Batch-to-Batch Variability of a Brand Product and Its Implications on Generic Bioequivalence Standards: PK Variability of Advair Diskus and Its Implications on BE Assessment Critera for Generic Drugs

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Let me acknowledge

- All of my experience on this topic comes from my activities as a consultant to Oriel Therapeutics, Inc., an indirect wholly-owned subsidiary of Novartis AG.
- The studies were directed by Elise Burmeister Getz, PhD, Director, Clinical Pharmacology at Oriel.
- Collaborators on the published studies include: Kevin J Carroll, PhD, KJC Statistics, Stockport, Chesire, UK; Byron Jones, PhD and Johanna Mielke, PhD, Novartis Pharma, Basel, Switzerland
- I am grateful to Dr. Burmeister Getz for allowing me to adapt a number of her slides, including those for her presentation at the meeting of the American College of Clinical Pharmacology, yesterday.

Publications

- **Batch-to-Batch Pharmacokinetic Variability Confounds Current Bioequivalence Regulations: A Dry Powder Inhaler Randomized Clinical Trail. E. Burmeister Getz, K. J. Carroll, B. Jones and L. Z. Benet. *Clin. Pharmacol. Ther.* 100, 223-231 (2016).**
- **Between-Batch Pharmacokinetic Variability Inflates Type I Error Rate in Conventional Bioequivalence Trials: A Randomized Advair Diskus Clinical Trial. E. Burmeister Getz, K. J. Carroll, J. Mielke, L. Z. Benet and B. Jones. *Clin. Pharmacol. Ther.* 101, 331-340 (2017).**
- **Pharmacokinetic Behavior of Fluticasone Propionate and Salmeterol from Advair Diskus: The Consequences of Batch Variability. E. Burmeister Getz, K. J. Carroll, J. Mielke, B. Jones and L. Z. Benet. *Resp. Drug Deliv.* 1, 25-34 (2017).**

OIDP (oral inhaled drug product) pharmacokinetics present novel challenges for generic development

1. Manufacturing batches differ substantially with regard to pharmacokinetic performance

2. Batch variability impacts bioequivalence testing

3. Bioequivalence methodology should be adapted to account for batch variability

History of industry/regulatory discussion of batch-to-batch PK diversity …

2010: *"Batch-to-batch variability of R was therefore a topic of discussion at the Workshop."*[1]

2013: *"Should PK be treated as highly variable … including variability introduced batch to batch"*[2]

2014: *"**Interpreting PK for Inhalation BE -** How to approach batch to batch variability in the reference product?"*[3]

2015: *"The choice of the R batch might affect the outcome of the PK BE study."*[4]

1 **Equivalence Considerations for Orally Inhaled Products for Local Action—ISAM/IPAC-RS European Workshop Report.** Evans et al. *J Aerosol Med Pulm Drug Delivery.* Volume 25, 2012

2 Generics for Oral Inhaled Drugs: Knowledge Gaps for Streamlining Bioequivalence Approval. Hochhaus et al. Presentation at the FDA Generic Drug User Fee Amendments of 2012 Regulatory Science Initiatives Part 15 Public Hearing (June 21, 2013)

3 Interpreting Pharmacokinetics for Inhalation Bioequivalence. Lionberger. Presentation at the International Pharmaceutical Aerosol Consortium on Regulatory Science / University of Florida Orlando Inhalation Conference (Mar. 19, 2014)

4 Pharmacokinetics of Orally Inhaled Drug Products. Hochhaus et al. *AAPS J.* 17(3), 2015.

… yet PK batch variability is not accounted for in current guidances

Fluticasone propionate / salmeterol; Sep 2013
(Advair Diskus DPI)

Fluticasone furoate; Apr 2016
(ARNUITY Ellipta DPI)

Fluticasone furoate / vilanterol; Apr 2016
(BREO Ellipta DPI)

Indacaterol; Apr 2016
(Arcapta Neohaler DPI)

Mometasone furoate; Apr 2016
(Asmanex HFA)

Pharmacokinetic (PK) BE Study

The following PK BE study is recommended to be conducted for all strengths of the T and R products.

Design: Single-dose, two-way crossover

Objective #1:

Confirm the presence of batch-to-batch pharmacokinetic variability for an example OIDP

ADVAIR Diskus 100/50 chosen as an example OIDP

Low systemic availability

Fluticasone propionate absolute bioavailability of

5.5%[1] **– 17%**[2,3]

following inhalation of 1 mg in healthy volunteers

Wide *in-vitro* acceptance range

Fine particle mass[4]:

15 – 30 µg (fluticasone propionate)

7 – 13 µg (salmeterol)

1 Advair Diskus Prescribing Information. Research Triangle Park, NC. GlaxoSmithKline.

2 Pharmacokinetics of fluticasone propionate inhaled via the Diskhaler® and Diskus® powder devices in healthy volunteers. Mackie AE *et al*. *Clin. Pharmacokinet.* 39:23–30. 2000.

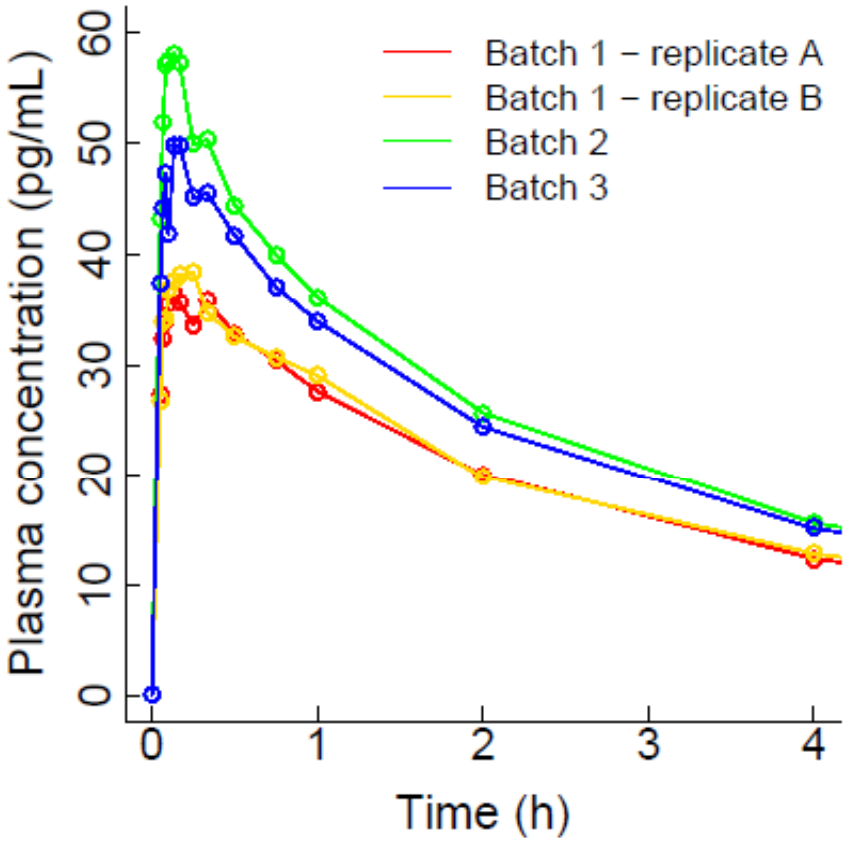
3 Absorption kinetics after inhalation of fluticasone propionate via the Diskhaler®, Diskus® and metered-dose inhaler in healthy volunteers. Brindley C *et al. Clin. Pharmacokinet.* 39:1–8. 2000.

