Comparative Analytical Method Transfer

Setting Acceptance Criteria

Andrew Rugaiganisa
Pharmaceutical Sciences & PGS Statistics, Pfizer Inc.

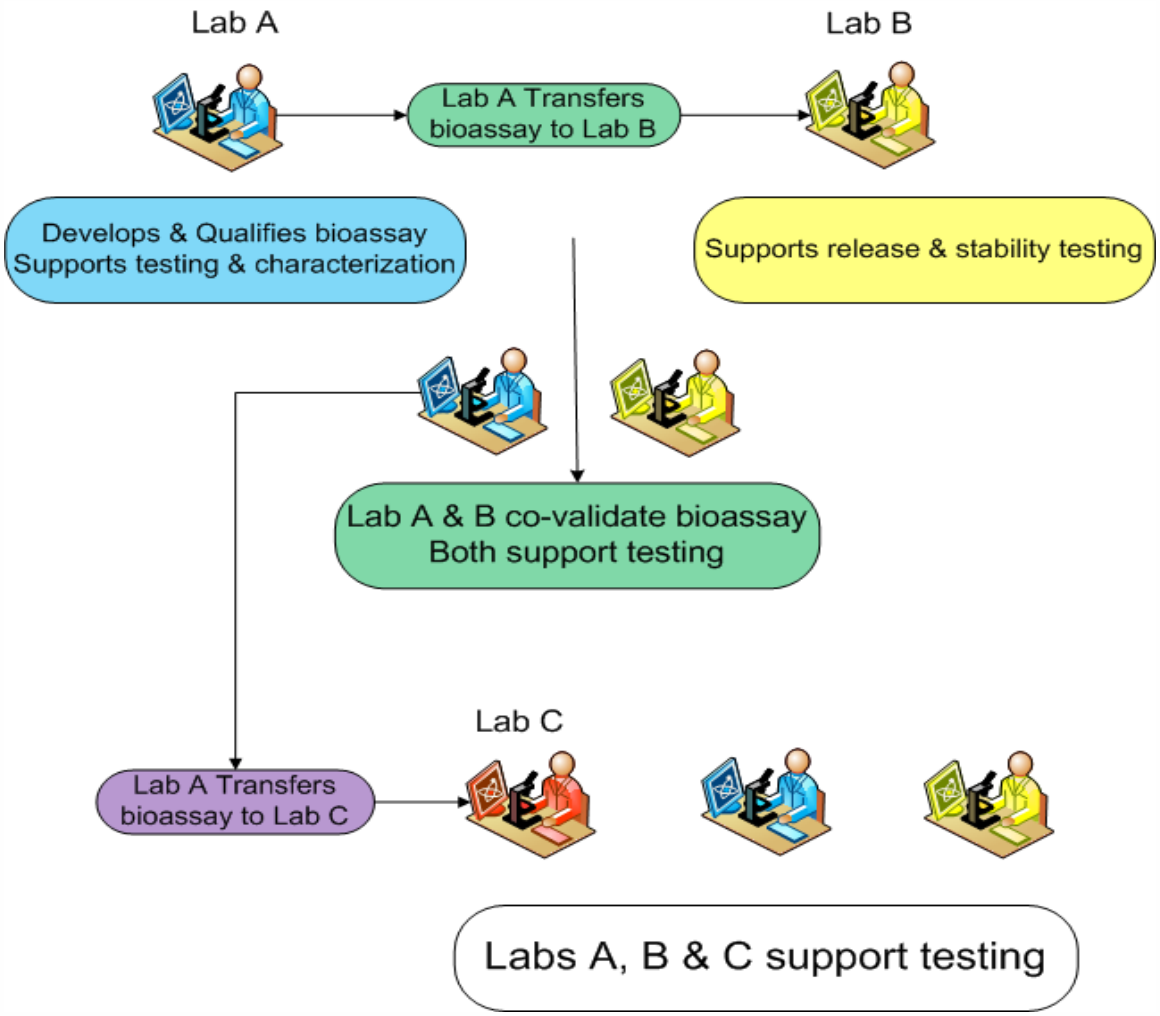
Bioassays 2017: Scientific Approaches & Regulatory Strategies

Pfizer
WORLDWIDE RESEARCH & DEVELOPMENT
PharmaTherapeutics Pharmaceutical Sciences

