U.S. FOOD & DRUG ADMINISTRATION

# Dose-Scale ($E_{max}$) Modeling in Pharmacodynamic Bioequivalence Studies – FDA Perspective

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**SAAMnow 2019 Spring Workshop, Rockville, MD**
**April 4-5, 2019**

# Disclaimer

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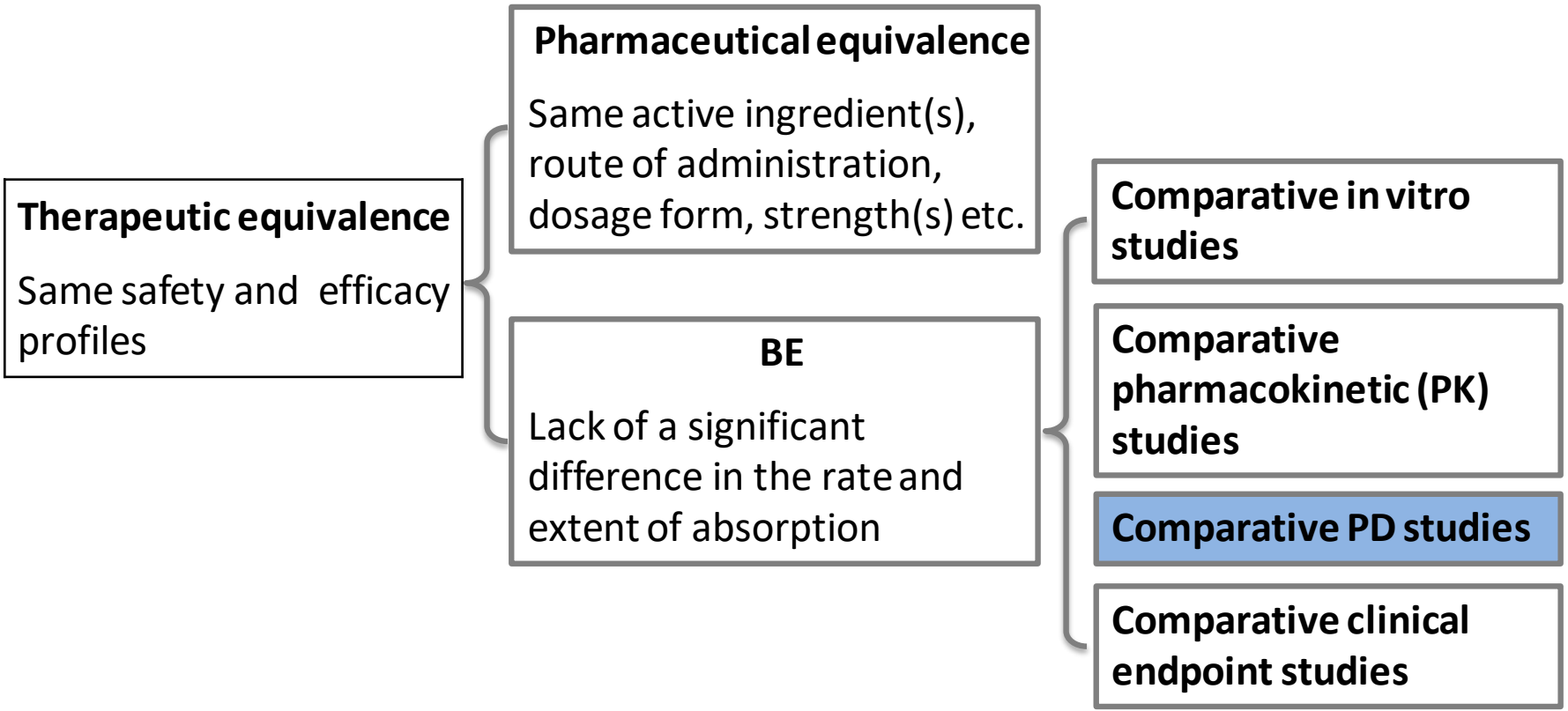
# Outline

- Pharmacodynamic (PD) equivalence studies
- Dose-scale analysis
  - Methodology
  - PSG recommendation
    - Bronchoprovocation study
    - Bronchodilatation study
    - Fecal fat excretion study
- Challenges and tips
- Closing remarks