4 USP 39 NF 34 Fluticasone Propionate and Salmeterol Inhalation Powder. Official May 1, 2016.

Between-batch PK variability: *fluticasone propionate*

single-dose, 4-sequence, 4-period crossover in 30 healthy adult subjects

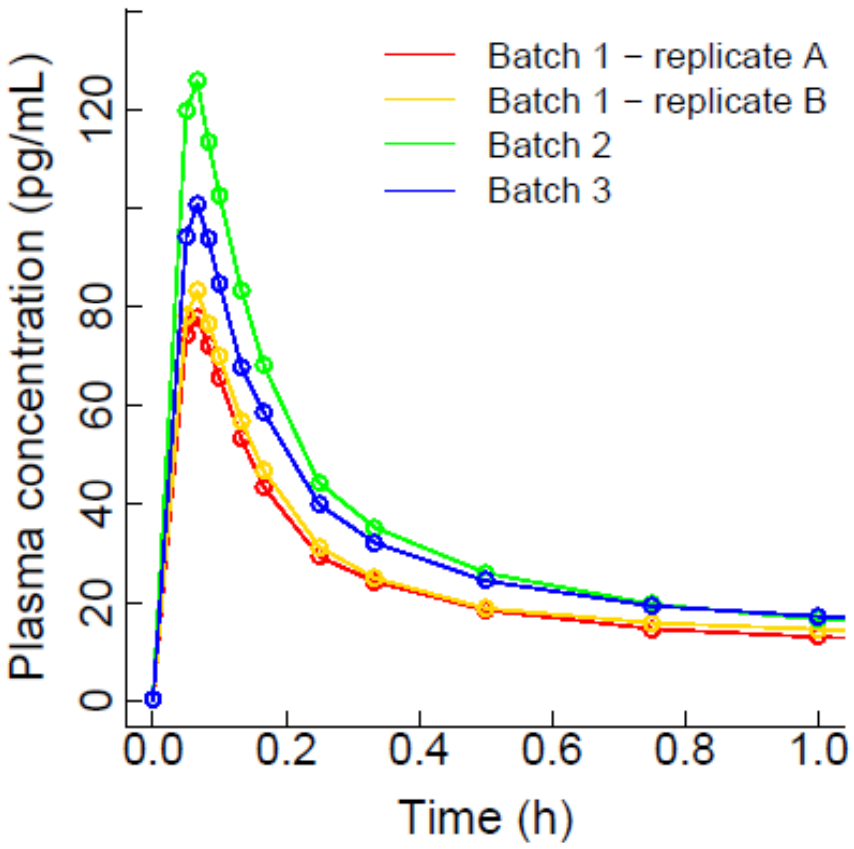
	Geometric Mean Ratio	
	Estimate	*90% CI*
Batch 1A *vs* Batch 1B		
C_{max}	99%	87% – 112%
$AUC_{(0\text{-}t)}$	100%	92% – 109%
Batch 1 *vs* Batch 2		
C_{max}	65%	59% – 72%
$AUC_{(0\text{-}t)}$	77%	72% – 83%
Batch 1 *vs* Batch 3		
C_{max}	76%	69% – 85%
$AUC_{(0\text{-}t)}$	81%	75% – 87%
Batch 2 *vs* Batch 3		
C_{max}	118%	104% – 133%
$AUC_{(0\text{-}t)}$	105%	96% – 114%



Between-batch PK variability: *salmeterol*

single-dose, 4-sequence, 4-period crossover in 30 healthy adult subjects

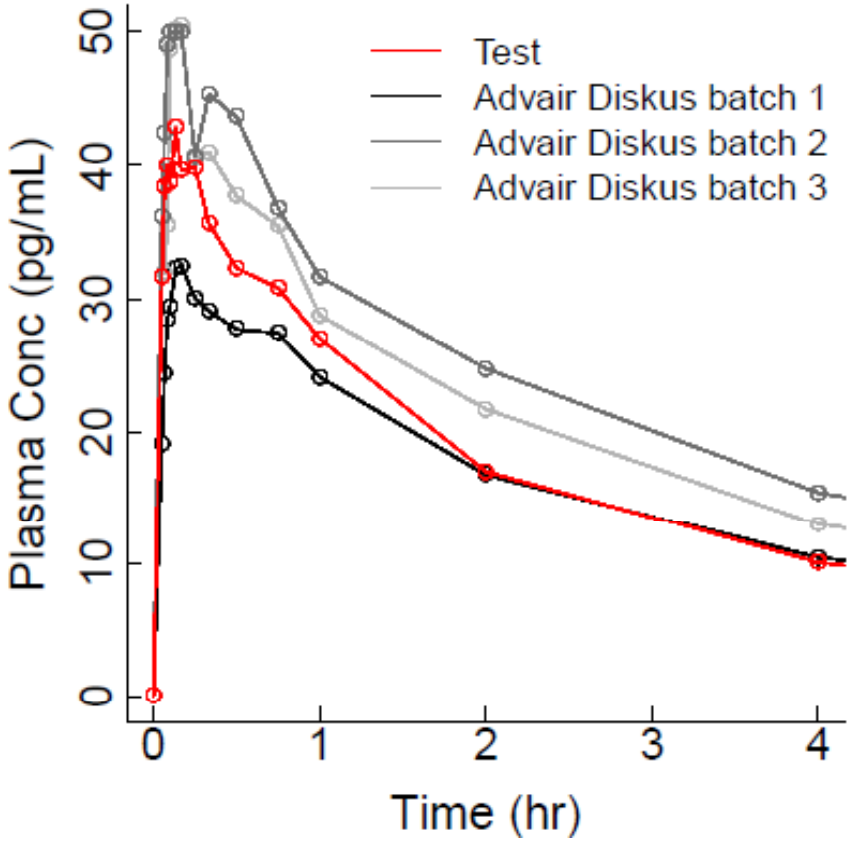
	Geometric Mean Ratio	
	Estimate	*90% CI*
Batch 1A *vs* Batch 1B		
C_{max}	95%	83% – 109%
$AUC_{(0\text{-}t)}$	94%	87% – 101%
Batch 1 *vs* Batch 2		
C_{max}	63%	56% – 72%
$AUC_{(0\text{-}t)}$	77%	72% – 82%
Batch 1 *vs* Batch 3		
C_{max}	80%	71% – 90%
$AUC_{(0\text{-}t)}$	81%	76% – 87%
Batch 2 *vs* Batch 3		
C_{max}	126%	110% – 145%
$AUC_{(0\text{-}t)}$	106%	98% – 114%



