A Step-wise Procedure for Population Bioequivalence (PBE) Analysis of Orally Inhaled and Nasal Drug Product (OINDP) Bioequivalence Studies

Breakout Session:
Inhalation Product Update

Bing V. Li, Ph.D.
Ke Ren, Ph. D
OGD/CDER/FDA

GPhA/FDA 2011 Fall Technical Conference, Oct. 04, 2011

Looking Back…

- Oct. 28, 2009, GPhA/FDA 2009 Fall Technical Conference:
  - Presented “Introduction to a Standardized Bioequivalence Review Procedure for Nasal Spray Products: Review Template and CTD Data Summary Tables”
  - Subsequently, 40 CTD tables published on the FDA public website
    - Positive feedback from industry
    - Average review time of the BE portion of a nasal spray product has been reduced from ~5 weeks to ~2 weeks currently (internal DB reviewer survey)

Today, I am going to introduce…

A Step-wise Procedure for Population Bioequivalence (PBE) Analysis of Orally Inhaled and Nasal Drug Product (OINDP) Bioequivalence Studies

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Background

- Population Bioequivalence (PBE) has been widely utilized as the key statistical approach for many in vitro BE evaluations of OINDP
  - For nasal drug products, out of the 6 in vitro BE studies recommended by the draft Nasal BA/BE guidance, 4 of the tests are evaluated using PBE
  - For oral inhalation drug products, the majority of the recommended in vitro tests will be evaluated using PBE

Population Bioequivalence (PBE) Criterion

- The PBE criterion and BE limit are:

$$\frac{(\mu_T-\mu_R)^2+(\sigma_T^2-\sigma_R^2)}{\sigma_R^2}\le\theta_p \quad \text{or} \quad \frac{(\mu_T-\mu_R)^2+(\sigma_T^2-\sigma_R^2)}{\sigma_{T0}^2}\le\theta_p$$

- Linearized criteria:

$$\eta_1=(\mu_T-\mu_R)^2+(\sigma_T^2-\sigma_R^2)-\theta_p\bullet\sigma_R^2<0 \quad \textbf{for} \quad \sigma_R>\sigma_{T0}$$

$$\eta_2=(\mu_T-\mu_R)^2+(\sigma_T^2-\sigma_R^2)-\theta_p\bullet\sigma_{T0}^2<0 \quad \textbf{for} \quad \sigma_R\le\sigma_{T0}$$

Where: $\mu_T-\mu_R$: Mean difference of T (log scale) and R (log scale) products

σ_T^2,σ_R^2 : Total variance of T and R products

σ_{TO} : Regulatory constant (σ_{TO}= 0.1)

θp: : Regulatory constant (θp= 2.0891) calculated as: $\frac{[\ln(1.11)]^2+0.01}{0.1^2}=2.089$

Two FDA Guidances Related to PBE

1. *Statistical Information from the June 1999 Draft Guidance and Statistical information for in vitro bioequivalence data posted on August 18, 1999 (refers as 1999 guidance)*

   – Accompanying guidance for Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003

2. *Guidance for Industry: Statistical approaches to establishing Bioequivalence, posted on January 2001 (refers as 2001 guidance)*

   – Provides general information about the equivalence criteria in analyzing in vivo or in vitro BE studies of various types of applications

Comparison of the Two Guidances

1999 Guidance (draft)	2001 Guidance
The 95% upper confidence bound is calculated based procedures outlined in a published paper*, and the difference of the mean of T and R is calculated using Behrens-Fisher method, which involves rather complicated calculation steps	The 95% upper confidence bound is calculated using the simplified T-distribution for the difference of the mean of T and R

***. Lee A.F.S., N.S. Fineberg, "A fitted test for the Behrens-Fisher problem," *Comm Statist- Theory Meth*, 20, 653-666, 1991**

Issues

- Up to current, the method described in the 1999 guidance has been routinely used for regulatory review of OINDP drug products

- However, since it involves rather complicated computation, it had led to many inquiries for clarification from sponsors

