Review of the Population Bioequivalence Criterion (PBE)

"Digital Poster" Prepared for the IPAC-RS/RDD 2020 Joint Symposium

by the PBE and GRRO Brazil Working Groups

Corresponding Authors: Beth Morgan (AstraZeneca) and Dave Christopher (Merck)

info@ipacrs.org

April 2020

Note

- This slide pack contains slides presented March 12th as part of a joint IPAC-RS and ANVISA webinar regarding statistical approaches for *in vitro* bioequivalence.

- The full recording of the webinar can be accessed digitally at the following location https://register.gotowebinar.com/recording/2340265825341045507?assets=true

- For additional details on the information presented, references are provided following the webinar content.

Topics to Cover Today

- General Background on Equivalence
- Statistical Approaches for *In-Vitro* Equivalence
- Understanding the PBE
  - IPAC-RS PBE Working Group Research results

General Background on Equivalence

In this section, we will cover:

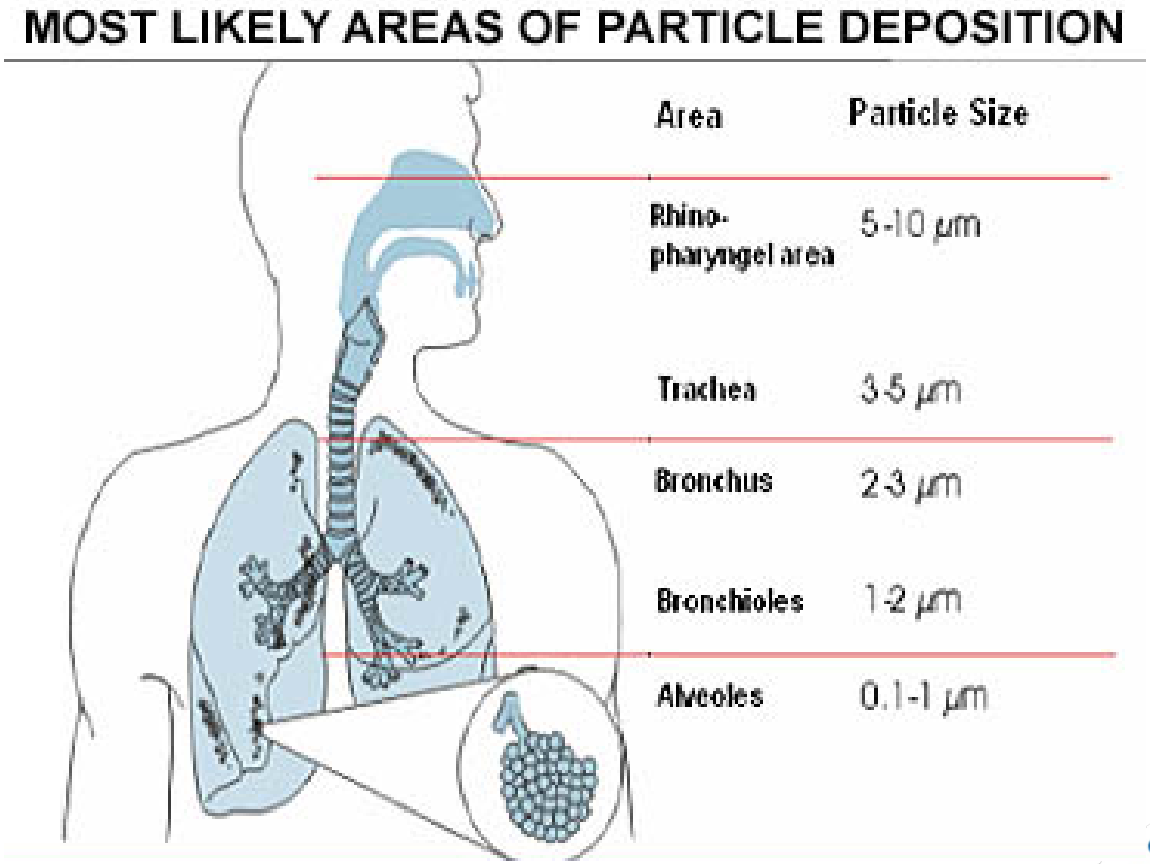
* The bioequivalence concept

* Components of bioequivalence and the role of *in-vitro* equivalence

The Bioequivalence Concept

Pharmaceutical equivalence + Bioequivalence = Therapeutic equivalence

Bioequivalence ensures that differences between pharmaceutically equivalent products do not substantially affect *in vivo* performance.



Bioequivalence Applications

The pharmaceutical industry uses bioequivalence to:

- bridge across changes in manufacturing process, scale, or location
- link batches used in safety/efficacy testing to the commercial product
- confirm the substitutability of a generic candidate

Bioequivalence testing plays an important role in both innovator and generic drug development.