Outline

- Introduction
- Statistical Approach to Establishing Equivalence Acceptance Criterion for Comparative Testing Analytical Method Transfer (AMT)
- Concluding Remarks

Introduction



Introduction

- Transfers are typically executed per analytical method transfer protocols that detail
  - The type of analytical method transfer to be executed
  - The relevant parameters to be evaluated
  - Acceptance criteria against which the parameters are to be assessed (set *a priori*)
  - Contingency plan for failed transfers

- No specific guidance exists for setting acceptance criteria especially for comparative analytical method transfers

- A statistical method for establishing comparative testing AMT's acceptance criteria that leverages the historical performance of the transferring laboratory (TL) will be presented

Analytical Method Transfers (AMT)

Comparative Testing	• Analysis is conducted on samples of the same (API/drug substance or drug product batches) by both transferring laboratory (TL) and receiving laboratory (RL) • Acceptance criteria are outlined in the transfer protocol *a priori* • Predetermined test sample size (Transfer Design) at both TL and RL
Co-validation	•TL and RL work together in an inter-laboratory validation effort. •An assessment is conducted, using a transfer protocol, to evaluate relevant analytical characteristics per USP <1225> *Validation of Compendia Procedures*
Revalidation/Partial Revalidation	•RL execute complete or partial validation per USP <1225> *Validation of Compendia Procedures*
Transfer Waiver	•USP <1224> *Transfer of Analytical Procedures*

Comparative Testing

Leveraged historical data to evaluate TL's performance

- Span of data should capture relevant sources of variability (and assumes data variability is fully representative)

Establish acceptance criteria that for a given design

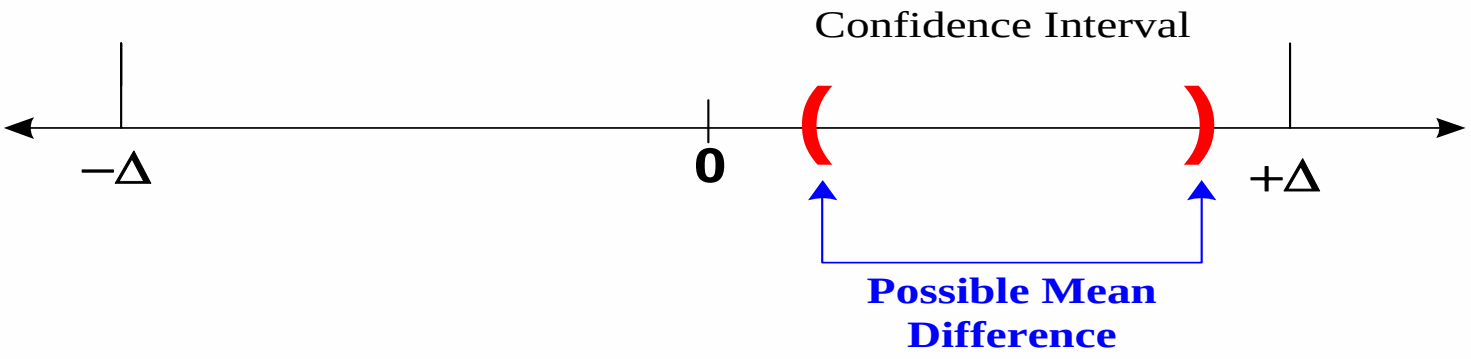
- Predict a high probability of a successful transfer if RL's performance is comparable to TL's, and
- Predict a low probability of a successful transfer if RL performance is dissimilar to TL's current and future specification limits need to be considered

Equivalence Test

Equivalence Test should be applied, when appropriate, to asses the similarity of laboratory performances

$$H_0: \mu_{TL} - \mu_{RL} \leq -\Delta \; or \; \mu_{TL} - \mu_{RL} \geq \Delta$$

$$H_A: -\Delta < \mu_{TL} - \mu_{RL} < \Delta$$



Equivalence Acceptance Criterion

- $(0 \pm \Delta)$ can be defined as a function of
  - $\boldsymbol{\theta}$ (allowable mean difference)
  - σ_{TL} (historic TL variability)
  - AMT Design i.e. $n_{TL} = n_{RL} = n$
  - α level, and
  - target power (1- β) at $\boldsymbol{\theta}$

Equivalence Acceptance Criterion

Confidence Interval Approach (Schuirmann, 1987)

- The $(1-2\alpha)100\%$ confidence interval of $\mu_{TL}-\mu_{RL}$ is given by

$$(\bar{X}_{TL}-\bar{X}_{RL}\ -\ t_{1-\alpha,2n-2}s\sqrt{2/n},\ \bar{X}_{TL}-\bar{X}_{RL}+t_{1-\alpha,2n-2}s\sqrt{2/n})$$

where $\bar{X}_{TL}-\bar{X}_{RL}$ is an estimator of $\mu_{TL}-\mu_{RL}$.