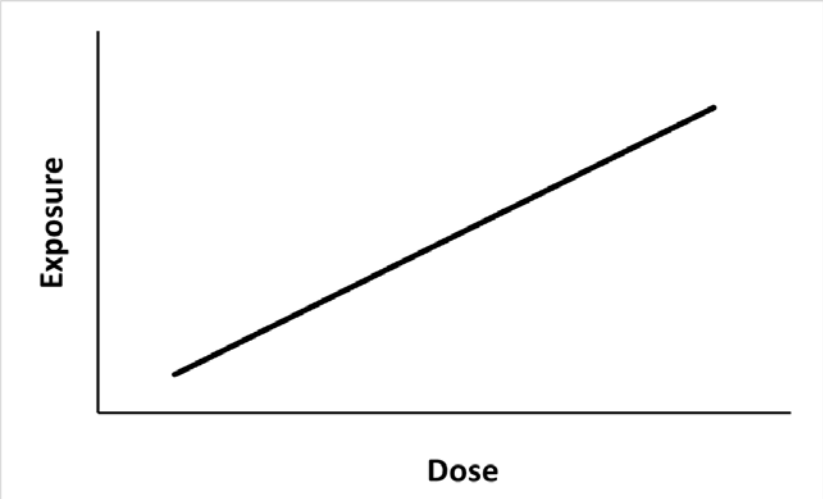
# Therapeutic equivalence of generic drugs

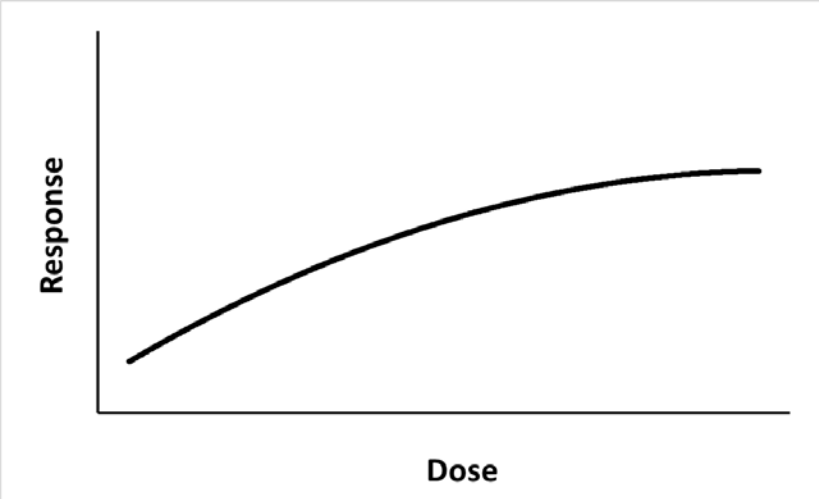


# Recommended comparative PD studies in product-specific guidance (PSG)

- Orally inhaled drug products
  - Short-acting bronchodilators (e.g., albuterol sulfate)
  - Long-acting bronchodilators (e.g., formoterol fumarate)
  - Corticosteroids (e.g., ciclesonide)
- Locally acting gastrointestinal (GI) drug products
  - Binding and protective agents (e.g., acarbose, orlistat)
- Low molecular weight heparin injectables etc.

# BE based on PK or PD endpoints




- Exposure is proportional to dose
- BE can be based on 90% confidence interval (CI) around exposure
- No exposure for placebo (or baseline correction)

- Nonlinear dose-response: response does not increase proportionally with dose
- Placebo effect can be substantial



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# Example – albuterol metered dose inhaler (MDI)

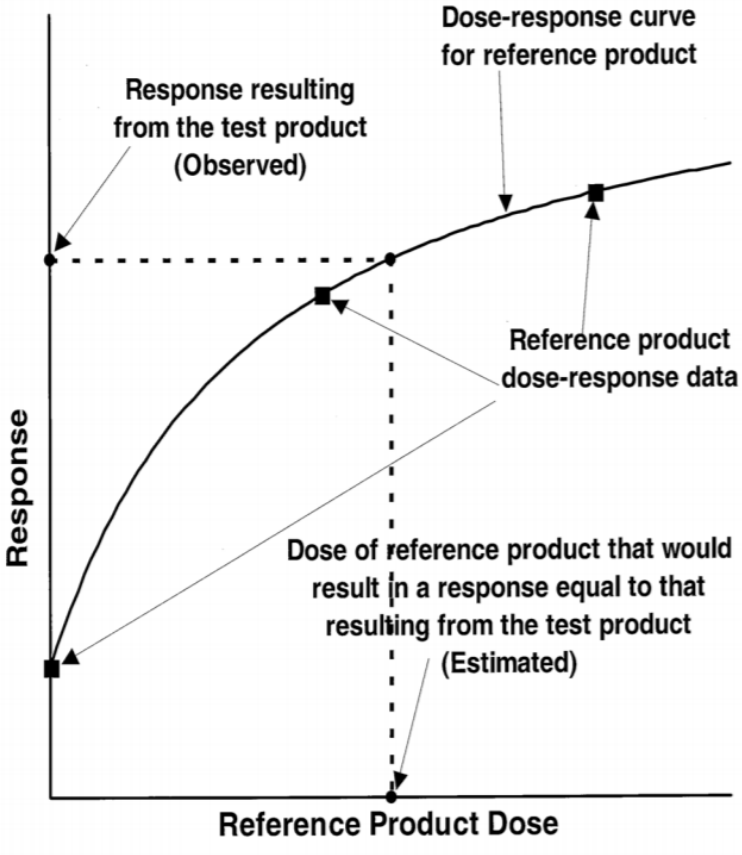
- Drug is delivered to the lung where bronchodilator effect occurs
- Drug may be absorbed from sites other than the lung
- Systemic exposure is not necessarily an accurate predictor of amount of drug reaching the site of action
- PD response (from bronchoprovocation or bronchodilatation studies) does not increase proportionally with dose