Bioequivalence in Practice

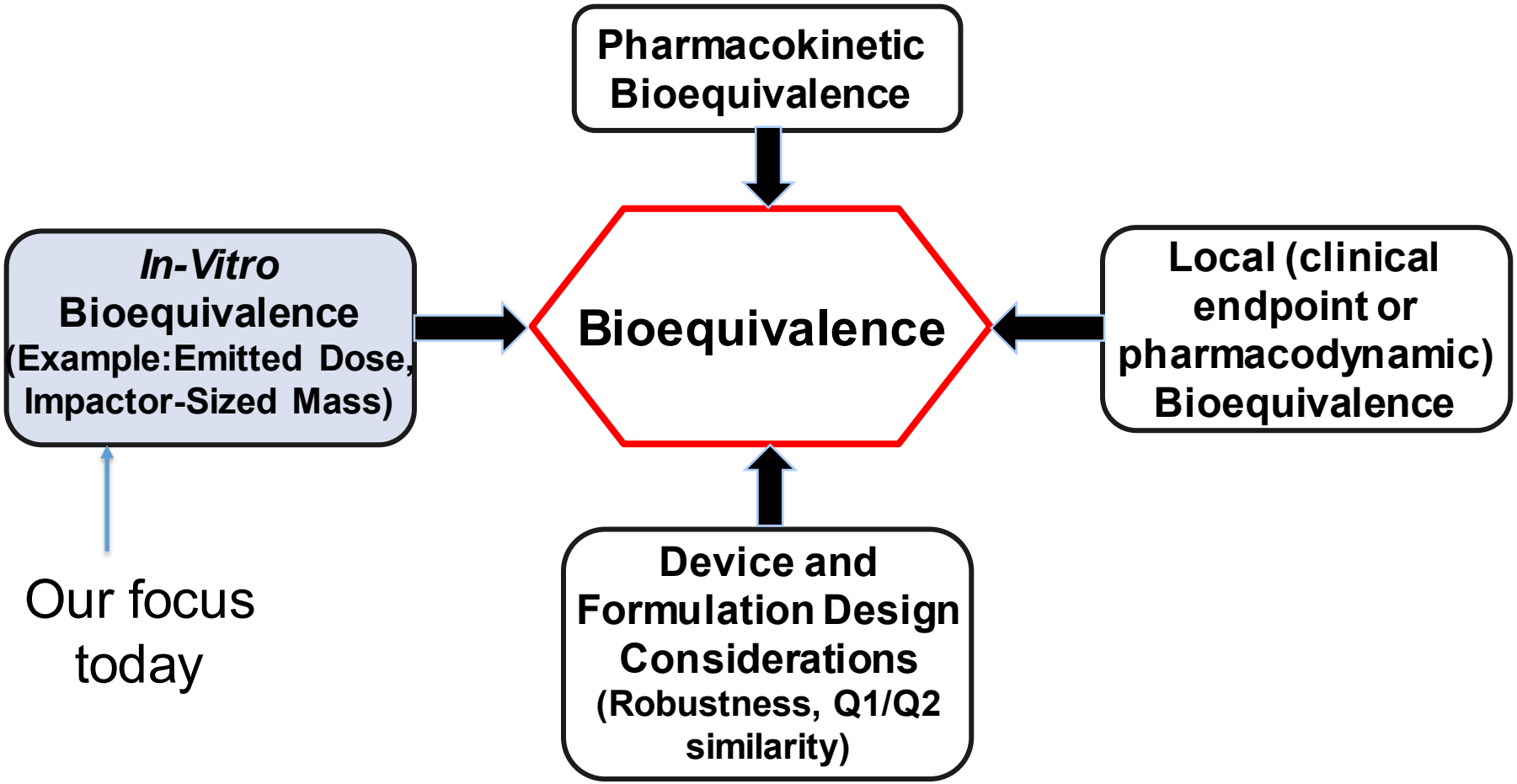
Bioequivalence: the absence of a significant difference in the rate and extent to which the active ingredient … in pharmaceutical equivalents … becomes available at the site of drug action

[Code of Federal Regulations – Title 21]

For drugs that reach their targets via the circulation, measure the rate and extent of drug appearance in the blood. Bioequivalence is assessed via pharmacokinetics (PK).

For locally-acting products (including OINDPs), blood PK is not directly linked to efficacy, and drug concentration at the local site is not easily measured.