Second clinical study confirms between-batch PK variability: fluticasone propionate

single-dose, 4-sequence, 4-period crossover in 24 healthy adult subjects

	Geometric Mean Ratio		
	Estimate	*90% CI*	
Batch 1 *vs* Batch 2			
C_{max}	66%	60% – 73%	*
$AUC_{(0\text{-}t)}$	68%	62% – 74%	*
Batch 1 *vs* Batch 3			
C_{max}	68%	61% – 75%	*
$AUC_{(0\text{-}t)}$	76%	70% – 83%	
Batch 2 *vs* Batch 3			
C_{max}	102%	92% – 113%	
$AUC_{(0\text{-}t)}$	112%	103% – 123%	

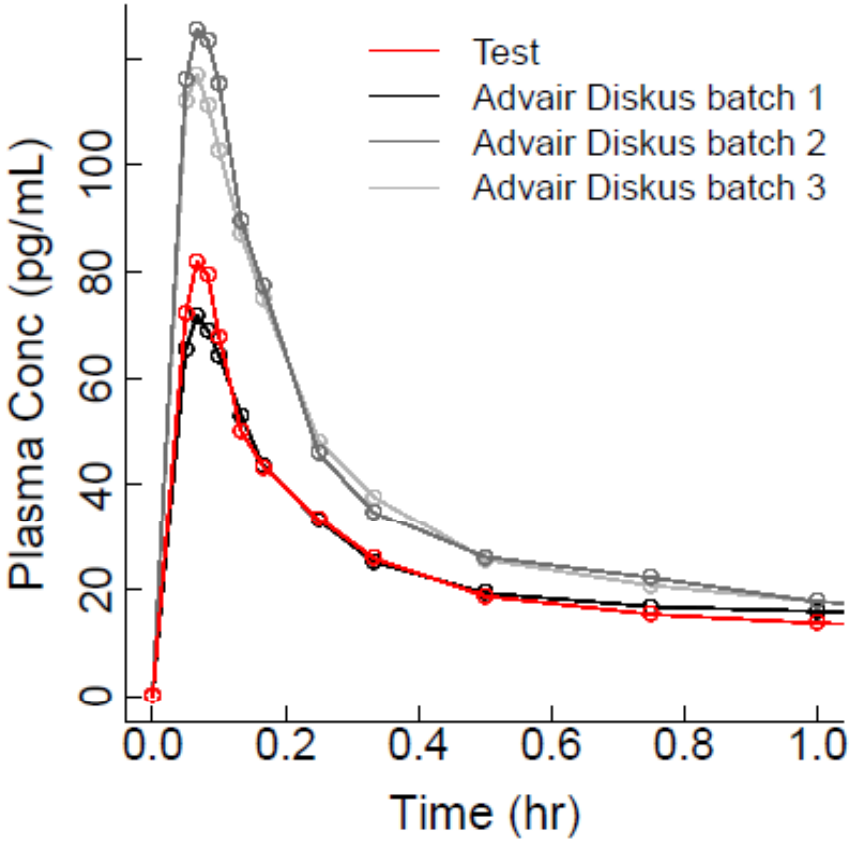


batch-to-batch PK bioin**equivalence*

Second clinical study confirms between-batch PK variability: salmeterol

single-dose, 4-sequence, 4-period crossover in 24 healthy adult subjects

	Geometric Mean Ratio		
	Estimate	*90% CI*	
Batch 1 *vs* Batch 2			
C_{max}	63%	55% – 71%	*
$AUC_{(0\text{-}t)}$	71%	64% – 79%	
Batch 1 *vs* Batch 3			
C_{max}	71%	62% – 81%	
$AUC_{(0\text{-}t)}$	78%	70% – 87%	
Batch 2 *vs* Batch 3			
C_{max}	113%	99% – 129%	
$AUC_{(0\text{-}t)}$	110%	99% – 122%	



batch-to-batch PK bioin**equivalence*

Objective #1:
Confirm the presence of batch-to-batch pharmacokinetic variability for an example OIDP

Result:
Advair Diskus 100/50 demonstrates batch-to-batch pharmacokinetic variability. An approved and marketed example drug product is sometimes bio-inequivalent when compared to itself across batches

Objective #2:

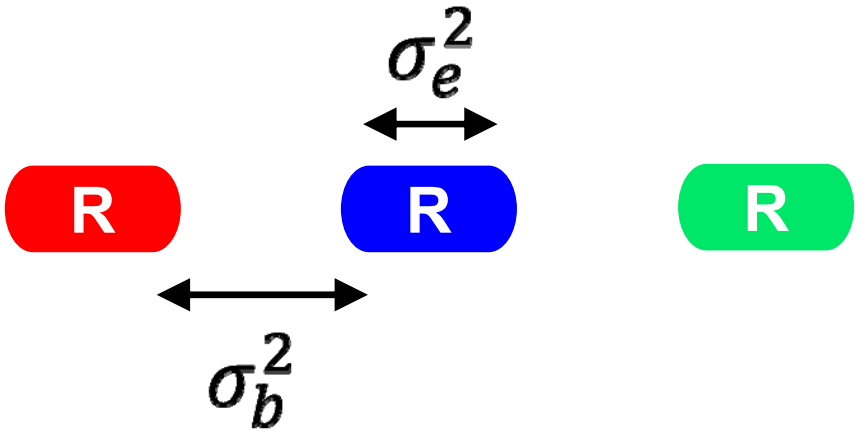
Assess the impact of batch-to-batch pharmacokinetic variability on bioequivalence testing

The bioequivalence test is based on the precision of the estimated treatment difference

The true treatment difference is unknown.	**Ln 0.80 ≤ [*mean*(Ln $Cmax_T$) – *mean*(Ln $Cmax_R$)] ≤ Ln 1.25**
BE is based on an estimate of the treatment difference, and the precision of this estimate	**Ln 0.80 ≤ [*90% confidence interval*] ≤ Ln 1.25**

Bioequivalence is concluded when ***the precision of the estimated treatment difference*** indicates there is less than a 5% chance that the current data arise from two non-equivalent products.

