})$$

$$C = \sqrt{\frac{n-1}{2}} \Gamma(\frac{n-1}{2}) / \Gamma(\frac{n}{2})$$

	n = 10	n = 20	n = 50	n = 100
Std. Dev.	0.55	0.39	0.24	0.17
Upper Spec. Range	**(0.90, 3.1)**	(1.22,2.78)	(1.52, 2.48)	**(1.66, 2.34)**
True Upper Spec.	2			

Table 1 – Approx. Ranges of Upper Specification Limit Estimated using Reference Interval Method

II.1 Reference Interval (3)

- Actual vs. Intended Coverage (95%):

Table 2 – Quantiles of Coverage from 10^5 Simulations using Reference Interval Method with Intended Coverage of 95%

Quantiles	n = 10	n = 20	n = 50	n = 100	n = 1,000
Min Cover.	27.2	46.9	75.2	84.3	92.6
25%	86.9	90.6	92.8	93.6	94.6
50%	92.9	94	94.6	94.8	95
75%	96.6	96.4	96.1	95.9	95.3
Max Cover.	100	99.9	99.5	99	96.8

II.2 (Min, Max)

- Specification = (Min, Max) of Obs.
- Not suitable to define spec. :
  - coverage can't be defined.
  - Insensitive to identify OOS obs. as "atypical" or "abnormal" results.
  - With small samples, neither the manufacturer's risk nor the consumer's risk is clear;
  - with large samples, consumer's risk will be greatly inflated due to over-wide spec.

II.2 (Min, Max) (2)

- Spec. = (Min, Max) , say intended coverage = 95%

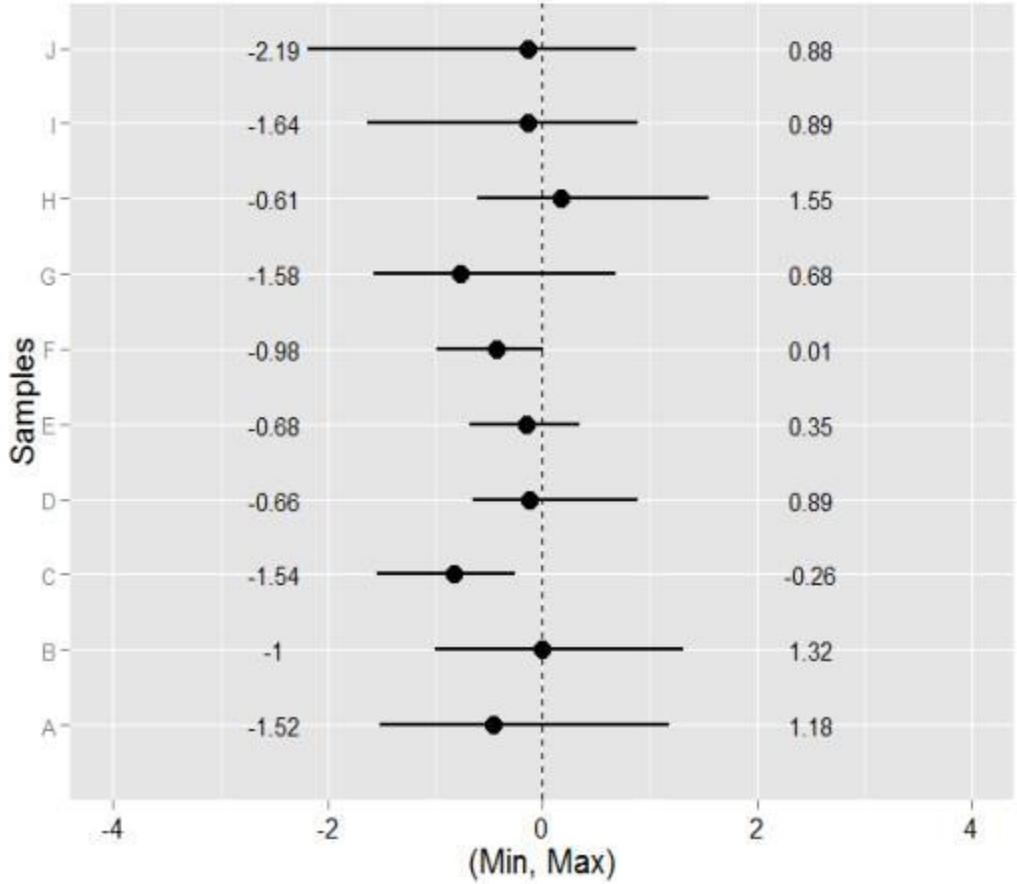


Figure 1 – Plots of (Min, Max) of 10 Simulations with N = 5 from N(0,1)

Coverage
80%
76%
67%
69%
34%
38%
56%
34%
75%
82%

II.2 (Min, Max) (3)

- Spec. = (Min, Max) , say intended coverage = 95%

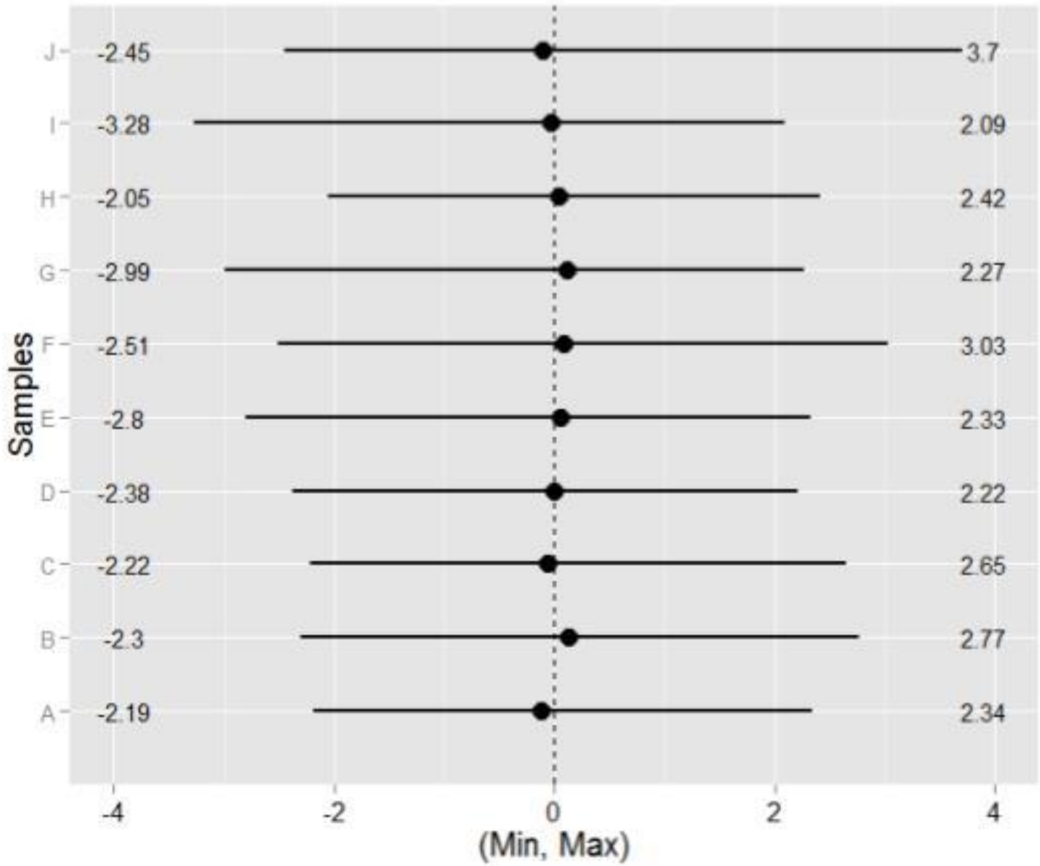
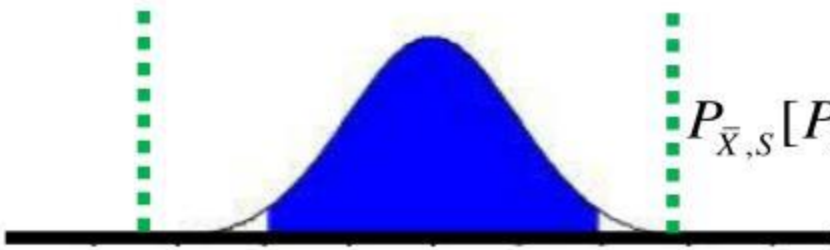