Components of Bioequivalence



See *Adams et al. 2010. JAMPDD 23(1):1-29*

Types of statistical equivalence assessments: PBE and ABE

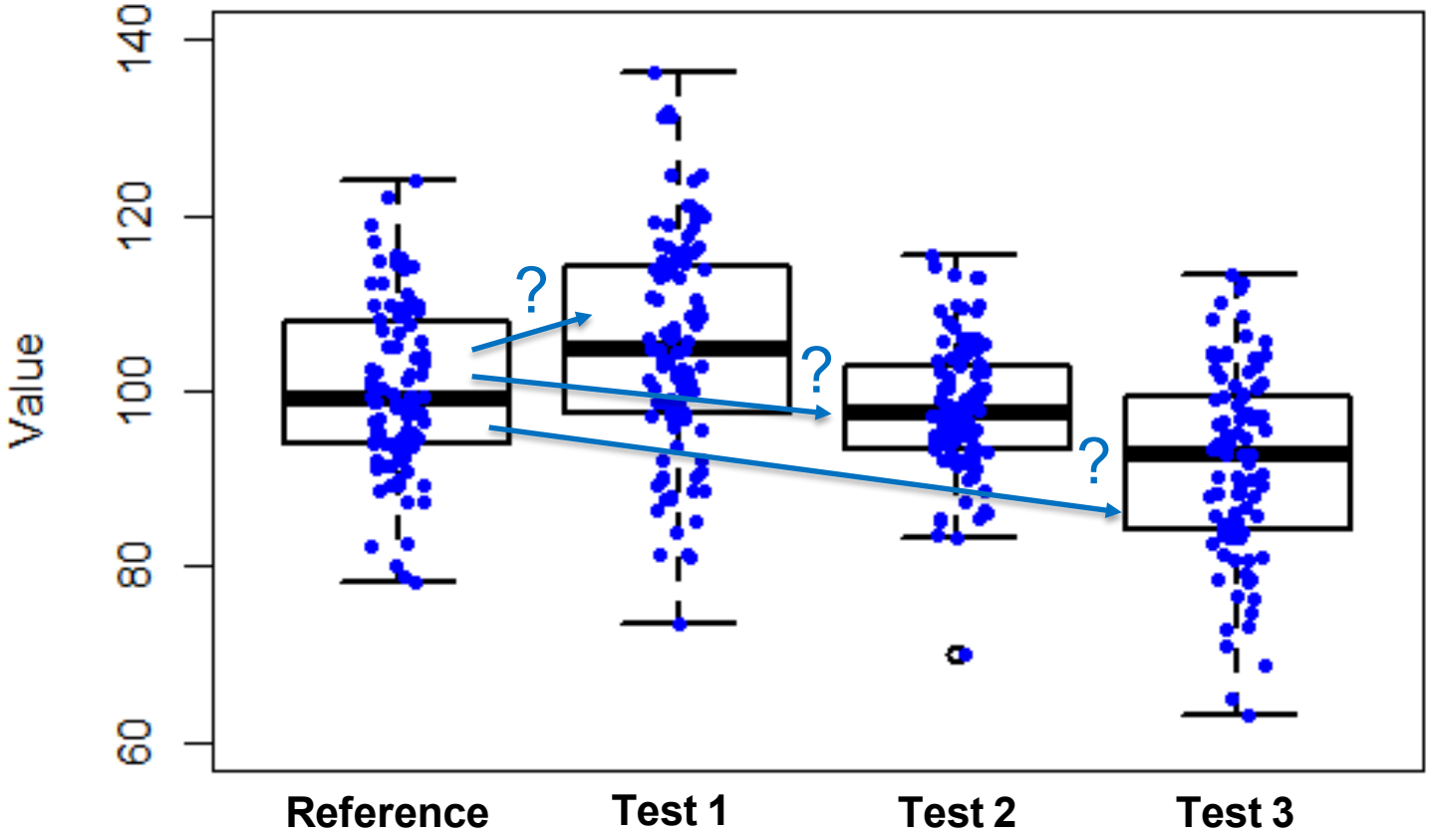
Pharmacokinetic Bioequivalence

PK BE is typically assessed using “average bioequivalence” (ABE) statistical methods

***In Vitro* Bioequivalence (Emitted Dose, Impactor-Sized Mass)**

In vitro BE can be assessed using “average bioequivalence” (ABE) or “population bioequivalence” (PBE) statistical methods

Motivating Example: *In vitro* Equivalence



How similar does a new (Test) product need to be to an existing (Reference) product to determine *in vitro* bioequivalence?

Statistical Approaches for *In-vitro* Equivalence

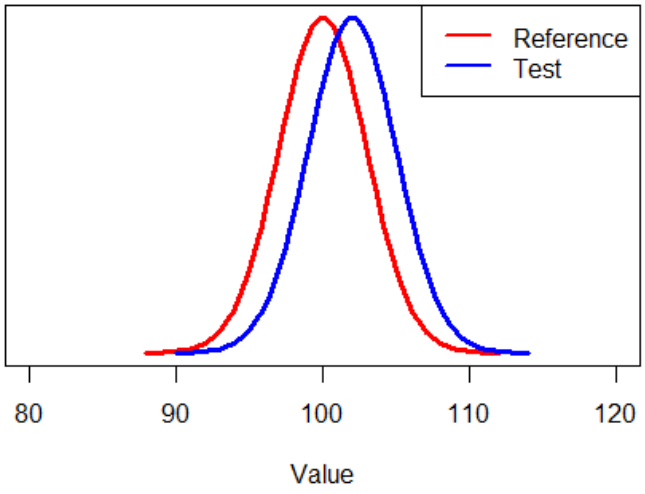
In this section, we will cover:

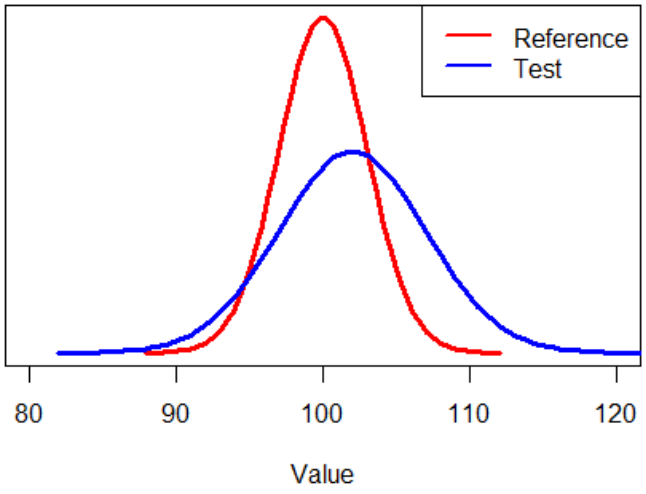
* Types of statistical equivalence methods:
  average bioequivalence or
  population bioequivalence

* CMC tests considered for equivalence assessment

PBE versus ABE

- PBE is an extension of Average Bioequivalence (ABE) and was developed for PK/in vivo data
  - ABE compares Test vs Reference product means
  - PBE compares Test vs Reference product means and variances
- PBE was developed to incorporate comparisons between products with similar means but different variances
- Both assume skewed data distribution (log normal)





Side by Side Summary of ABE and PBE

Component	ABE	PBE
Comparison from the Data	Equivalence defined as the difference between **means**	Equivalence defined as the combined difference between **means** and between **variances**
Assumed Data Distribution	Log-normal	Log-normal
Acceptance Criterion	Difference in **means** of transformed data within +/- 10% relative mean difference	Combined difference in **means** and **variability** of transformed data < 2.0891
Is a confidence interval assessment used?	**YES** Confidence interval from Two One-Sided t test (TOST) on transformed data	**YES** Large sample confidence interval used on transformed data (Reference below)

Overview of the ABE Approach

- The ABE answers the question whether the difference in ***means*** between test and reference products is within a pre-defined acceptance criterion.