- The power of the test is

$$P\{-\Delta<\bar{X}_{TL}-\bar{X}_{RL}-t_{1-\alpha,2n-2}s\sqrt{2/n}\ \ \textbf{and}\ \ \bar{X}_{TL}-\bar{X}_{RL}+t_{1-\alpha,2n-2}s\sqrt{2/n}<\Delta|\ \mu_{TL}-\mu_{RL}=\theta\}$$

$$P\{\frac{-\Delta-\theta}{s\sqrt{2/n}}+t_{1-\alpha,2n-2}<\frac{\bar{X}_{TL}-\bar{X}_{RL}-\theta}{s\sqrt{2/n}}<\frac{\Delta-\theta}{s\sqrt{2/n}}-t_{1-\alpha,2n-2}\ \}$$

Equivalence Acceptance Criterion

- Under H_A

$$\frac{\bar{X}_{TL}-\bar{X}_{RL}-\theta}{s\sqrt{2/n}} \sim t_{2n-2}$$

- Therefore, the power of the equivalence test can be calculated from a central t-distribution

$$\Phi_{2n-2}\left(\frac{\Delta-\theta}{s\sqrt{2/n}} - t_{1-\alpha,2n-2}\right) - \Phi_{2n-2}\left(\frac{\Delta-\theta}{s\sqrt{2/n}} + t_{1-\alpha,2n-2}\right)$$

where $\Phi_v(x)$ is the cumulative probability at x of a central *t*-distribution with v degrees of freedom

- For a given AMT Design (sample size) and α level, an EAC (Δ) that ensures desired power (1- β) at $\boldsymbol{\theta}$ allowable mean shift, can be obtained from the power function

Equivalence Acceptance Criterion

AMT designs and corresponding EAC's that ensure ≥ 80% power with α = 0.05 (type I error) at allowable mean shift ($\boldsymbol{\theta}$)

n_{TL}	n_{RL}	θ	EAC (0 ± Δ)
10	10	0 σ_{TL}	0 +/- 1.37 σ_{TL}
10	10	0.5 σ_{TL}	0 +/- 1.66 σ_{TL}
10	10	1 σ_{TL}	0 +/- 2.16 σ_{TL}
10	10	1.5 σ_{TL}	0 +/- 2.66 σ_{TL}
15	15	0 σ_{TL}	0 +/- 1.10 σ_{TL}
15	15	0.5 σ_{TL}	0 +/- 1.43 σ_{TL}
15	15	1 σ_{TL}	0 +/- 1.93 σ_{TL}
15	15	1.5 σ_{TL}	0 +/- 2.43 σ_{TL}

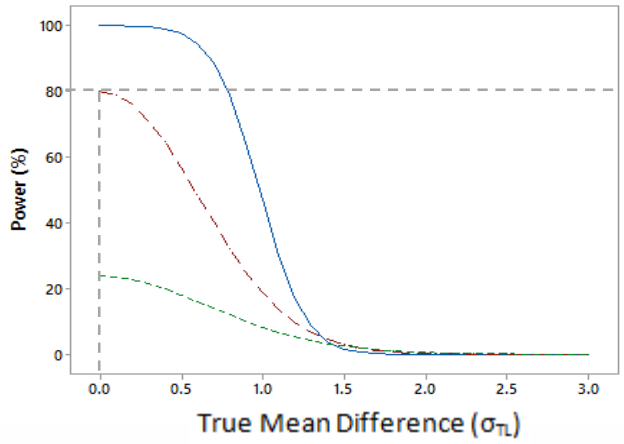
Power Plots (AMT Design = 10 Samples, α = 5%)