Figure 2 – Plots of (Min, Max) of 10 Simulations with N = 100 from N(0,1)

Coverage
99.3%
98.1%
97.2%
98.7%
99.3%
98.8%
97.8%
98.3%
98.6%
97.6%

II.3 Tolerance Interval

- Spec. = Tolerance Interval (TI)= Mean ± *k* ×SD
  - Aims to cover **at least** *p*% (say 95%) of the population with conf. level of 1-α.



$$P_{\bar{X},S}[P_X(\bar{X} - kS < X < \bar{X} + kS \mid \bar{X}, S) \geq \beta] = 1 - \alpha$$

  - *k* is (*p*, 1-α) tolerance factor $k = t_{n-1,\gamma}(Z_p\sqrt{n})/\sqrt{n}$

- By definition, TI is almost always **wider than** the targeted interval, especially with small samples.

	n = 5	n = 10	n = 50	n = 100	n = 1000
95%, Z_p = 2.00	4.91	3.40	2.43	2.28	2.05

II.3 Tolerance Interval (2)

- Tolerance interval has issues of over-coverage

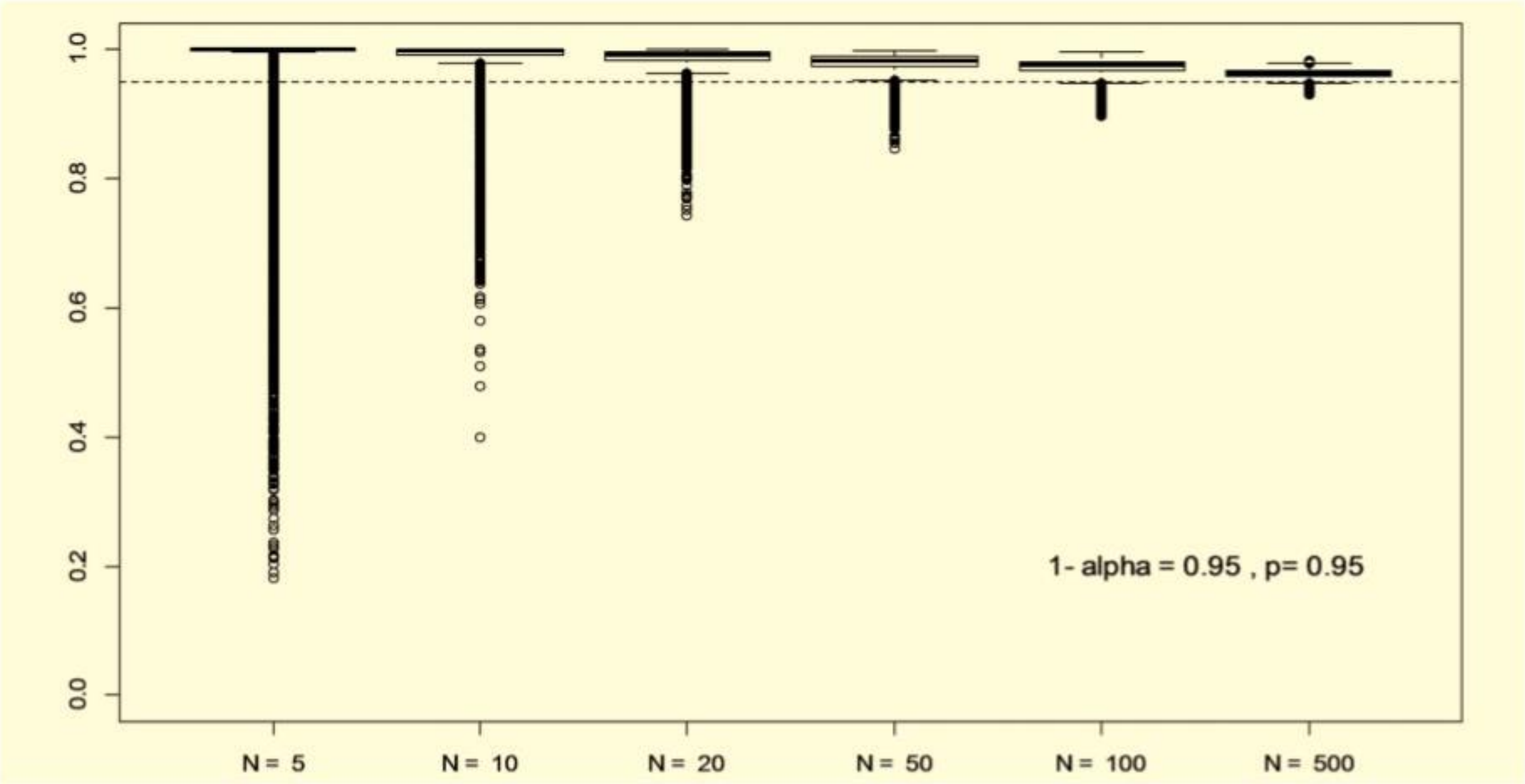


Figure 3 – Box Plots of Coverage Obtained from 10^5 Simulations using Tolerance Interval

II.3 Tolerance Interval (3)