- The analysis is based on data in the log scale.

- The data are assumed to follow a normal distribution on the log scale, varying randomly around the overall product mean.

- The products will be declared in vitro equivalent if the equivalence confidence interval lies completely within the pre-defined acceptance criterion.
  - Typically, for *in vitro* data, that acceptance criterion is taken to be a 10% relative difference.

Form of the ABE

- ABE is based on differences in means in the log-scale

- The confidence interval on the mean difference needs to be within defined acceptance criterion

General Form:

$$Lower\ acceptance\ criterion \leq Difference\ in\ Means\ on\ Log\ Scale \leq Upper\ acceptance\ criterion$$

$$-(Ln\ (100) - Ln(90)) \leq \mu_T - \mu_R \leq (Ln\ (100) - Ln(90))$$

  - The pre-defined acceptance criterion is often taken as a 10% relative mean difference but a 10% ratio, log transformed, is the same as a difference in logs

- The analysis is conducted by constructing a two one sided t-test confidence interval on ***transformed*** data

  - $\overline{Y_T} - \overline{Y_R} \pm t_{0.90,df} \times Standard\ Error\ (\overline{Y_T} - \overline{Y_R})$ where
  - *df*=Degrees of freedom from pooled estimate of variability

Overview of the PBE Approach

- The PBE answers the question of whether the difference in means ***and*** variances between test and reference products is within pre-defined acceptance criterion.

- The analysis is (again) based on data in the log scale.

- The data are (again) assumed to follow a normal distribution on the log scale, varying randomly around the overall product mean.

- The products will be declared *in-vitro* equivalent if the equivalence confidence interval lies completely within the pre-defined acceptance criterion.
  - FDA defined an acceptance criterion based on allowable differences between means and variances on the log scale.

Form of the PBE

- PBE is based on differences in means and variances in the log-scale

$$\theta = \frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\max(\sigma_{T0}^2, \sigma_R^2)} \leq 2.0891$$

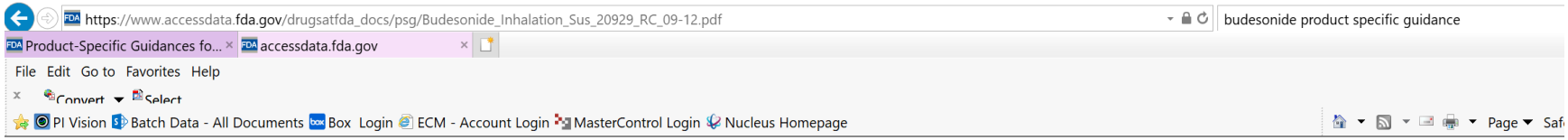
or

$$\eta = (\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2) - 2.0891 * \max(\sigma_{T0}^2, \sigma_R^2)$$

- Equivalence defined as $\theta \leq 2.0891$ or $\eta \leq 0$, $\sigma^2_{T0} = 0.01$

- Allows for reference product scaling

FDA Documentation: Detailed Algorithm



Contains Nonbinding Recommendations

Draft Guidance on Budesonide

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Budesonide

Form/Route: Suspension/Inhalation

Explanation of Acceptance Criterion

- The acceptance criterion of 2.0891 comes from defining what is allowable or what is equivalent for different pieces of the equation:

$$\theta = \frac{(\mu_T - \mu_R)^2 + ({\sigma_T}^2 - {\sigma_R}^2)}{\max({\sigma_{TO}}^2, {\sigma_R}^2)} = \frac{A + B}{C}$$

- $A = (\mu_T - \mu_R)^2 = (Ln\,(100) - Ln\,(90))^2 = \left(Ln\,(\frac{100}{90})\right)^2 = (Ln(1.11))^2 = 0.010891$
- $B = (\sigma_T^2 - \sigma_R^2) = 0.01$
- $C = \sigma_0^2 = 0.01$
- $\theta = \frac{A+B}{C} = \frac{0.010891+0.01}{0.01} = 2.0891$

Exact calculations for these quantities and the corresponding confidence intervals are provided in the FDA Reference, given above

Implementing the PBE Following FDA Approach

Data collected as part of Comparability Protocol

Reference: min 3 batches with 10 units per batch

and

Test: min 3 batches with 10 units per batch:

N=30 v. N=30

Data Analysis

Analyze data in log-scale

Estimate Reference product's (log-scale) variance

If Ref Variance > 0.01, use reference scaled criterion and

Calculate 95% Upper Confidence Bound:

$$H_{\eta_1} = \left(E_D + E_1 + E_2 + E_{3s} + E_{4s}\right) + \sqrt{U_D + U_1 + U_2 + U_{3s} + U_{4s}}$$

If Ref Variance < 0.01, use constant scaled criterion and

Calculate 95% Upper Confidence Bound:

$$H_{\eta_2} = \left(E_D + E_1 + E_2 + E_{3c} + E_{4c} - \theta_p \sigma_{T0}^2\right) + \sqrt{U_D + U_1 + U_2 + U_{3c} + U_{4c}}$$