But the 2-way crossover ignores an important additional variance component



σ_e^2: within-subject, within-batch residual error variance

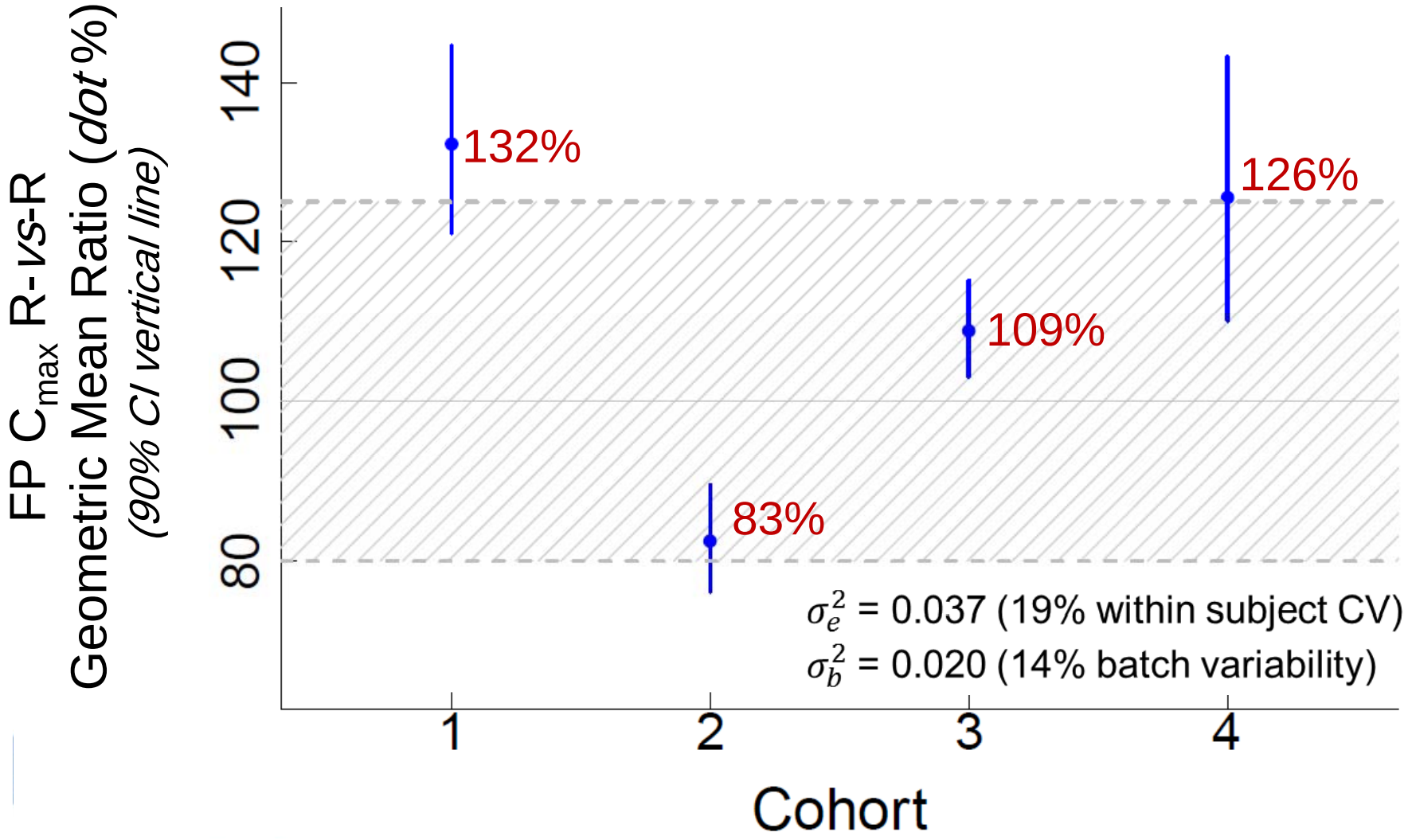
σ_e^2 = 0.06 (within-subject CV = 25%)

σ_b^2: within-subject, between-batch variance

In the proof-of-concept studies,

σ_b^2 = 0.05 - 0.06 (~25% batch variability

Here we randomly selected 8 reference batches and compared 2 in each cohort, resulting in failing a two-way PK bioequivalence study in 3 of 4 attempts