- Tolerance interval is too wide

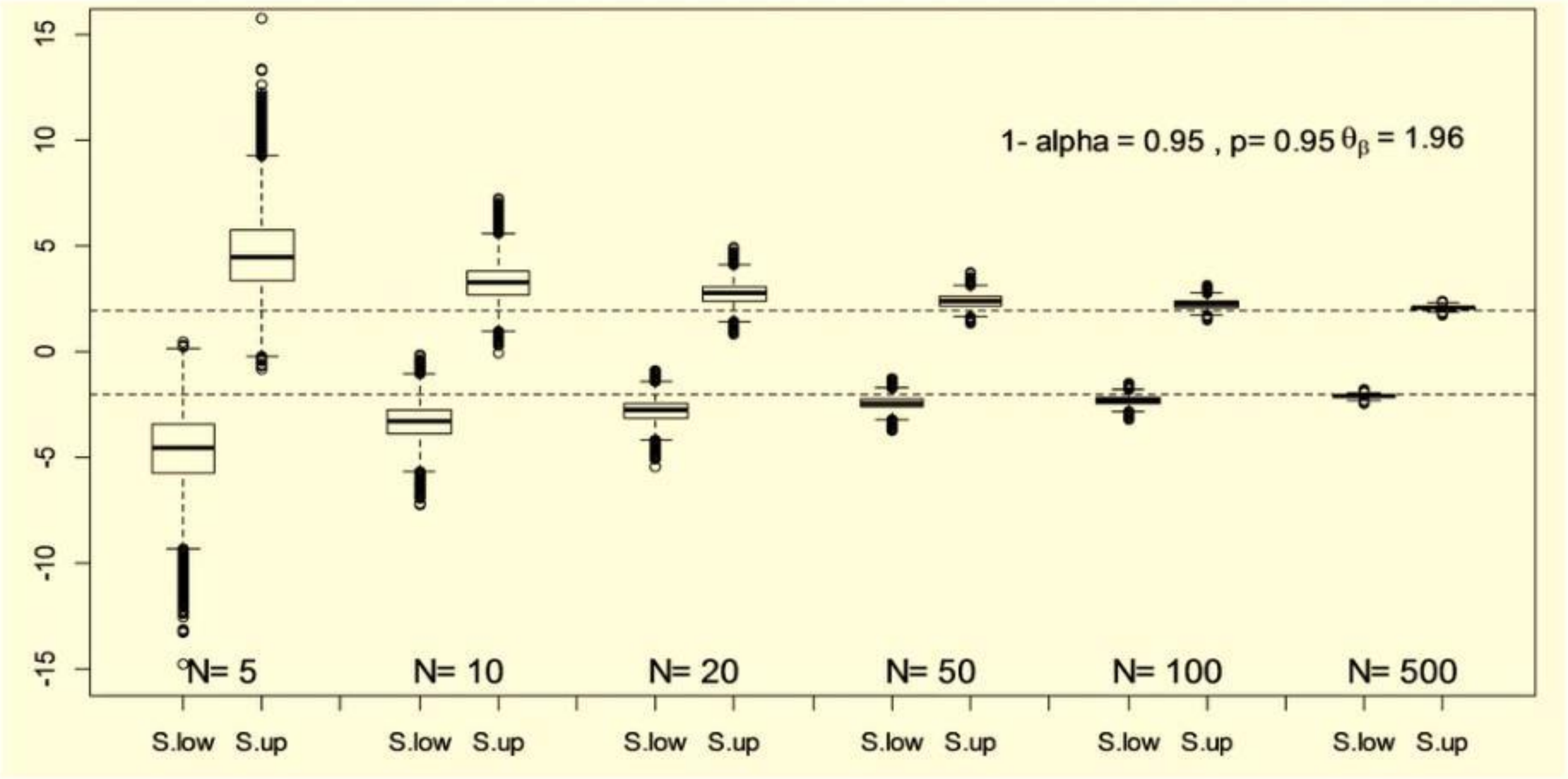


Figure 4 – Box Plots of Lower and Upper Bounds Obtained from 10^5 Simulations using Tolerance Interval

II.4 Confidence Limits of Percentiles

- Basic Idea

Tolerance Interval

Lower CL of LB, Upper CL of UP

$$\mu - Z_p\sigma\,, \qquad \mu + Z_p\sigma$$

(UCL of LB, LCL of UB)

Conf. Limits of Percentiles

II.4 Confidence Limits of Percentiles (2)

- Let the true interval be

$$\left(\theta_{low} = \mu - Z_p\sigma, \theta_{up} = \mu + Z_p\sigma\right)$$

- 1-α upper CL of θ_{low}:

$$\theta_{lowCL} = \hat{\theta}_{low} + Z_{1-\alpha}\sqrt{\hat{\text{var}}(\hat{\theta}_{low})} = (\bar{X} - CZ_pS) + Z_{1-\alpha} \times \frac{S}{\sqrt{n}}\sqrt{1 + nZ_p^2(C^2 - 1)}$$

- 1-α Lower CL of θ_{up}:

$$\theta_{upCL} = \hat{\theta}_{up} - Z_{1-\alpha}\sqrt{\hat{\text{var}}(\hat{\theta}_{up})} = (\bar{X} + CZ_pS) - Z_{1-\alpha} \times \frac{S}{\sqrt{n}}\sqrt{1 + nZ_p^2(C^2 - 1)}$$

II.4 Confidence Limits of Percentiles (3)