Equivalence met if 95% Upper Confidence Bound of η ≤ 0

In-vitro (CMC) tests that could be considered for equivalence assessment

Nebulized Aerosols	MDIs / DPIs	Nasal Sprays
• Unit Dose Content • Mean Nebulization Time • Mean Delivered Dose	• Delivered Dose (Single Actuation Content) • Mass Balance • Impactor Sized Mass • Fine Particle Mass • Spray Pattern	• Delivered Dose (Single Actuation Content) • D50 • Span at 2 distances [(D90-D10)/D50] • Drug in small particle/droplet • Spray Pattern

Understanding the PBE

In this section, we will cover:

* The Definition of Equivalence for PBE in original units

* Factors Impacting the Performance of the PBE (IPAC-RS PBE Working Group output)

* Online tools for better understanding performance of PBE

IPAC-RS PBE Working Group

Remit of the group:

IPAC-RS established a PBE Working Group in December 2012 to study the performance of the PBE method as applied to *in vitro* data

Objectives:

- characterize the real-world data to which PBE is applied (what do industry-generated *in vitro* data look like?)
- understand the consequences (bioequivalence decisions) when applying PBE across the range of real-world data
- communicate findings to industry, regulators, academics
- provide educational support to other IPAC-RS WGs

Understanding the PBE

- PBE can be re-written as a function of differences between product means and RSD's in the data's <u>original-scale</u>

$$\theta = \frac{(\mu_T - \mu_R)^2 + (\sigma_T{}^2 - \sigma_R{}^2)}{\max(\sigma_{TO}{}^2, \sigma_R{}^2)} \quad \text{Log-scale}$$

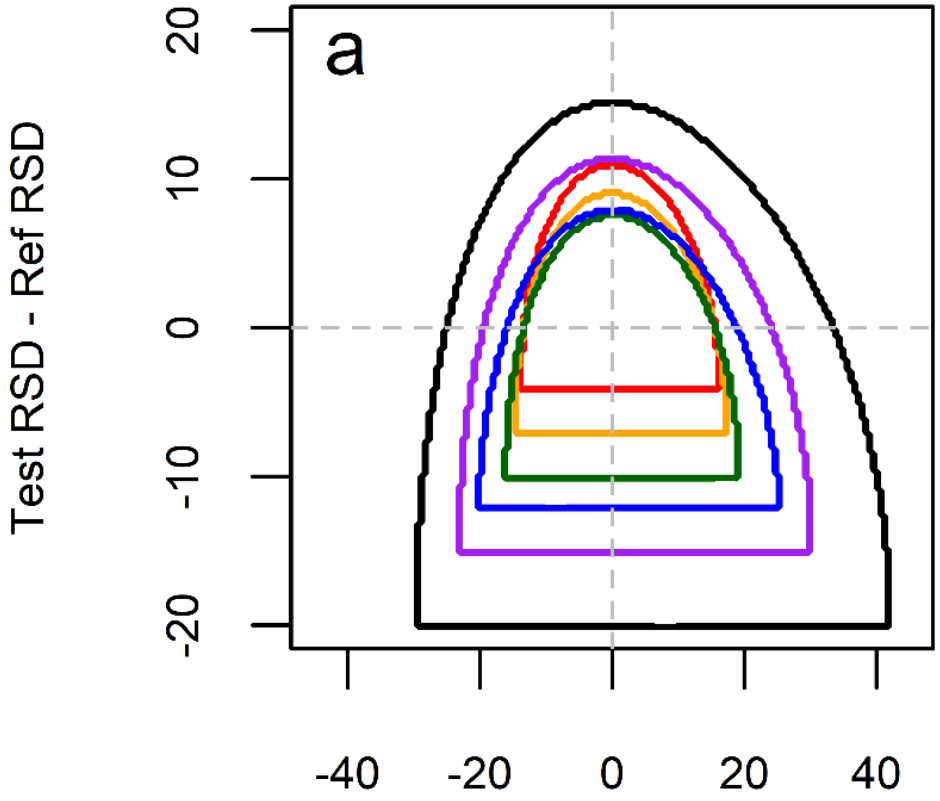
$$\approx \frac{\ln(1+\gamma)^2 + (RSD_T{}^2 - RSD_R{}^2)}{\max(\sigma_{TO}{}^2, RSD_R{}^2)} \quad \text{Original-scale}$$