Inquiries from Industry

- "*We worked through the guidance and also read the guidances on statistic evaluation of bioequivalence studies. Where can we get further advice on study design and especially on statistics and statistical evaluation? How is population BE established and verified?*"
- "*What acceptance criteria were applied to the determination of PBE? Would a copy of the calculation be provided to us?*"
- "*Could the FDA confirm the formula we have used in our analysis for the calculation of the confidence interval? Could the Agency send us a breakdown of the results for the population bioequivalence analysis?*"

An FDA Working Group Was Formed…

- To select a simplified method in the evaluation of PBE for OINDP without compromising the rigor of the regulatory decision

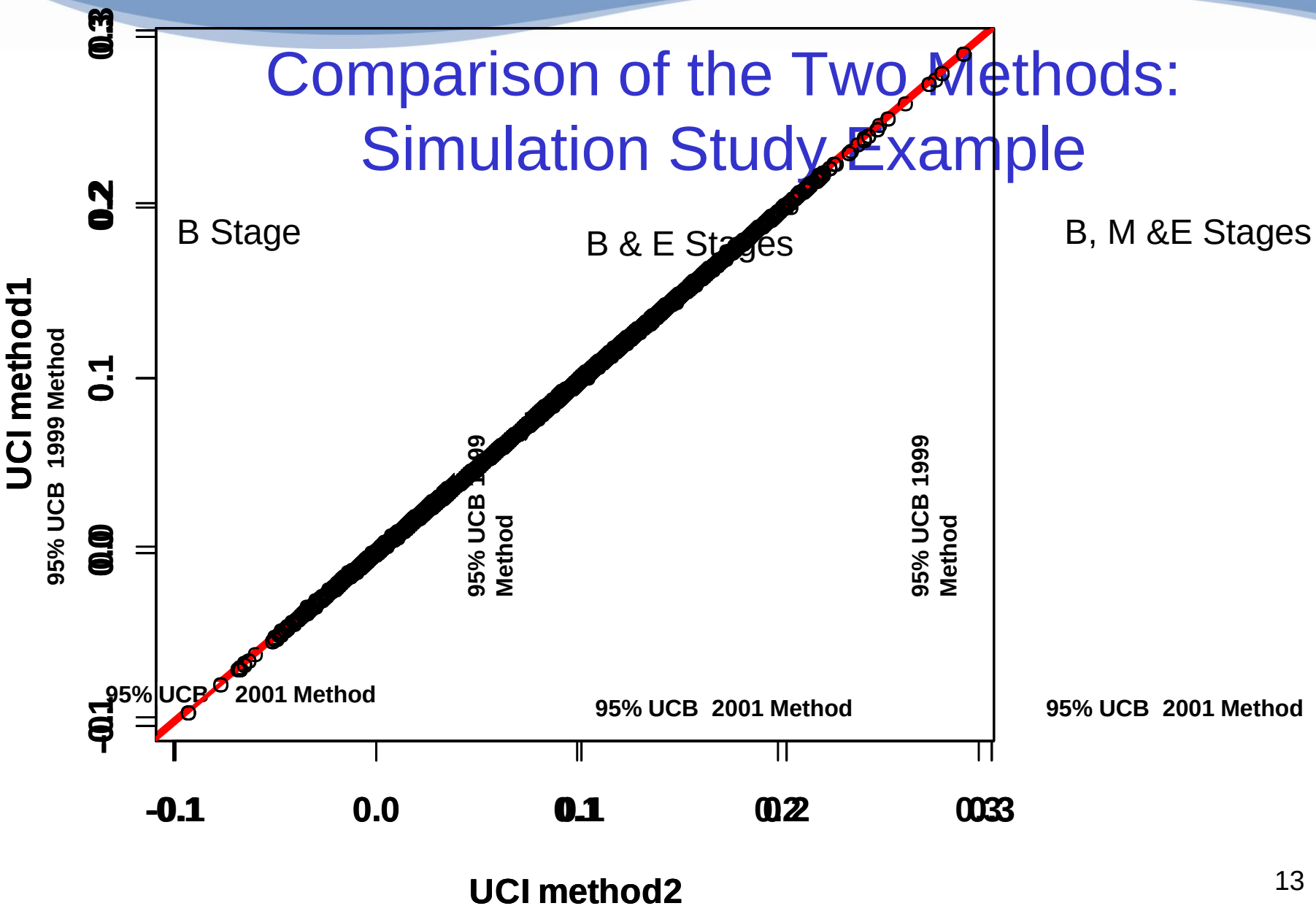
- To provide specific recommendations related to the application of PBE for the evaluation of in vitro equivalence studies of OINDP