- Intended Coverage = 95%

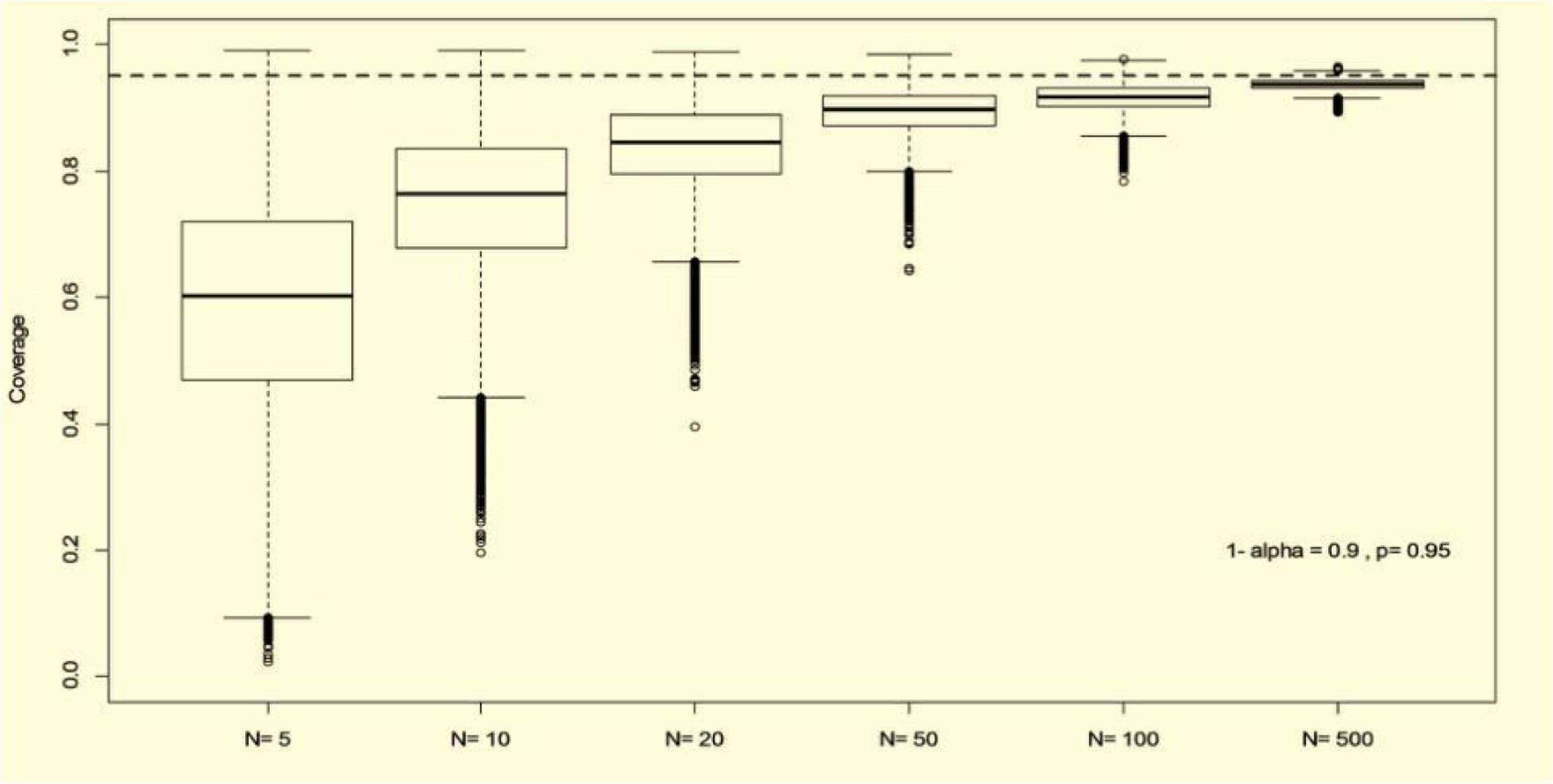


Figure 5 – Box Plots of Coverage from 10^5 Simulations using Conf. Limits of Percentiles

II.4 Confidence Limits of Percentiles (4)

- Intended interval= (-1.96, 1.96)

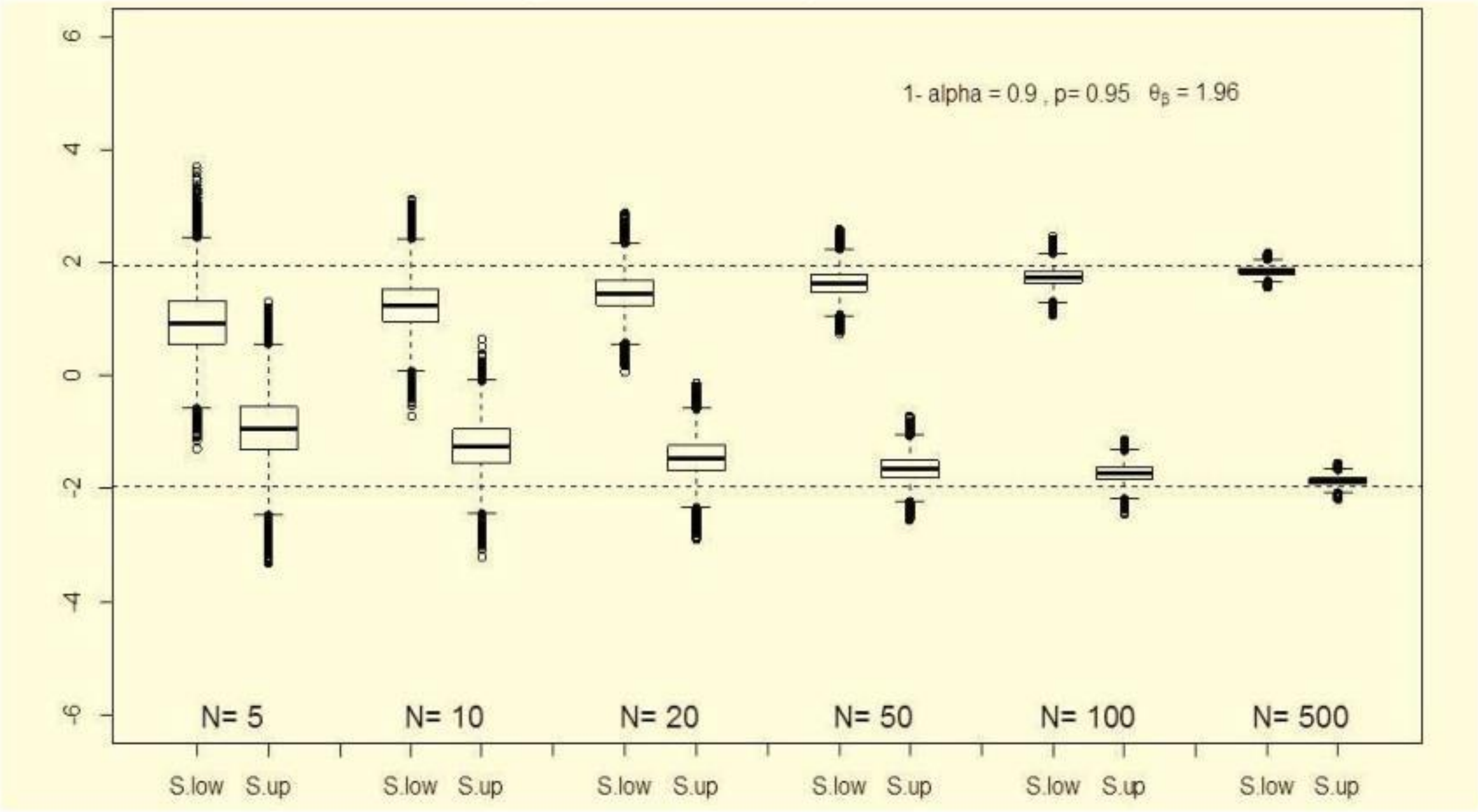


Figure 6 – Box Plots of Lower and Upper Bounds from 10^5 Simulations using Conf. Limits of Percentiles