- γ is the relative mean difference between Test and Reference

$$\gamma = \frac{Test\ Mean - Ref\ Mean}{Ref\ Mean}$$

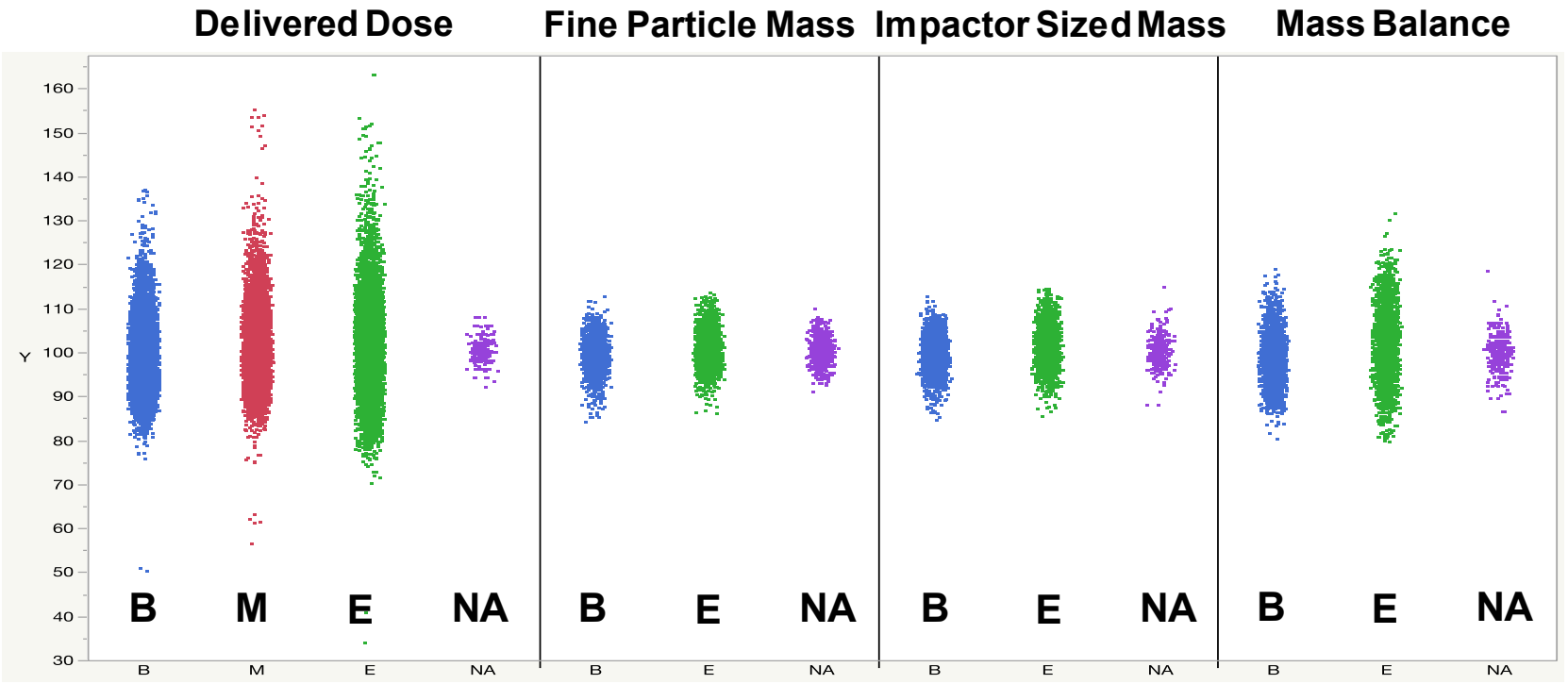
Mapping the Definition of Equivalence

What product differences are defined as equivalent (θ ≤ 2.0891)?



Legend: (Reference RSD)
Red = 4%
Orange = 7%
Green = 10%
Blue = 12%
Purple = 15%
Black = 20%

Data Characteristics from an MDI Industry Database



Have now published from delivered dose (18,825 measurements from 856 batches) and impactor sized mass (5197 measurements from 117 batches).

Results from studying these metrics can be applied to other tests.

Important Data Characteristics Impacting Performance

1. **Batch Variation**
   - PBE assumes no batch variation is present in its calculations
   - Batch variation exists, even for comparability protocols
   - Failing to account for Batch variation increased decision making errors
2. **Log-transformation**
   - Not necessary, data appears to be normally distributed
   - Log-transformation meant that equivalence depended on direction of product differences (e.g. if Test > Ref or Ref < Test)
3. **Total Variability**
   - Total variability ranged from 3 – 11% RSD (relative standard deviation)
   - High variability increased decision making error

Additional Characteristics with Minimal Impact on Performance

4. Lifestage Difference

- PBE assumes lifestage effect is random
- Industry data shows non-random increase for beginning- to end-of-use
- Minimal impact for the magnitude of difference typically seen in data

5. Extreme Values

- High and low extreme values exist, particularly for dose
- Low extreme values had a larger impact than high extreme values on equivalence conclusions, but overall, had little effect