- To publish a step-wise set of instructions regarding PBE analysis computation procedures in FDA's public website

Comparison of the Two Methods

- Simulation Study:
  - Conducted under different scenarios
    - geometric mean differences of T and R ranged from 0 to 20%
    - overall variability differences of T and R ranged from 0 to 30%
  - Data were analyzed by these two methods under different scenarios
  - For estimation of power, 5000 simulations were conducted

Comparison of the Two Methods: Simulation Study Example



Comparison of the Two Methods: Simulation Study Example

N	Type I error (2001 method)	Type I error (1999 method)	Life stages
5000	0.0555	0.0626	1
5000	0.0538	0.0542	2
5000	0.0550	0.0558	3

Comparison of the Two Methods: Simulation Study Example

N	Study Power (2001 method)	Study Power (1999 method)	Life stages
1000	0.973	0.979	1
1000	0.973	0.973	2
1000	0.974	0.975	3

Comparison of the Two Methods

- Real ANDA Study:
  - Two methods were compared using three ANDAs representing different drug products
  - A typical design for nasal/inhalation products was used, i.e., the in vitro studies were conducted using 3 batches and 10 containers per batch for each T and R
  - Comparisons were conducted for various in vitro BE studies at different life stages of the drug products, such as beginning, middle and end

Comparison of the Two Methods: Real Case Example

ANDAs	Constant Scale 95% Upper Confidence Bound		Reference Scale 95% Upper Confidence Bound	
	1999 Method	2001 Method	1999 Method	2001 Method
ANDA 1 Test 1	-0.0189109	-0.01891049	-0.001114811	-0.001114535
ANDA 1 Test 2	-0.017962848	-0.017962549	-0.001669028	-0.001668823
ANDA 1 Test 3	0.015677416	0.015695358	-0.036748896	-0.036737071
ANDA 1 Test 4	0.030507028	0.030507958	-0.03991934	-0.039991305
ANDA 2, Test 5	-0.02170561	-0.021700441	-0.017243532	-0.017241153
ANDA 2, Test 6	-0.014457372	-0.014455345	-0.002340026	-0.002338566
ANDA 2, Test 7	-0.024330906	-0.02432152	-0.024765754	-0.024761829
ANDA 2, Test 8	-0.0158553897	-0.015854909	-0.004079686	-0.004079012
ANDA 3, Test 9	-0.018910889	-0.01891049	-0.001114811	-0.001114535

Comparison of the Two Methods: Real Case Example

ANDAs	PBE Outcome Constant Scale		PBE Outcome Reference Scale	
	1999 Method	2001 Method	1999 Method	2001 Method
ANDA 1 Test 1	Pass	Pass	Pass	Pass
ANDA 1 Test 2	Pass	Pass	Pass	Pass
ANDA 1 Test 3	Fail	Fail	Pass	Pass
ANDA 1, Test 4	Fail	Fail	Pass	Pass

Summary

- Results from a simulation study showed the type I error for the two methods are similar
- Results from both simulation studies and real ANDA data showed the values for the 95% upper confidence bound calculated by the two methods are nearly identical; differences appear at the fifth digit after the decimal point
- The real ANDA data showed the overall conclusions (e.g., pass or fail PBE) are the same for these two methods