III. Comparisons at Large Samples

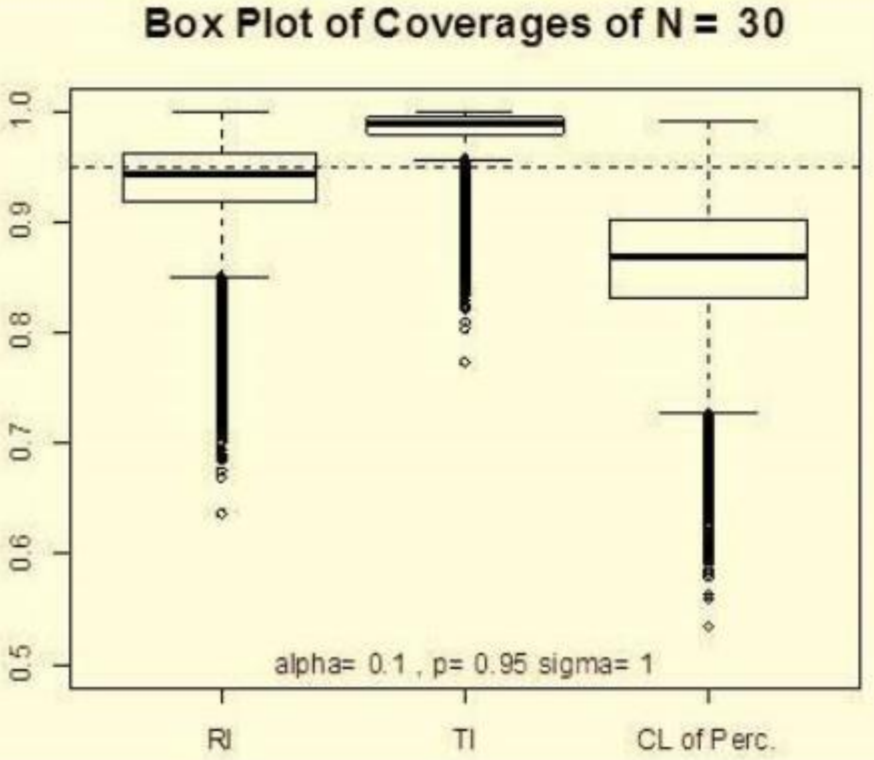
Small Samples	Reference Interval	(Min, Max)	Tolerance Interval	Conf. Limits of Percentiles
Coverage	Not assured	Not assured	$\geq$ p%	< p%
Interval Width	Large Var.	Large. Var.	Too wide	Too narrow
Our RECOM.	✗	✗	✗	✗

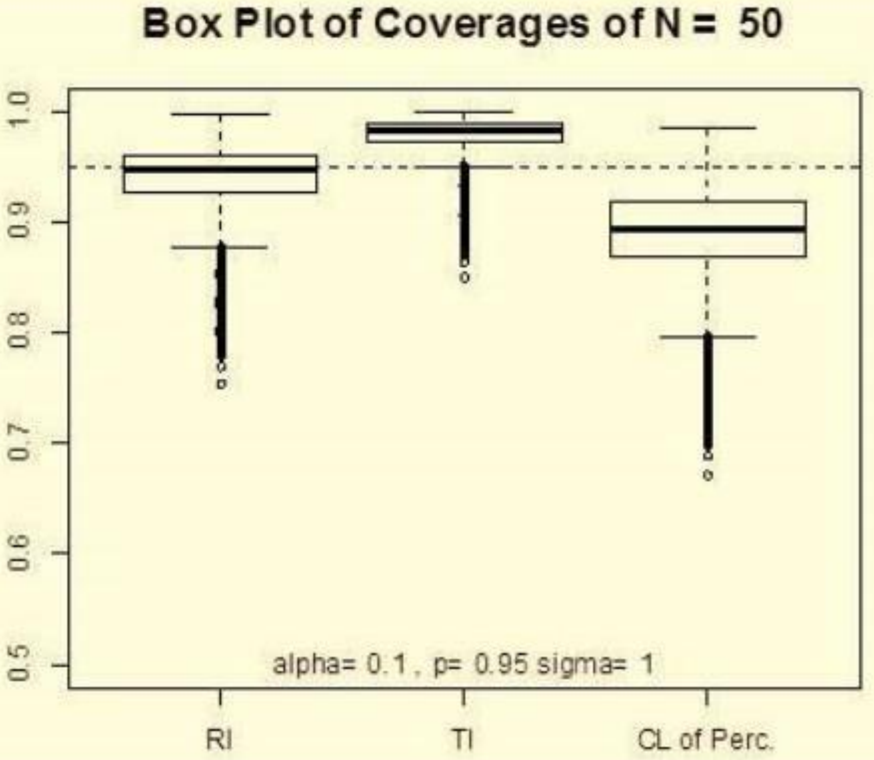
It is not suitable to set specification when small sample sizes are small, especially when the data variability is large.

What about large samples?

III. Comparisons at Large Samples (2)

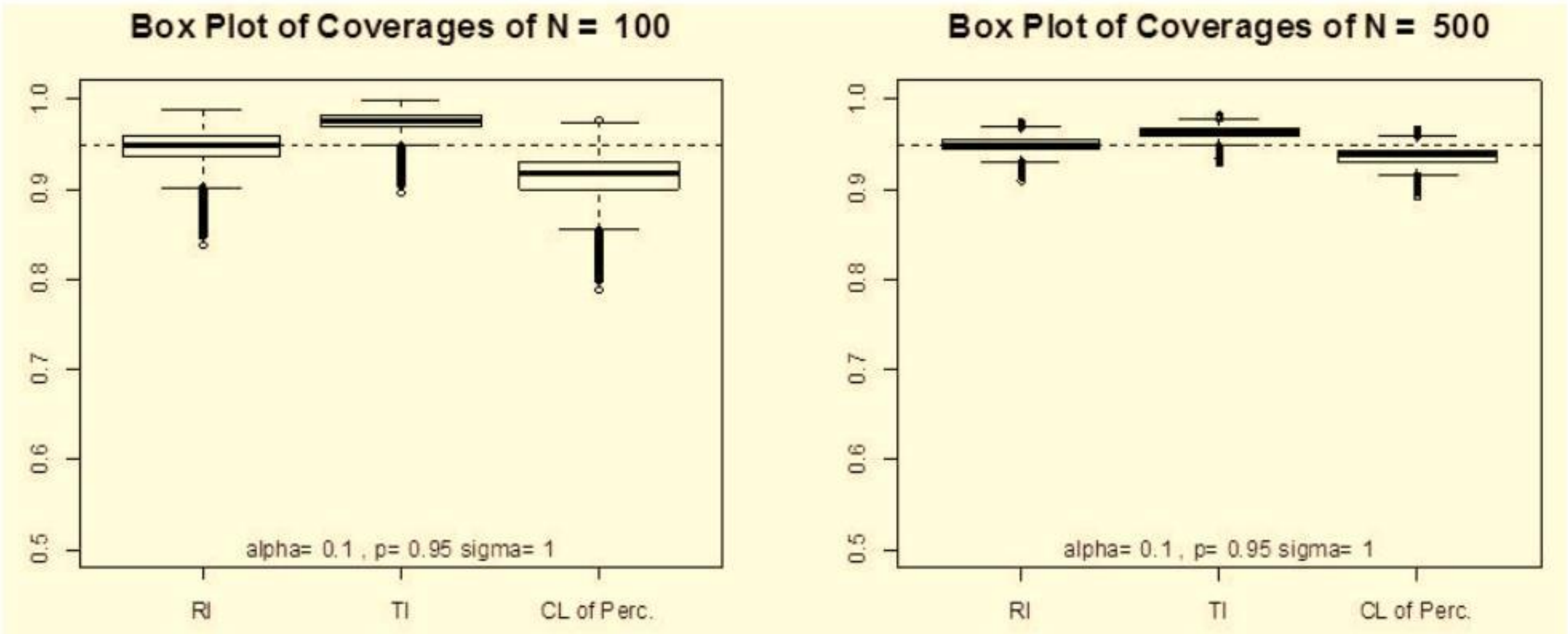
- Intended Coverage (95%)