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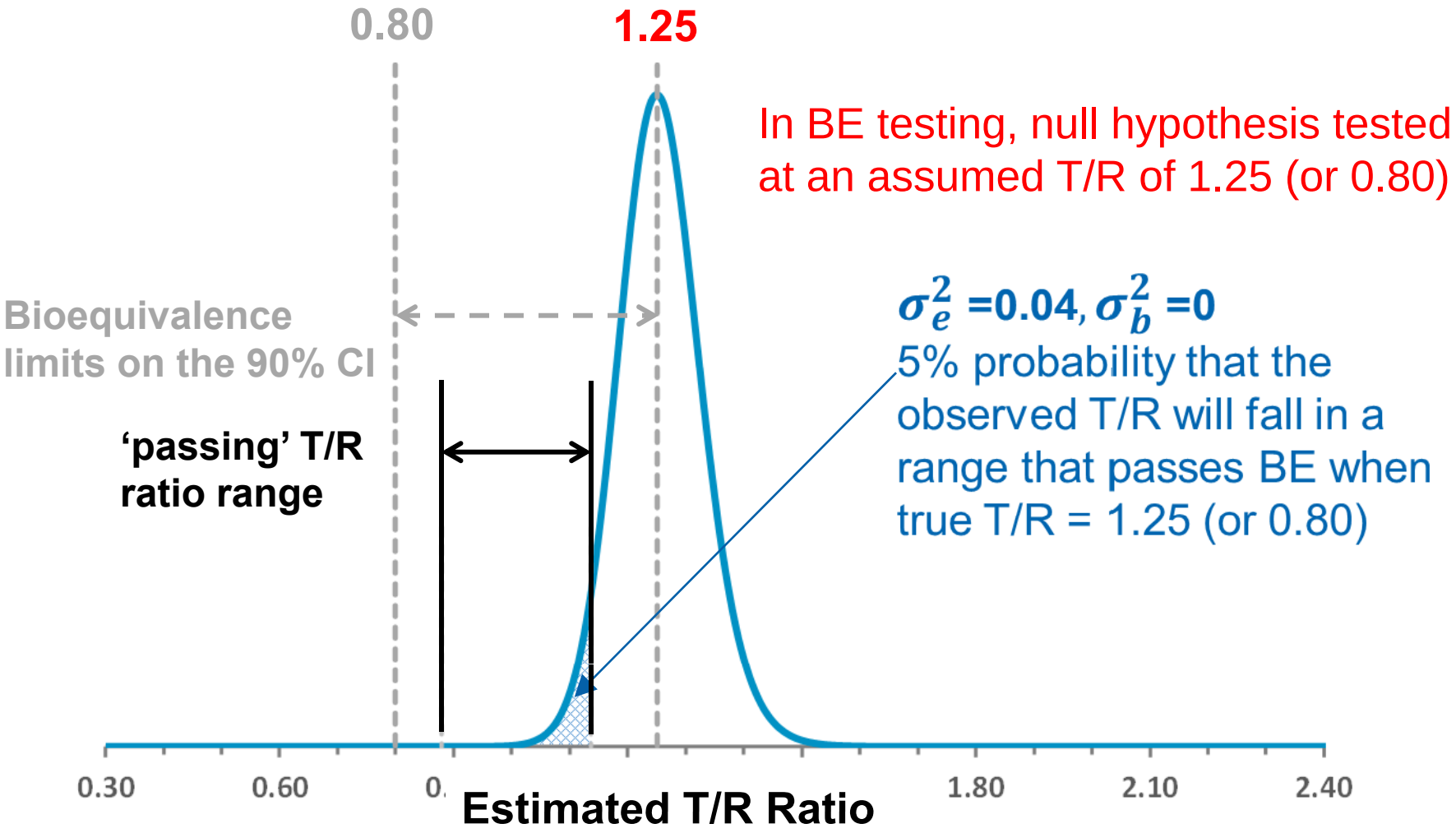
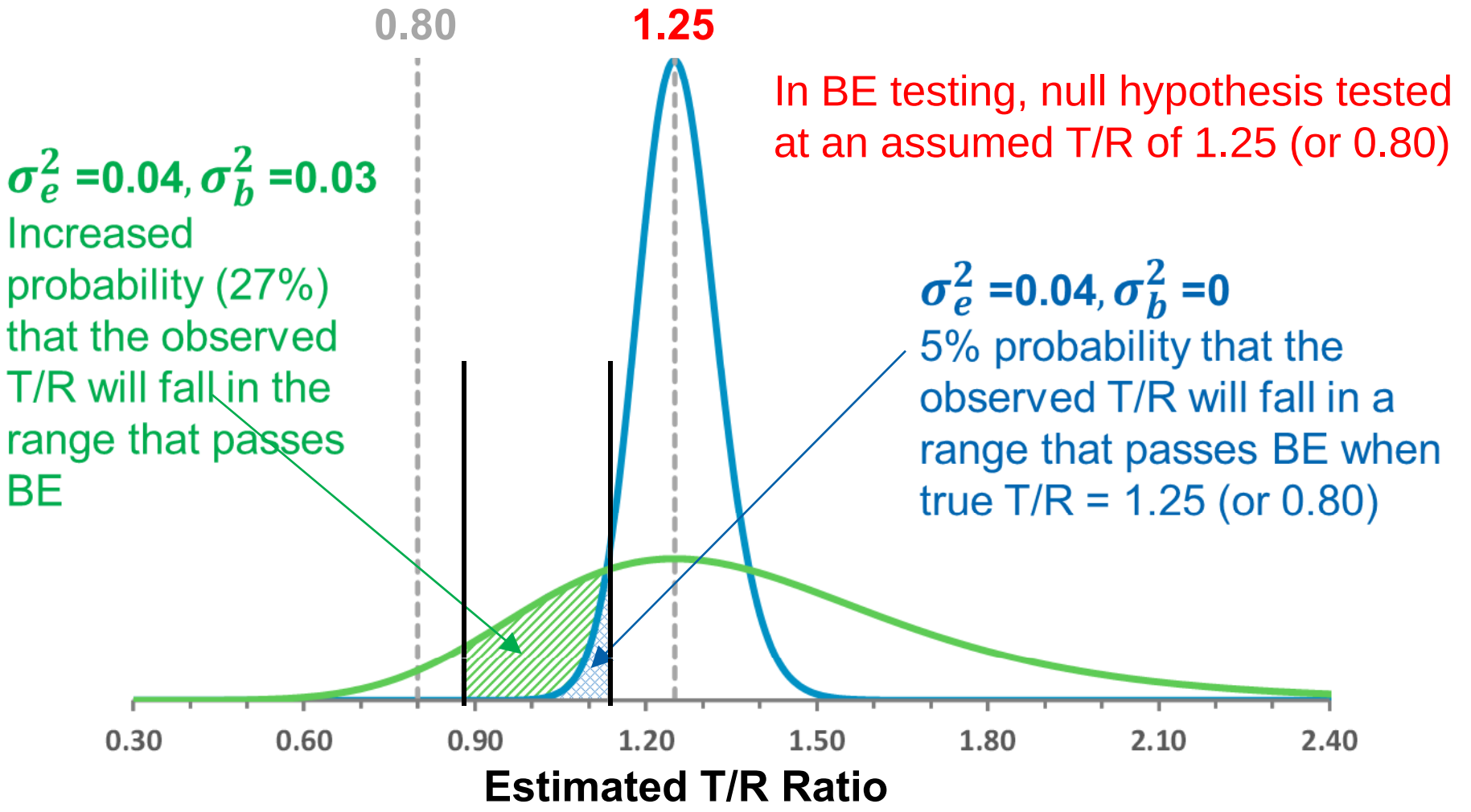
Now let's consider the statistics

Regulatory convention recommends ≤ 5% chance of incorrectly concluding BE



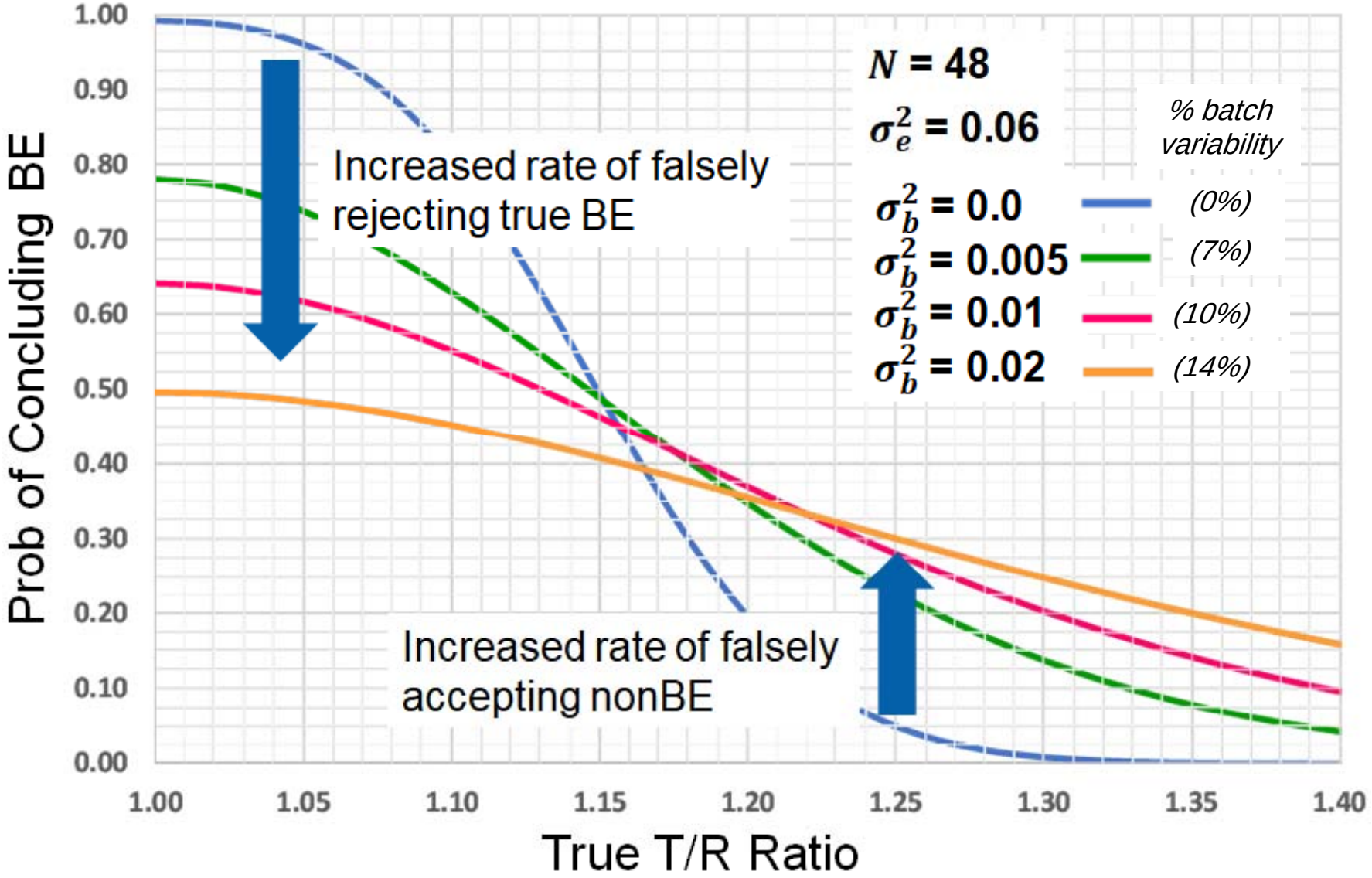
Expected T/R ratio distributions from a 2-way crossover BE study; N=26 subjects, 20% residual error.