$\sigma_{RL} = 0.5\sigma_{TL}$

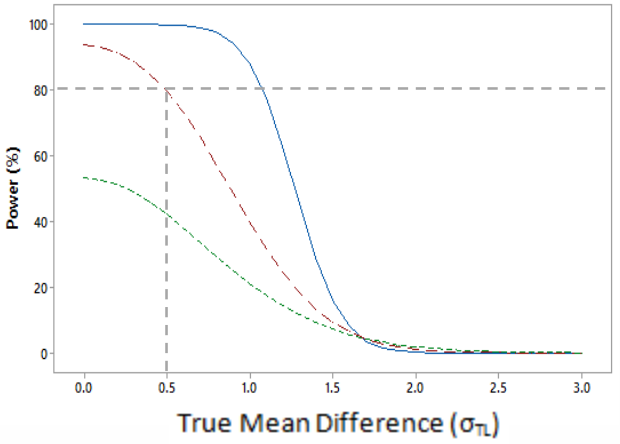
$\sigma_{RL} = 1\ \sigma_{TL}$

$\sigma_{RL} = 1.5\sigma_{TL}$

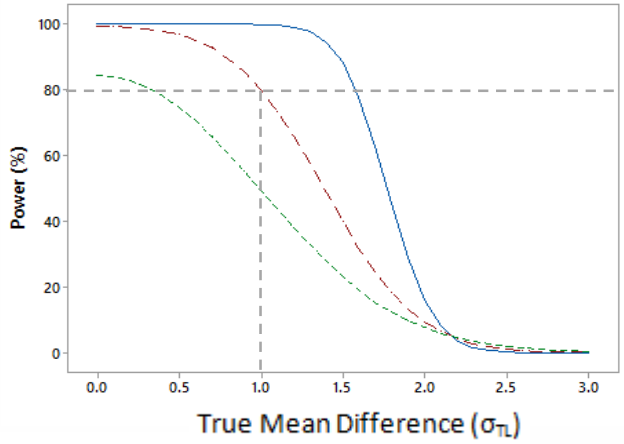
$\boldsymbol{\theta} = 0\sigma_{TL}$, EAC = 0 +/- $1.37\sigma_{TL}$



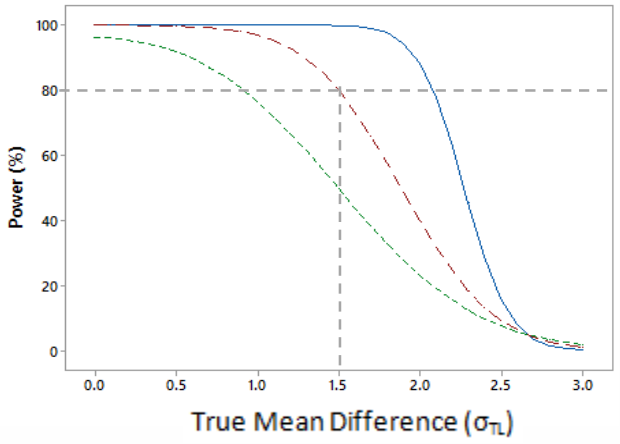
$\boldsymbol{\theta} = 0.5\sigma_{TL}$, EAC = 0 +/- $1.66\sigma_{TL}$