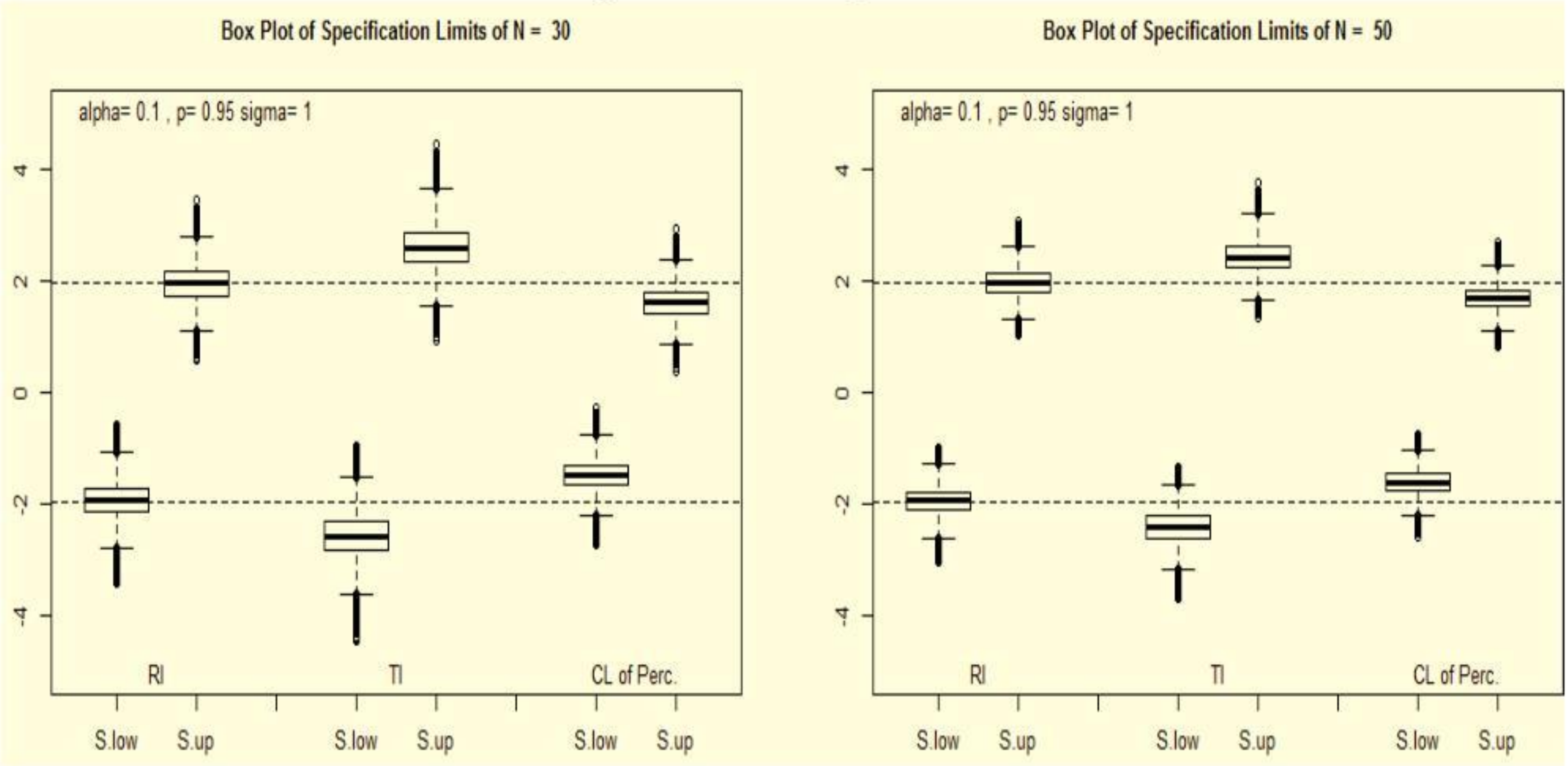
III. Comparisons at Large Samples (3)

- Intended Coverage (95%)