If σ_b^2 is ignored, Type I error increases



Expected T/R ratio distributions from a 2-way crossover BE study; N=26 subjects, 20% residual error, two levels of between-batch variance. Variance estimates are assumed to be identical in the T and R products.

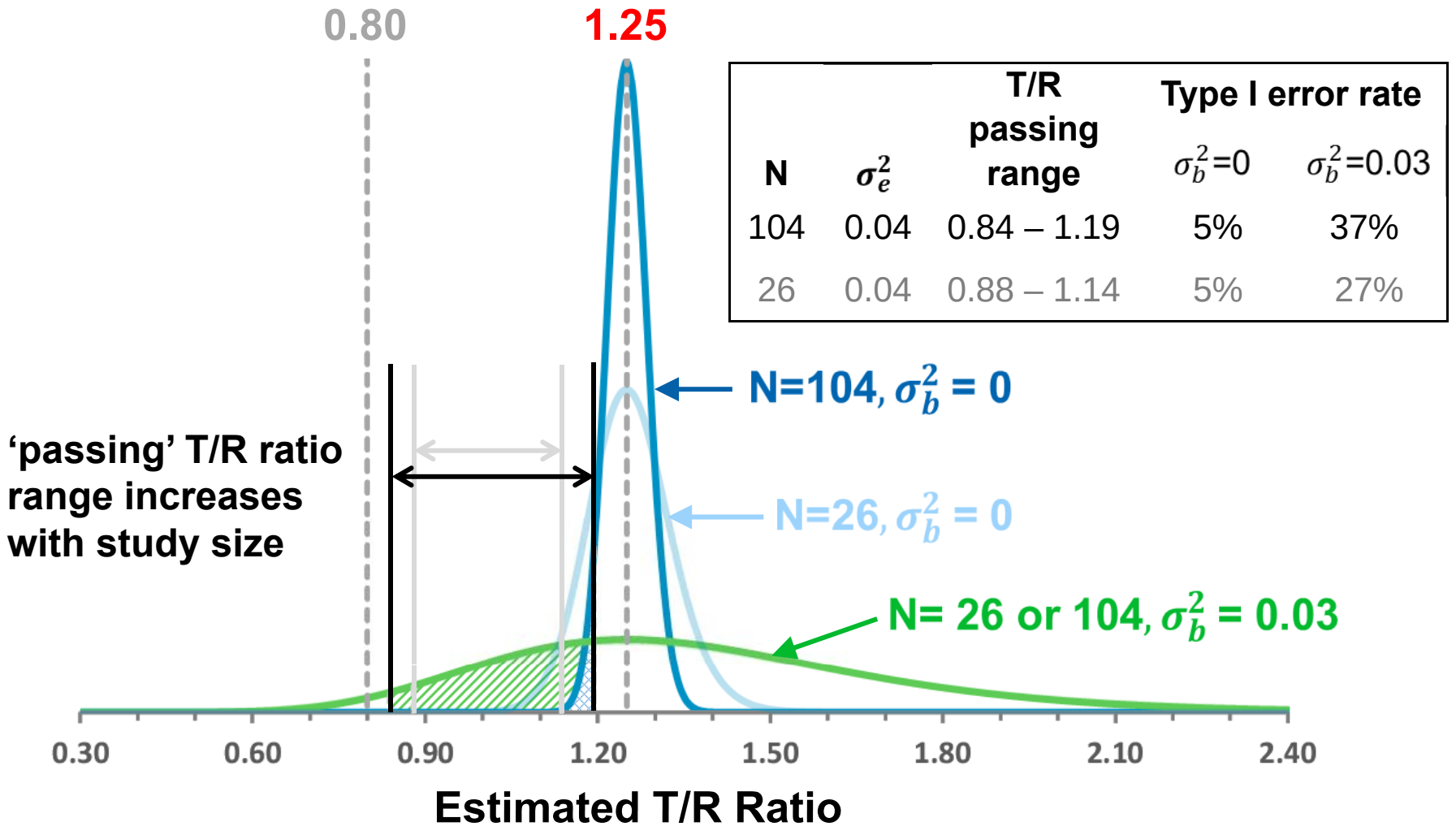
PK batch variability limits the value of a conventional two-way crossover PK BE study



Batch-to-Batch and Within-Subject Variability: What Do We Know and How Do These Variabilities Affect Clinical Pharmacology and Bioequivalence? LZ Benet, P Jayachandran, KJ Carroll and E Burmeister Getz, *Clin Pharmacol Ther*, submitted.

Impact of ignoring σ_b^2 is even greater

N	σ_e^2	T/R passing range	Type I error rate σ_b^2=0	Type I error rate σ_b^2=0.03
104	0.04	0.84 – 1.19	5%	37%
26	0.04	0.88 – 1.14	5%	27%



Expected T/R ratio distributions from a 2-way crossover BE study.
Variance estimates are assumed to be identical in the T and R products.

Objective #2:

Assess the impact of batch-to-batch pharmacokinetic variability on bioequivalence testing

Results:

When batches differ but only a single batch is used in BE testing the result of the study isn't easily interpreted; repeated studies may give different results, and the observed batch ratio may differ substantially from the true product ratio. Agreement between single batches to within 80-125% delivers to the patient products that may agree much less well.