$\boldsymbol{\theta} = 1\sigma_{TL}$, EAC = 0 +/- $2.16\sigma_{TL}$

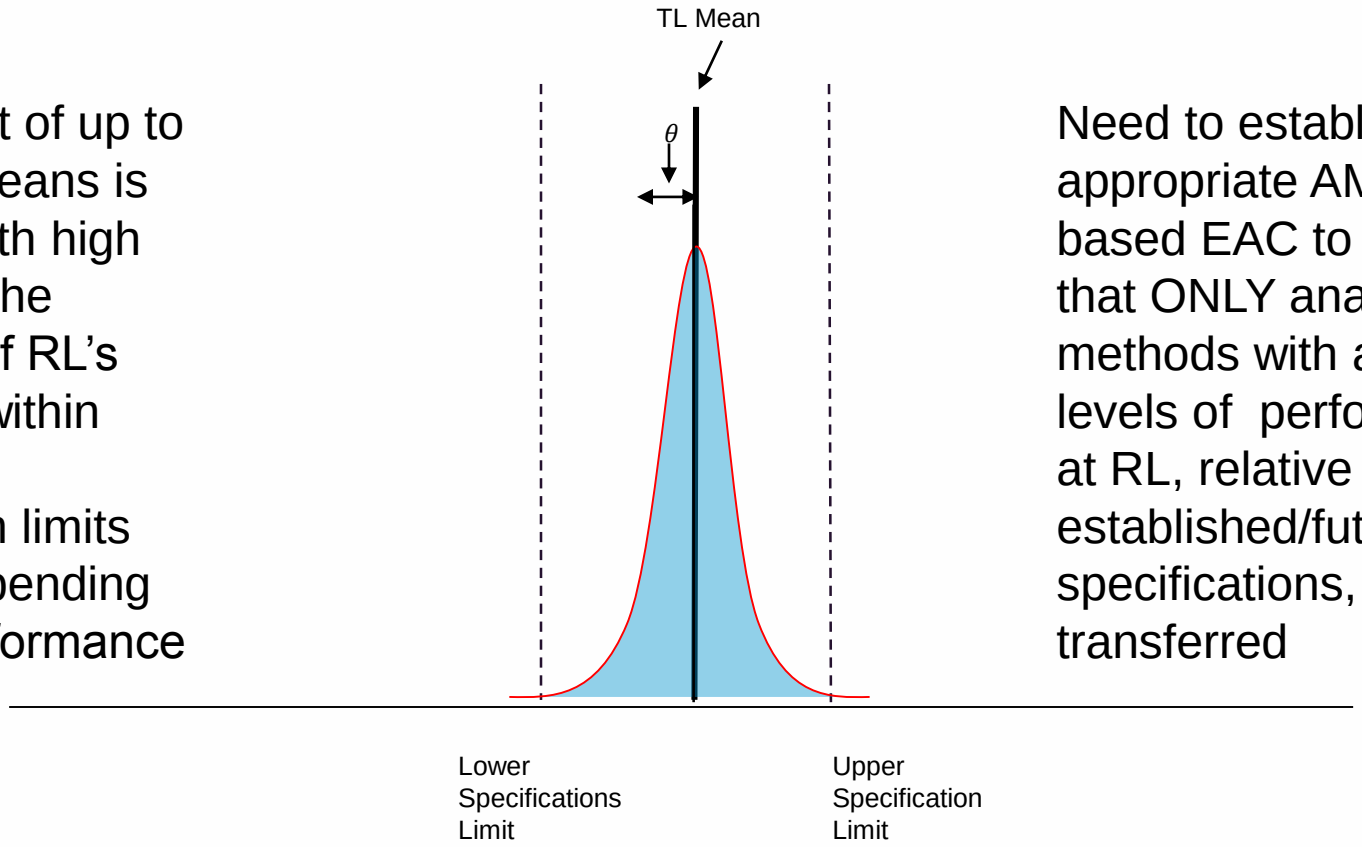


$\boldsymbol{\theta} = 1.5\sigma_{TL}$, EAC = 0 +/- $2.66\sigma_{TL}$



Specification Consideration