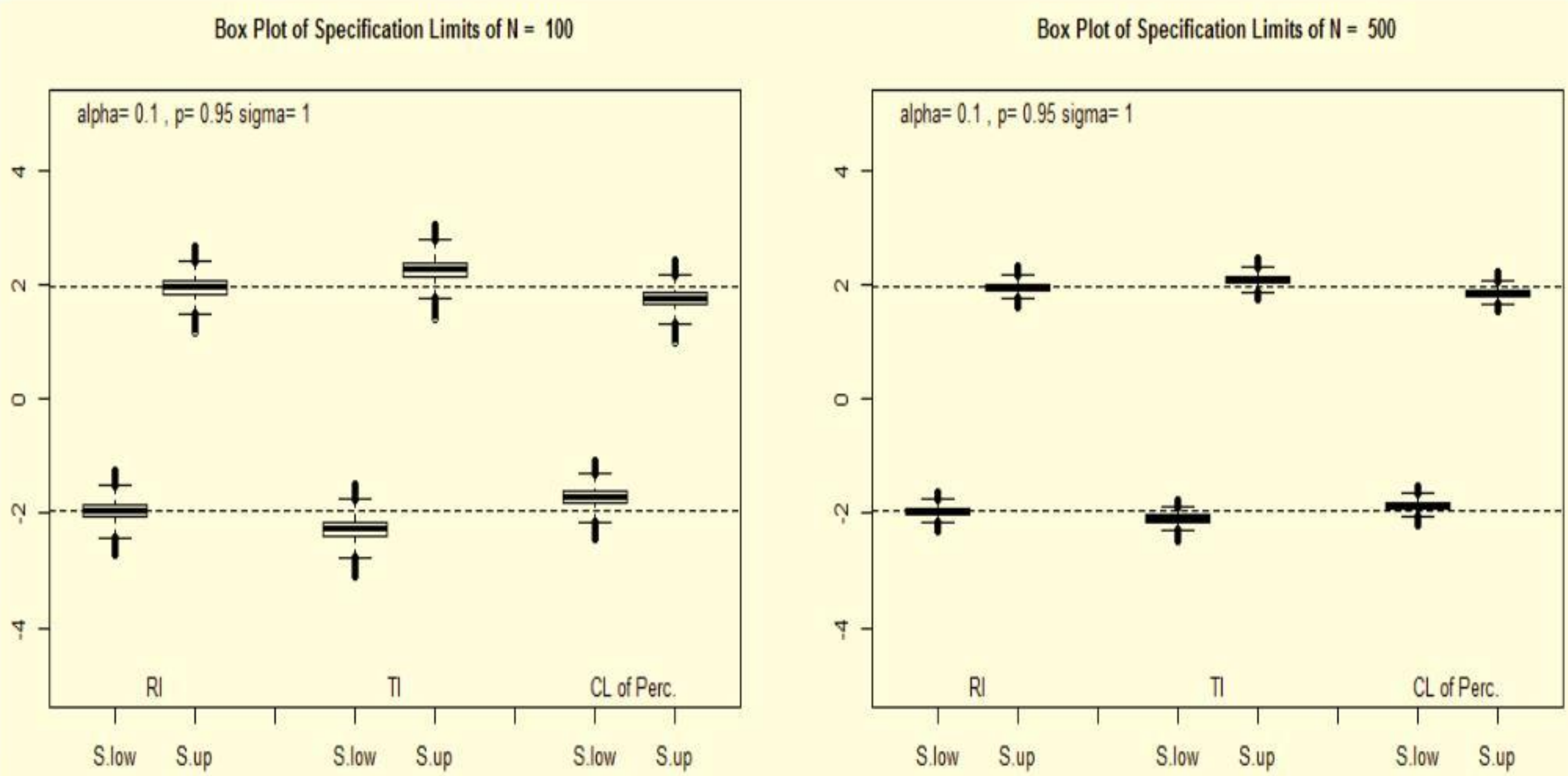
III. Comparisons at Large Samples (4)

- Intended Interval = (-1.96, 1.96)



III. Comparisons at Large Samples (5)

- Intended Interval = (-1.96, 1.96)



III. Comparisons at Large Samples (6)

- Inflation of Consumer's Risk: too wide

outside (μ ± 2σ)	Within Spec.	Outside Spec.
Poor Quality Product	**Pass**	Fail

$$P_{consumr\ \text{inflate}} = I(\hat{\theta}_{low} < \theta_{low})\Pr(\hat{\theta}_{low} < X < \theta_{low} \mid \hat{\theta}_{low}) + I(\hat{\theta}_{up} > \theta_{up})\Pr(\theta_{up} < X < \hat{\theta}_{up} \mid \hat{\theta}_{up})$$

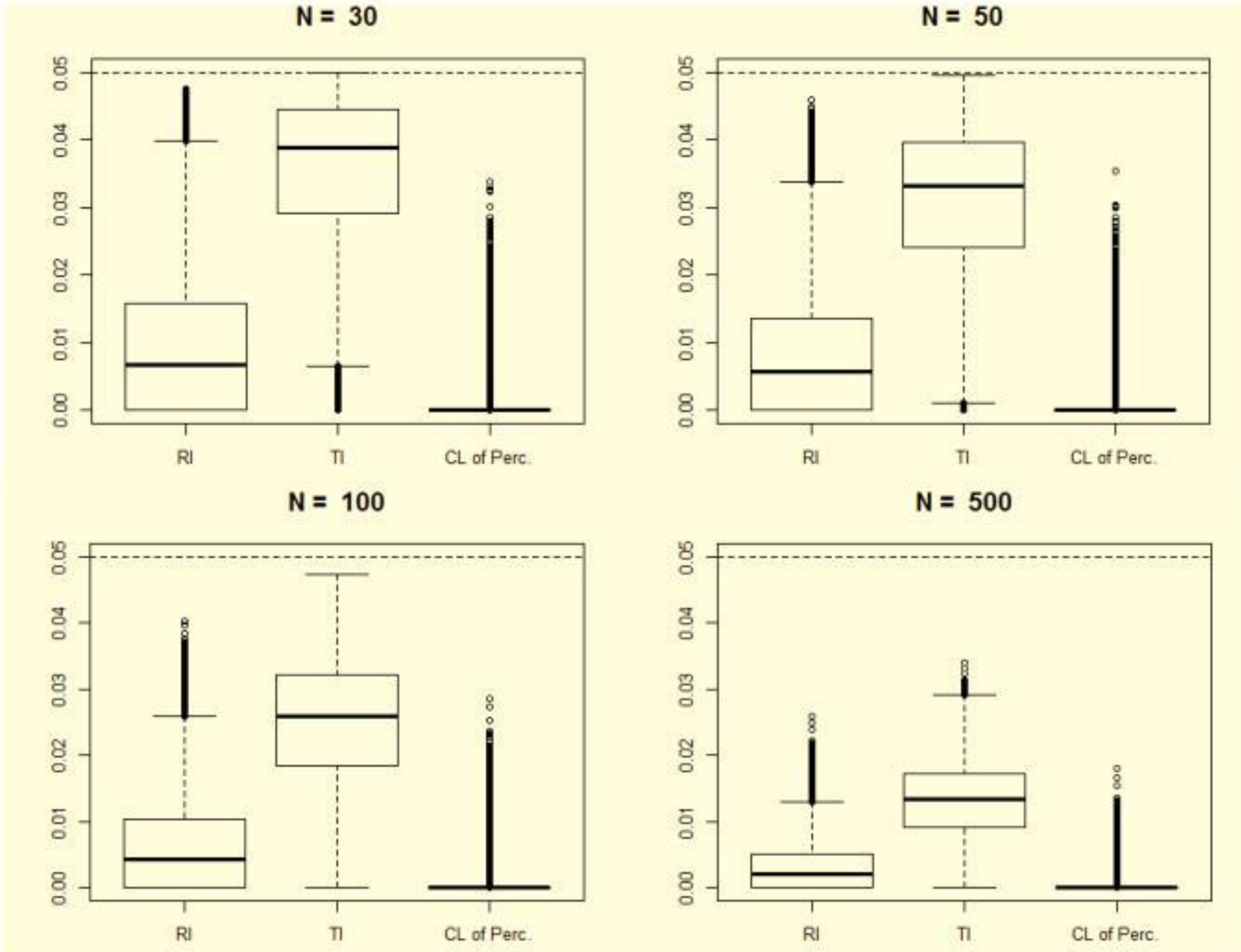
- Inflation of Manufacturer's Risk: too narrow

within (μ ± 2σ)	Within Spec.	Outside Spec.
Good Quality Product	Pass	**Fail**

$$P_{\text{manufacture inflate}} = I(\hat{\theta}_{low} > \theta_{low})\Pr(\theta_{low} < X < \hat{\theta}_{low} \mid \hat{\theta}_{low}) + I(\hat{\theta}_{up} < \theta_{up})\Pr(\hat{\theta}_{up} < X < \theta_{up} \mid \hat{\theta}_{up})$$