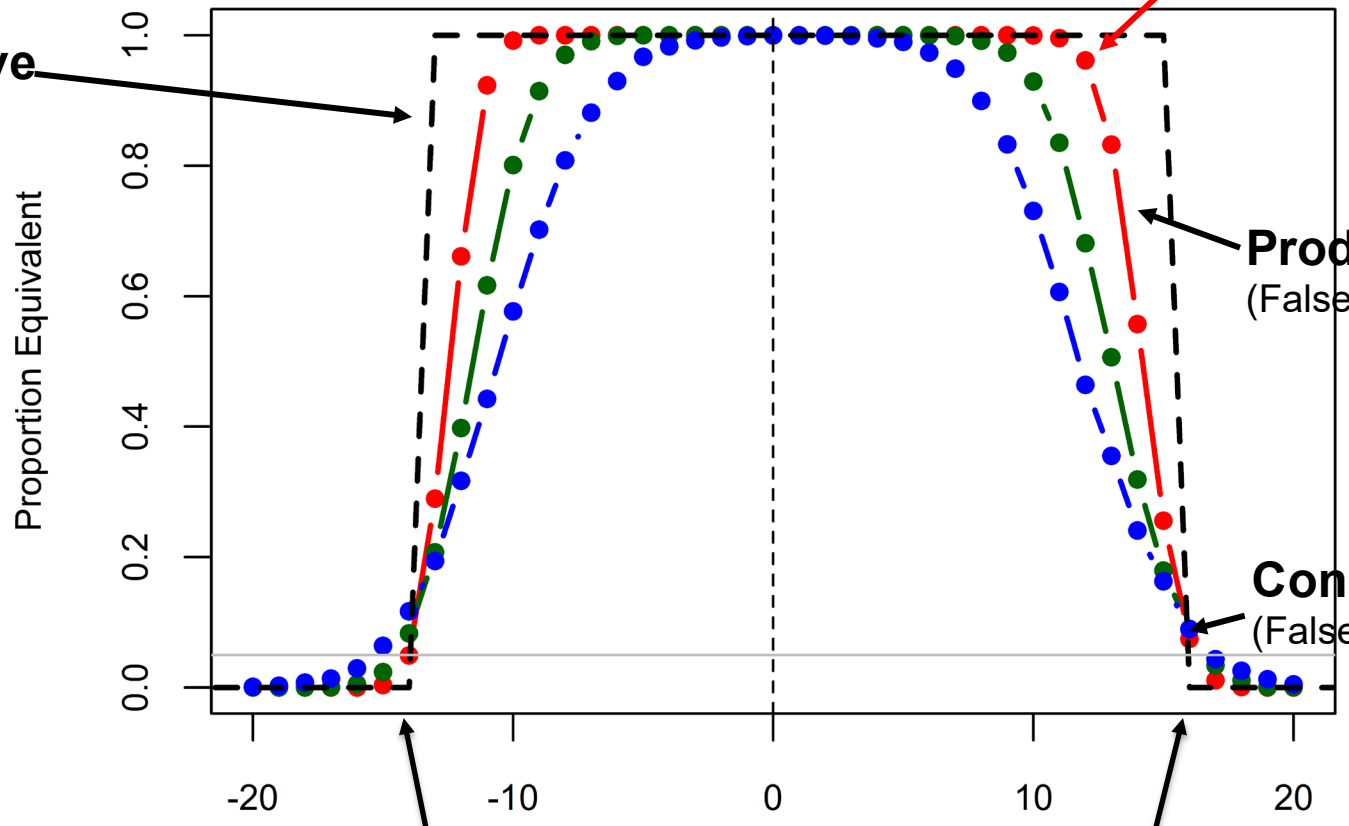
Online Tools for Understanding PBE

All output from the simulation study from DDU are available online, and presented as Operating Characteristic (OC curves):

1. Supplementary Material: Online at the IPAC-RS PBE Working Group's page

2. Interactive Web Application: Hosted online

Review of OC curves



Legend:

4% Test = Ref RSD

7% Test = Ref RSD

10% Test = Ref RSD

2. Interactive Web Application

https://stchen3.shinyapps.io/ddshinyapp/

Screenshot

Delivered Dose Output

Number of Lifestages:
3

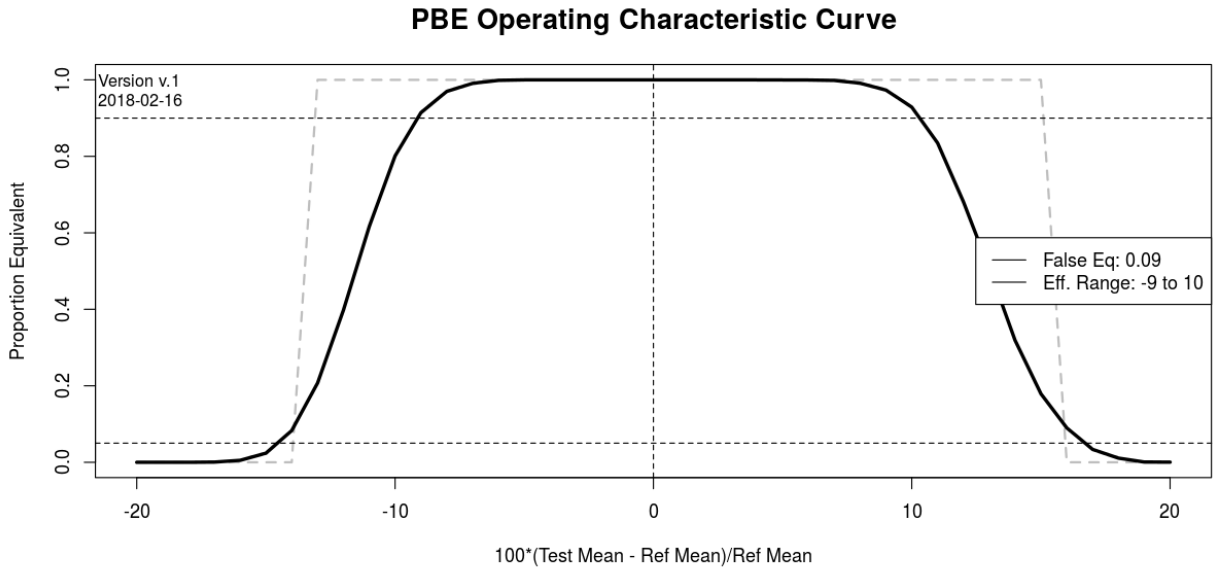
LS Difference:
NO

Total Reference RSD (%):
7

Total Test RSD (%):
7

Reference = Test Batch Variance (% of total variance):
10

Type of Extreme Values:
NONE



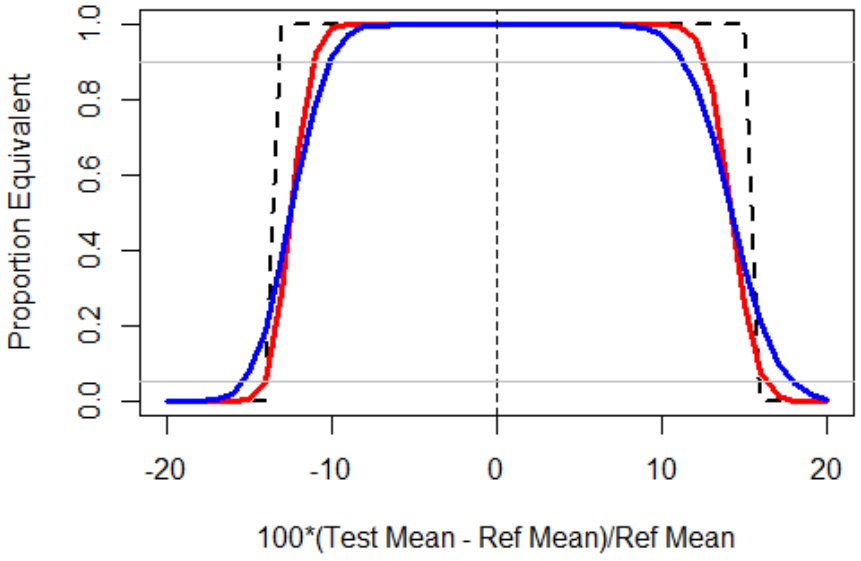
No software necessary and functions in any web browser.