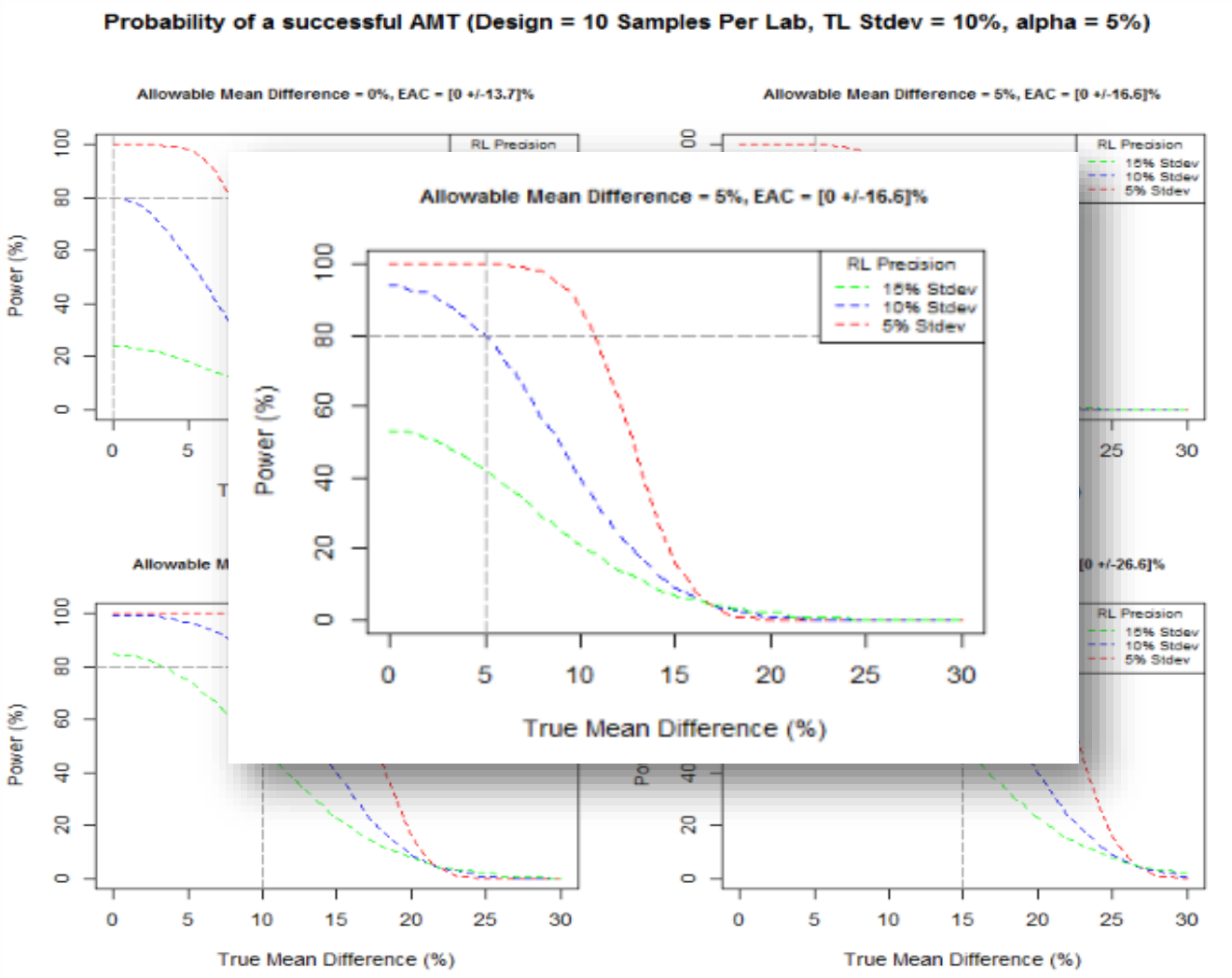
When a shift of up to ± θ in the means is accepted with high probability, the proportion of RL's population within established specification limits will vary depending on RL's performance