Objective #3:

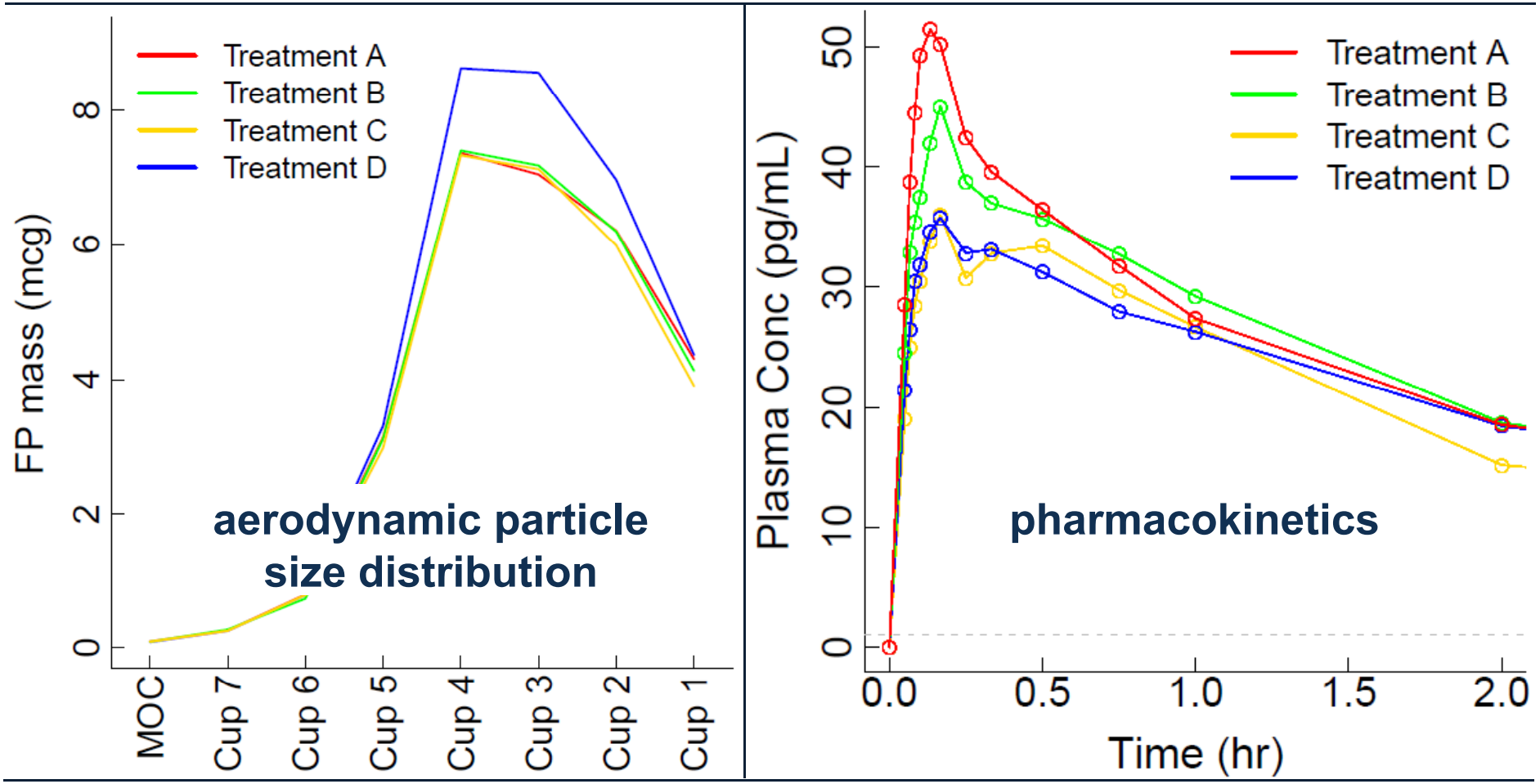
Consider potential solutions to batch-to-batch pharmacokinetic variability in bioequivalence testing

In response to a request for regulatory guidance regarding batch-to-batch variability in bioequivalence testing, the EMA Pharmacokinetics Working Party recommended that, "before the in vivo comparison, several batches of both test and reference products could be tested (in vitro) to identify representative batches.… of test and reference, respectively". The premise of batch selection via in vitro screening, assuming there exists an in vitro metric that accurately predicts in vivo metric, is that uncertainty in the pharmacokinetic estimate due to batch-to-batch variability can be reduced to a negligible level by increasing sample size.

SANDOZ A Novartis Division

Fluticasone dry powder pharmacokinetics is not well predicted by inertial impaction

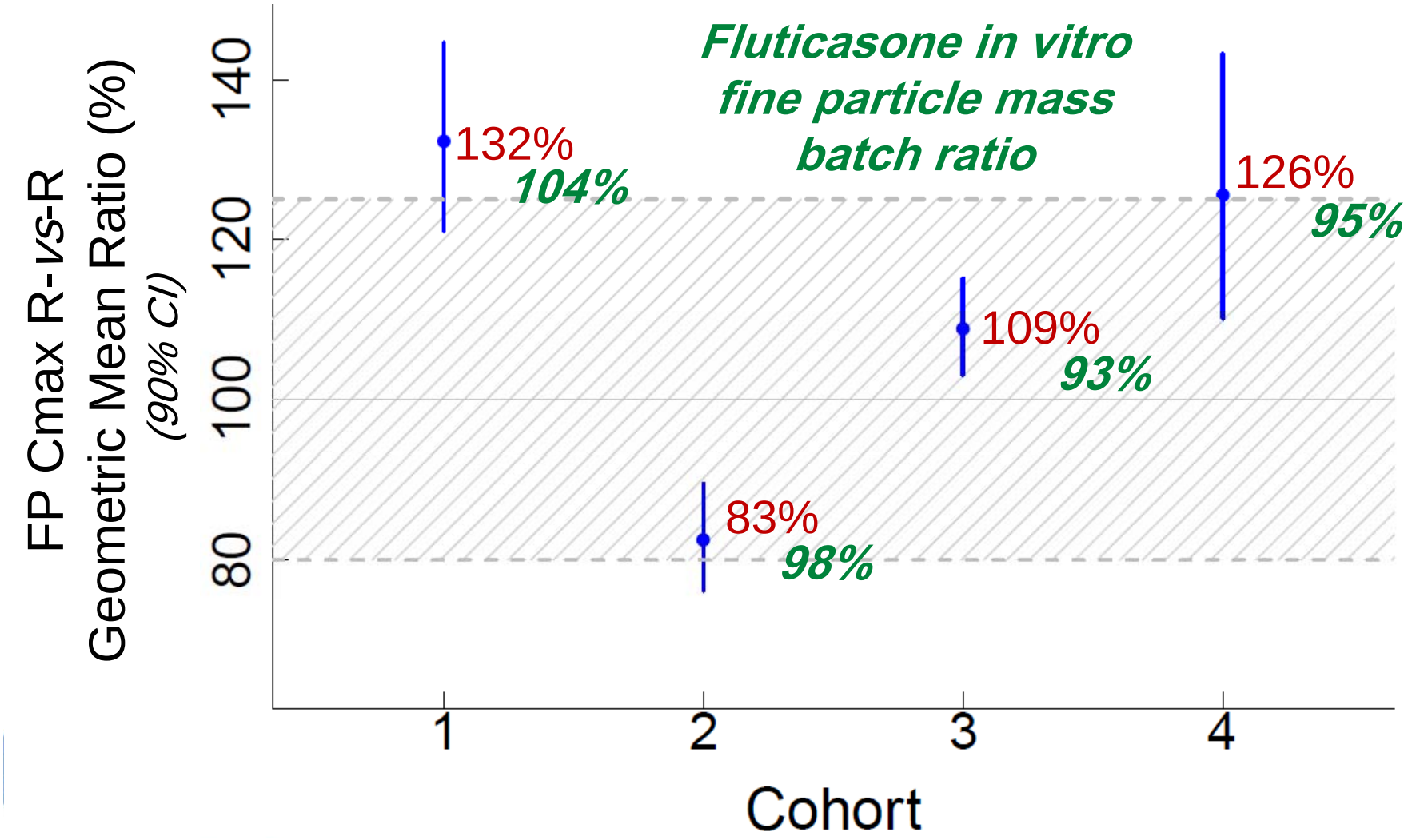
single-dose, 4-way crossover in 24 adult subjects
100 µg fluticasone propionate/50 µg salmeterol ODPI