Conclusions

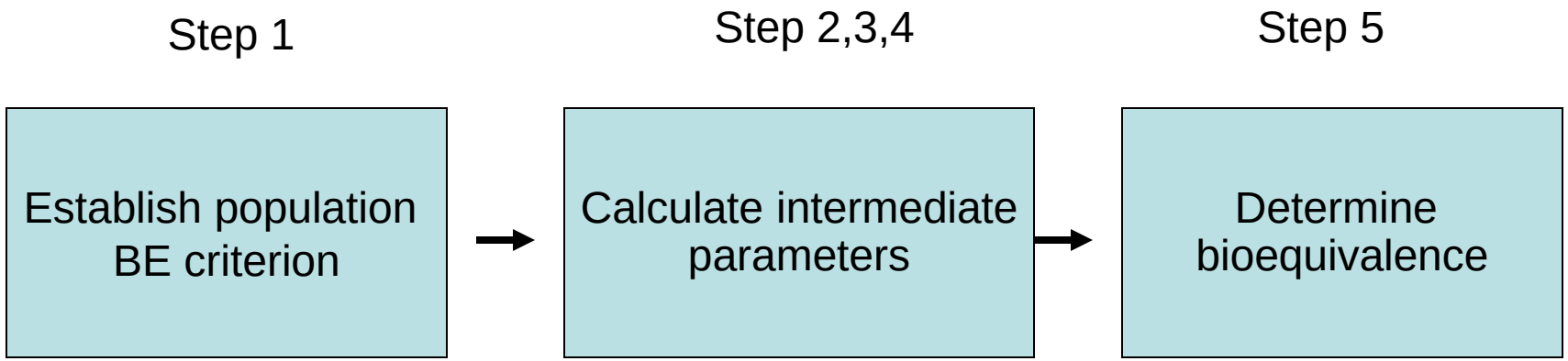
- Comparable PBE results are obtained by these two different methods
- 2001 method provides a simplified alternative to 1999 method without compromising the rigor of the regulatory decision
- Based the study results, the 2001 method is recommended for PBE analysis in the evaluation of PBE for OINDP

Firm's Inquiry

Could the Agency send us a breakdown of the results for the population bioequivalence analysis?

FDA's Response

FDA is developing a step-wise computation procedures for PBE analysis using 2001 method



Firm's Inquiry

- *Would a copy of the calculation be provided to us?*
- *Could the FDA confirm the formula we have used in our analysis for the calculation of the confidence interval?*

FDA's Response

FDA will provide an example data set for confirmation purpose

- In order for the applicants to confirm their calculation procedures, OGD will provide an example data set, to demonstrate the calculation outcomes of each intermediate and final step
- The applicants can use the data shown in our example, and follow the step-wise computation procedures, to check whether they obtain the same outcomes as indicated in our example

Common Technical Document (CTD) Tables

- FDA has also developed a set of CTD tables to be used to submit the in vitro data applied in PBE analysis
  - To guide pharmaceutical industry in submitting their data in an appropriate format
  - To reduce the time of reviewing process, therefore, improve the review efficiency and quality

Example of CTD Table: Single Actuation Content through Container Life

PRODUCT	SECTOR	LOT	CONTAIN	ACTUAT	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			…			

* Terms in this table are defined in the next slide

Example of CTD Table: Single Actuation Content through Container Life

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
ACTUAT	*Spray Number*	*Numeric*	*Numeric values*	*Actual spray number corresponding to B or E life stages.*
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Where to Find This Information

- OGD has published the CTD data format tables, designed for nasal product application, at FDA public website: http://wcms.fda.gov/FDAgov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm?SSContributor=true
- OGD is currently working on the development of the step-wise procedures for PBE analysis

Conclusions

- FDA has selected a simplified method for PBE analysis for the in vitro BE studies of OINDP products
- FDA is developing a step-wise instruction with computation procedures for the PBE analysis using the selected method
- FDA has developed a set of CTD tables to guide the industry to submit higher quality application
- FDA plans to make this information available to the public

Acknowledgements

- Yaning Wang
- Wallace Adams
- Sau (Larry) Lee
- Devvrat Patel
- Dale Conner
- Hoainhon Caramenico
- Barbara Davit