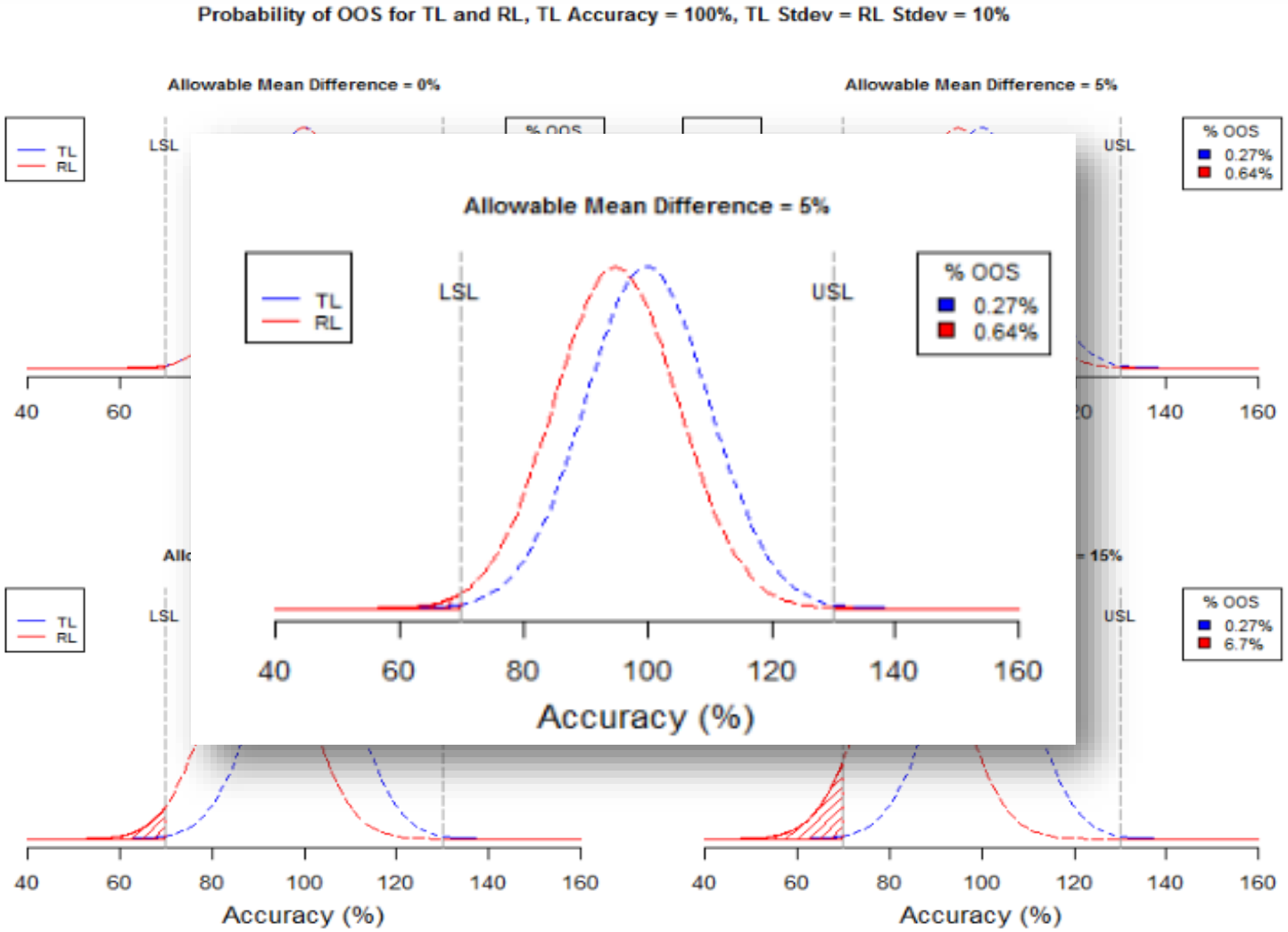
Need to establish appropriate AMT design-based EAC to ensure that ONLY analytical methods with acceptable levels of performances at RL, relative to established/future specifications, are transferred

Marion J. C and Phil J. B (2009)

Application



Application



Conclusion

- Proposed designs and criteria should warrant a successful transfer with very high probability, if TL and RL performances are comparable

- Proposed designs and criteria should have low probability of a successful transfer, if TL and RL performances are unacceptably dissimilar

- Designs and criteria that risk accepting a transfer with relatively high probability, if TL and RL performances are dissimilar or risk rejecting a transfer with relatively high probability, if TL and RL performances are similar, should be avoided

Conclusion

- The purpose of the method transfer is to ensure that the validated method post-transfer yields results consistent with the existing product control strategy.
- Thus, a method transfer should have no or negligible impact on the drug safety, efficacy and quality.
- Appropriate acceptance criteria and appropriate evaluation of AMT results against these criteria are critical to this objective.
  - Guard against the unexpected
  - Guard against the unacceptable

References

- USP <1224> “Transfer of Analytical Procedures”
- USP <1225> “Validation of Compendia Procedures”
- ICH Q6B (1999), “Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products”
- Chatfield, M.J. and Borman, P.J.: “*Acceptance Criteria for Method Equivalency Assessments*”, Anal. Chem. 2009, 81, 9841-9848
- Zhang, P : “*A simple Formula for Sample Size Calculation in Equivalence Studies*”, *Journal Of Pharmaceutical Statistics 2003*, Vol 13, No 3, 529 – 538
- Schuirmann, D. J.: “*A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability*,” *Journal of Pharmokinetics and Biopharmaceutics*, 15, 657–680. 451

Acknowledgement

Jia Liu, Pfizer

Aili Cheng, Pfizer

Brad Evans, Pfizer

David Cirelli, Pfizer


Thank
You

Equivalence Acceptance Criterion

- $\theta = 0$

$$0 \pm \left(t_{1-\alpha,2n-2} + t_{(1-\frac{\beta}{2}),2n-2}\right) s\sqrt{2/n}$$