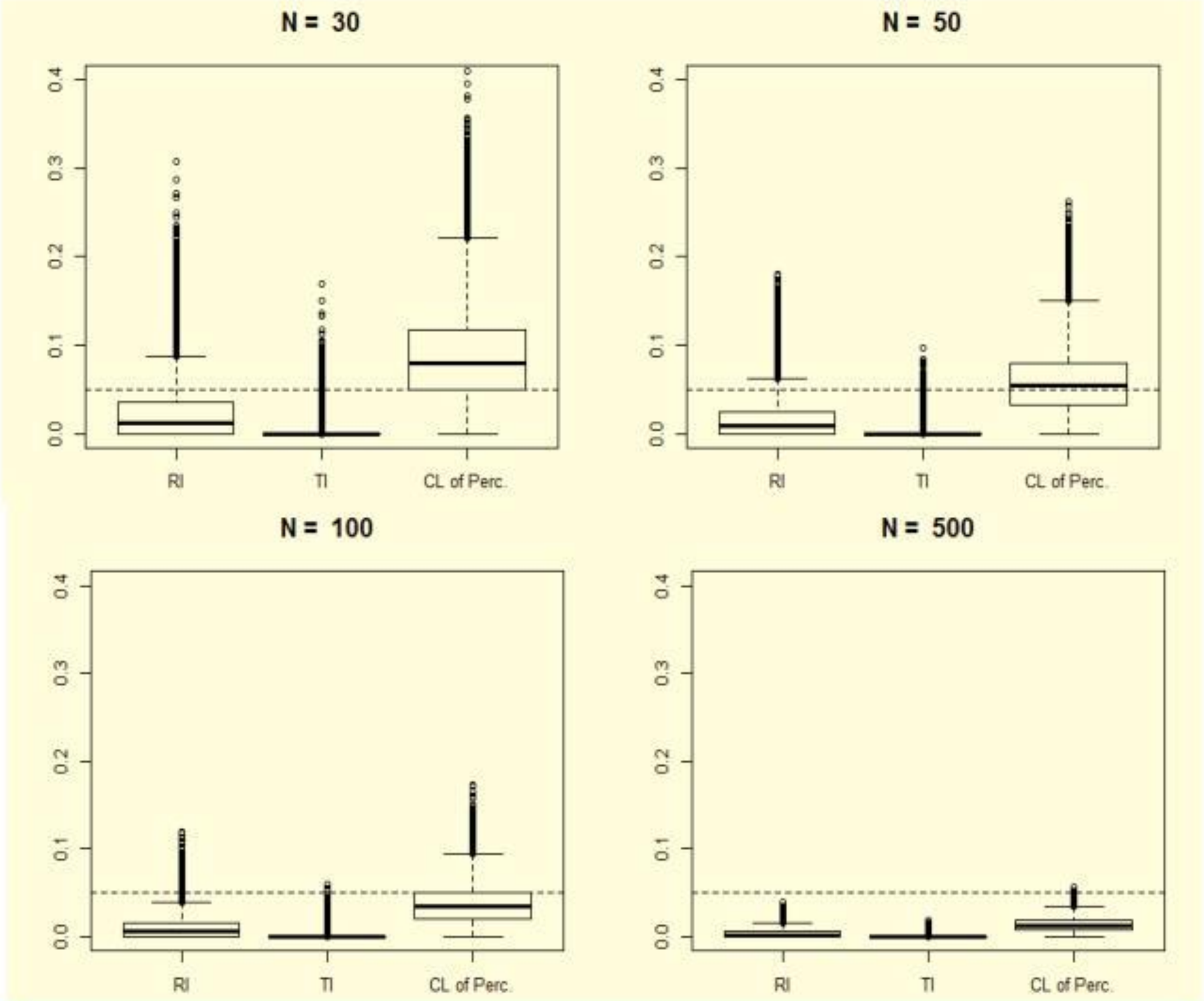
III. Comparisons at Large Samples (7)

- Inflation of Consumer's Risk: release the poor quality product



III. Comparisons at Large Samples (8)

- Inflation of Manufacturer's Risk: waste the good quality product



IV. Sample Size Calculation

- It would be helpful if we can plan the sample size of setting spec. in advance.
- Similar concept of SS calculation used in TI methods;
- Compute sample size so that

$$P_{\bar{X},S}\left[\, p-\delta \le P_X(\bar{X}-kS < X < \bar{X}+kS \mid \bar{X},S) \le p+\delta \,\right] \ge \gamma$$

Take p = 95%, δ = 3%, γ = 90% for example: Determine the sample size so that 90% (γ) of time, the absolute distance between the actual coverage and the targeted value of 95% (p) is less than 3% (δ).

IV. Concluding Remarks

Small Samples	Reference Interval	(Min, Max)	Tolerance Interval	Conf. Limits of Percentiles
Coverage	Not assured	Not assured	≥ p%	< p%
Interval Width	Large Var.	Large. Var.	Too wide	Too narrow
Our RECOM.	✗	✗	✗	✗

Large Samples	Reference Interval	(Min, Max)	Tolerance Interval	Conf. Limits of Percentiles
Coverage	Close to p%	~100%	≥ p%	< p%
Interval Width	Close to Target	Too Wide	Close to Target (Wider)	Close to Target (Narrower)
Our RECOM.	✓	✗	✓	✓

IV. Concluding Remarks (2)

- Specifications are a critical element of a total control strategy;
- Statistical considerations are important to set reasonable specifications in order to ensure quality, efficacy and safety of products at release and during the shelf life;
- When setting specifications, consumer's risk should be well controlled.
- Large sample size can't fix the issues caused by the underlying statistical concept of each method.
- Keep in mind, specifications estimated by statistical methods are subject to scientific or clinical justification.

Acknowledgment

- Dr. Yi Tsong
- Dr. Meiyu Shen
- Dr. Youngsook Lee
- Chemists and Biologists I have worked with.

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Thank you!