Motivating Example (continued)

How similar does a new (Test) product need to be to an existing (Reference) product to determine *in vitro* bioequivalence?

- What product differences pass equivalence ~ 90% of the time?

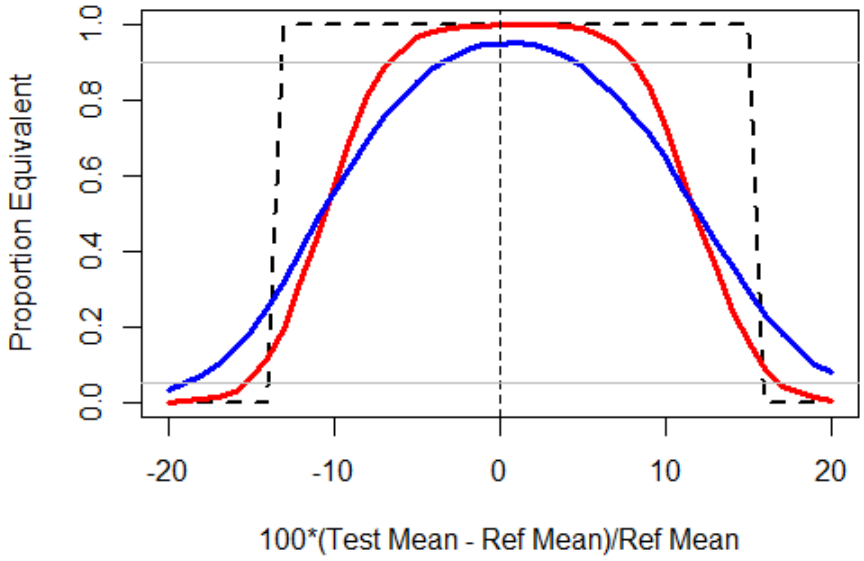
Test = Reference RSD = 4%



10% Batch Variance: -10% to +11%

50% Batch Variance: -8% to +10%

Test = Reference RSD = 10%



10% Batch Variance: -6% to +7%

50% Batch Variance: -3% to +4%

Summary

Webinar today intended to :

- Show *in-vitro* equivalence is one component in overall bioequivalence assessment

- Review statistical approaches for demonstrating *in-vitro* equivalence

- Summarize part of the output from IPAC-RS PBE Working Group, introducing online tools for using PBE

Acknowledgments

- IPAC/RS Executive Board
- PBE Working Group:
  - Daniela Acerbi (Chiesi Farmaceutici)
  - Hayden Beresford, Helen Derbyshire, Neha Patel, Christopher Wiggenhorn (3M)
  - Mark Berry (Mylan)
  - Elise Burmeister Getz (Oriel Therapeutics)
  - Stephanie Chen (North Carolina State University)
  - Dave Christopher, Monisha Dey (Merck)
  - Thomas Hoffelder (Boehringer Ingelheim Pharmaceuticals)
  - Keyurkumar Joshi (Catalent Pharma Solutions)
  - Goran Langstrom, Andrea Maes, Beth Morgan (AstraZeneca)
  - Svetlana Lyapustina (Drinker Biddle & Reath)
  - Mary McKenry (Teva Pharmaceuticals Industries)
  - Filipe Neves (Hovione)
  - Marisa Pertile (Chiesi Limited)
  - Helen Strickland (GSK)
  - David Wilcox (Catalent Pharma Solutions)

THANK YOU !

References

References for material used in Webinar:

- FDA. Draft Guidance on Budesonide; Formoterol fumarate dihydrate. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide_Inhalation_Sus_20929_RC_09-12.pdf.
- **Performance of the Population Bioequivalence (PBE) Statistical Test with Impactor Sized Mass Data** *AAPS PharmSciTech* (2019) 20:296. DOI: 10.1208/s12249-019-1507-8 Stephanie Chen, Beth Morgan, Hayden Beresford, Elise Burmeister Getz, David Christopher, Göran Långström, Helen Strickland, Christopher Wiggenhorn, and Svetlana Lyapustina. https://rdcu.be/bPqke or https://link.springer.com/content/pdf/10.1208%2Fs12249-019-1507-8.pdf
- **Performance of the Population Bioequivalence (PBE) Statistical Test Using an IPAC-RS Database of Delivered Dose from Metered Dose Inhalers.** Beth Morgan, Stephanie Chen, David Christopher, Göran Långström, Christopher Wiggenhorn, Elise Burmeister Getz, Hayden Beresford, Thomas Hoffelder, Daniela Acerbi, Steven Andrews, Mark Berry, Monisha Dey, Joshi Keyur, Mary McKenry, Marisa Pertile, Helen Strickland, David Wilcox, Svetlana Lyapustina AAPS PharmSciTech. 2018 Apr;19(3):1410-1425. doi: 10.1208/s12249-017-0941-8. Epub 2018 Feb 12. https://www.ncbi.nlm.nih.gov/pubmed/29435904.