- $\theta \neq 0$

$$\theta \pm \left(t_{1-\alpha,2n-2} + t_{(1-\frac{\beta}{2}),2n-2}\right) s\sqrt{2/n}$$

  - Too conservative as it leads to a higher power than desired

- Chow and Liu (2000)

$\theta \neq 0$

$$\theta \pm \left(t_{1-\alpha,2n-2} + t_{(1-\beta),2n-2}\right) s\sqrt{2/n}$$

  - Less conservative but might lead to lower actual power than desired

- Paul Zhang (2003)

Unified formula for $\theta = 0$ and $\theta \neq 0$

$$\theta \pm \left(t_{1-\alpha,2n-2} + t_{1-(1-c)\beta,2n-2}\right) s\sqrt{2/n}$$

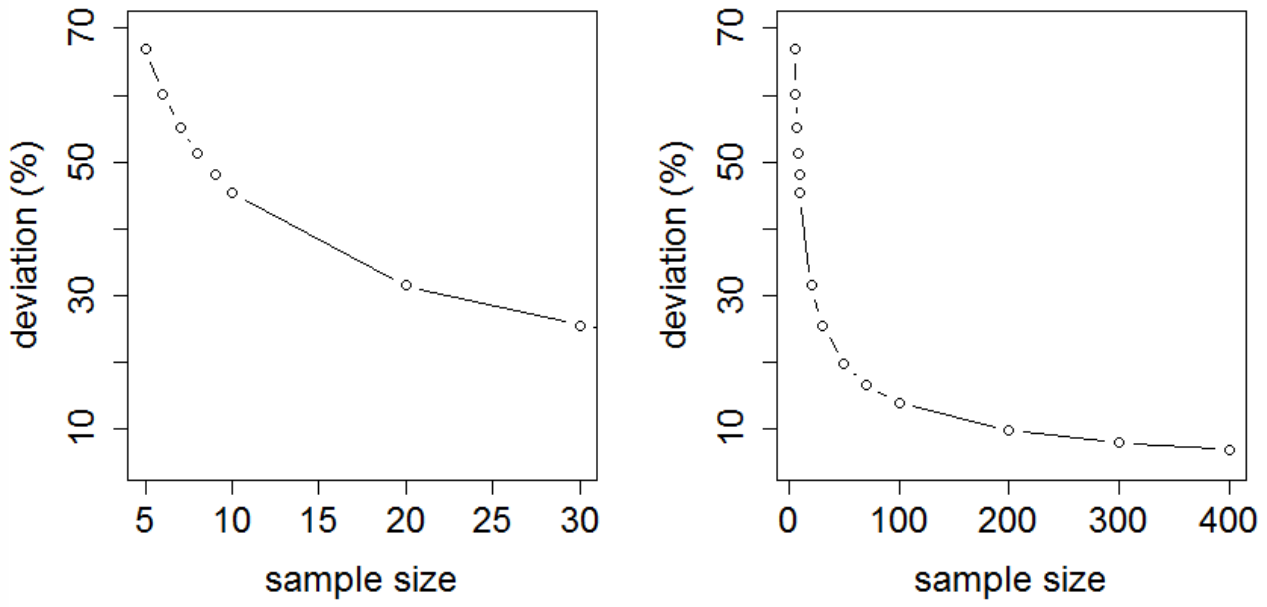
Where $0 \leq c \leq ½$

$$c = \frac{1}{2} e^{\left(-7.06 \frac{\theta}{\Delta}\right)}$$

Backup Slides

Relationship Between Sample Size and SD

For example, the estimated SD from a sample size of 10 can differ from the true SD by 45% with 95% chance



See details in : Robert W. Burnett, CLINICAL CHEMISTRY, Vol. 21, No. 13, 1975

Transfer Waiver

- The new product's composition is comparable to that of an existing product and/or the concentration of active ingredient is similar to that of an existing product and is analyzed by procedures with which the receiving unit already has experience.
- The analytical procedure being transferred is described in the *USP–NF*, and is unchanged. Verifiction should apply in this case (see ⟨1226⟩).
- The analytical procedure transferred is the same as or very similar to a procedure already in use.
- The personnel in charge of the development, validation, or routine analysis of the product at the transferring unit are moved to the receiving unit.