Oriel Therapeutics Study OTT329/213

Randomly selected reference batches fail a two-way PK bioequivalence study in 3 of 4 attempts

In vitro inertial impaction doesn't correlate with PK



Oriel Therapeutics Study OTT329/107

Scaling the Bioequivalence Standard to the Performance of the Reference

A single-batch two-way PK bioequivalence study yields poor precision in the T/R product ratio estimate when batches vary.

… But, I would suggest that batch variability in an approved Reference product indicates a wide therapeutic index.

Since for wide therapeutic index products, the bioequivalence limits are widened to reflect a less stringent equivalence requirement, couldn't this be an appropriate approach?

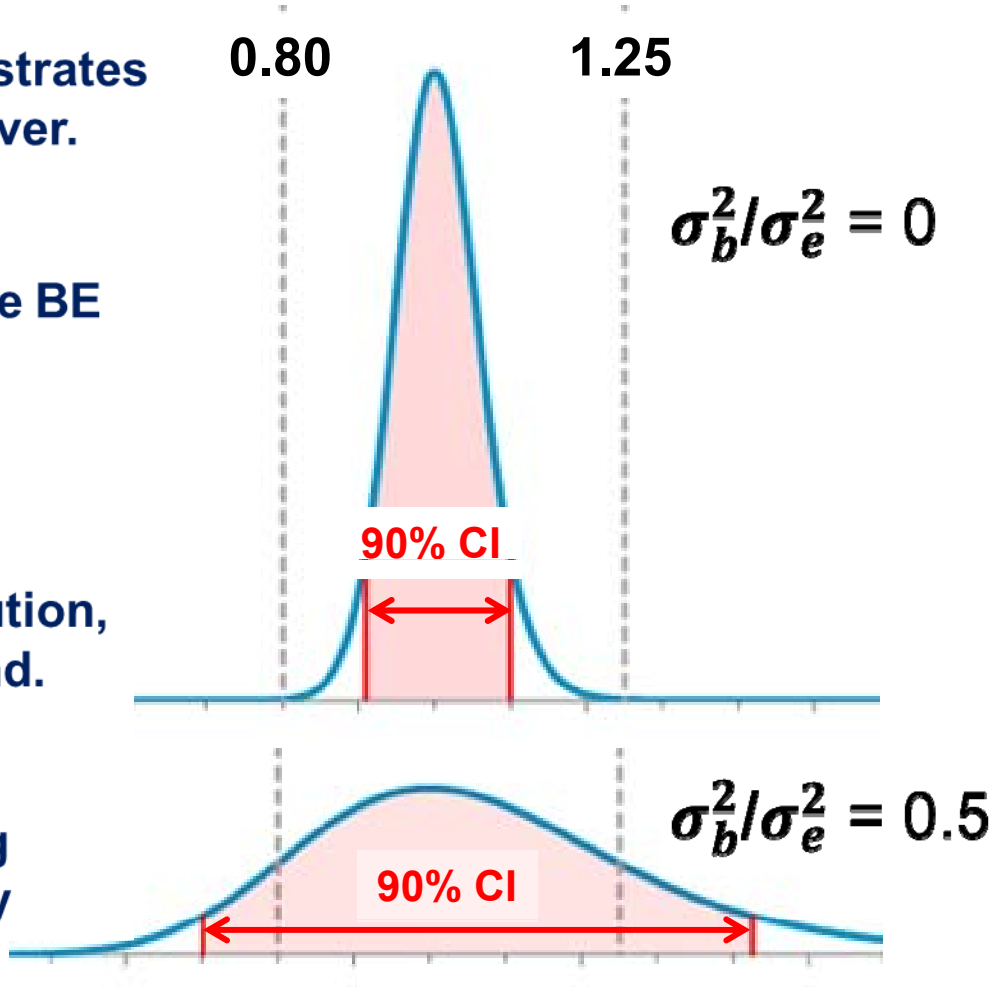
Batch variability requires modification to BE methodology

When $\sigma_b^2 > 0$, the correct 90% CI illustrates the futility of the two-way crossover.

Incorporate multiple batches in the BE assessment

When $\sigma_b^2 > 0$ widens the T/R distribution, allow the BE goalposts to respond.

Extend the Highly Variable Drug Reference-scaling methodology



Expected T/R ratio distributions from a 2-way crossover BE study; N=26 subjects, 20% residual error, T/R = 1.

Inclusion of multiple batches directly addresses batch variability

Orally-inhaled drug product *in vitro* bioequivalence testing already requires multiple batches:

Recommendations Related to the Batch Size Recommendation for In Vitro BE Studies:

1) In vitro BE studies for Budesonide Inhalation Suspension should generally be performed on samples from each of three or more batches of the test product and three or more batches of the reference listed drug.

2) The number of units per batch to be studied should not be fewer than 30 for each strength of the test and reference products (i.e., no fewer than 10 from each of three batches).

FDA Draft Guidance on Budesonide. Sep 2012

Multiple-batch study designs don't increase number of subjects, and offer opportunity for a form of Reference scaling

Objective #3:

Consider potential solutions to batch-to-batch pharmacokinetic variability in bioequivalence testing

Potential approaches:

- **Adapt the bioequivalence criterion to reflect variability of the Reference (i.e., extend Reference scaling)**
- **Consider more than one batch, when batches differ**

  In vitro screening to select a 'typical' batch

  Direct incorporation of multiple batches in the PK bioequivalence study

Ensuring patient access to substitutable generics

1. The PK of an example dry powder inhaler differs among batches; this reflects industry experience with inhaled drug products.

2. The single-batch two-way PK BE bioassay has reduced decision-making value when batches differ, unless only broad agreement between products is of interest. Reference-scaling principles have not been extended to batch variability.

3. Increasing batch sample size (*in vivo,* or *in vitro* if there is a predictive method) addresses batch variability, but does not circumvent an accounting for uncertainty due to sample size.

4. For some inhaled products, the PK bioassay provides product information (*e.g.*, *in vivo* dissolution rate) not captured by other bioequivalence tests.

Examination of the BE standard for products with substantial between-batch variability warrants further analysis by both regulators and sponsors

Thank you for your attention

A copy of the slides
can be obtained from
Leslie.Benet@ucsf.edu