# Example – orlistat oral capsule

- Drug binds lipases in the GI tract and inhibits dietary fat absorption
- Systemic exposure to orlistat is minimal
- Clinical efficacy (e.g., weight loss) study is lengthy and not ideal for BE determination
- PD effect (fecal fat excretion) plateaus at higher doses

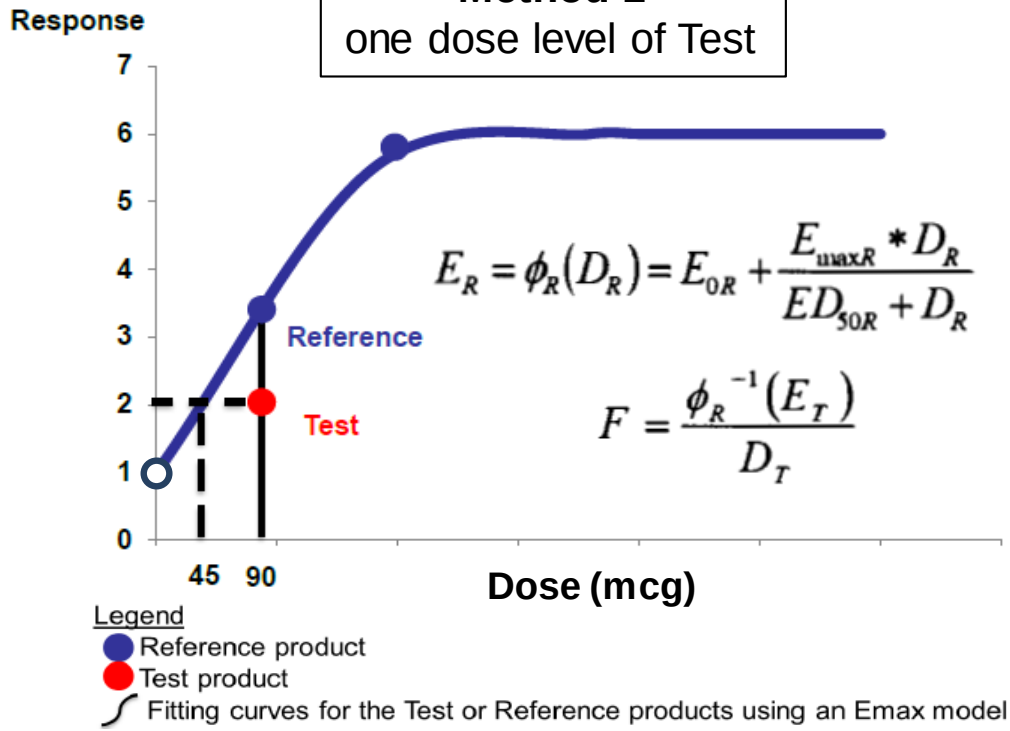
# Dose-scale analysis

- Assess the BE of drug products by estimating relative bioavailability on dose scale - not original scale of PD measurements
- Suggest equivalence of the amount of drug reaching the site of action



# Dose-scale methodology: $E_{max}$ model fitting

**Method 1**
one dose level of Test




$$E_R = \phi_R(D_R) = E_{0R} + \frac{E_{maxR} * D_R}{ED_{50R} + D_R}$$

$$F = \frac{\phi_R^{-1}(E_T)}{D_T}$$

**Method 2**
two dose levels of Test

$$y = E_0 + \frac{E_{max} * Dose * F^i}{ED_{50} + Dose * F^i}$$

| | |
|---|---|
| $y$ | response |
| $i$ | treatment indicator (0=R, 1=T) |
| $F$ | relative bioavailability |

# Dose-scale methodology: calculating 90% CI

- Generate “sample dose-response dataset”
  - Repetitive sampling with replacement (bootstrap)
- Calculate F
  - Fitting the $E_{max}$ model to each “sample dose-response dataset”
- Compute 90% CI for F
  - Using Efron’s bias corrected and accelerated (BCA) method

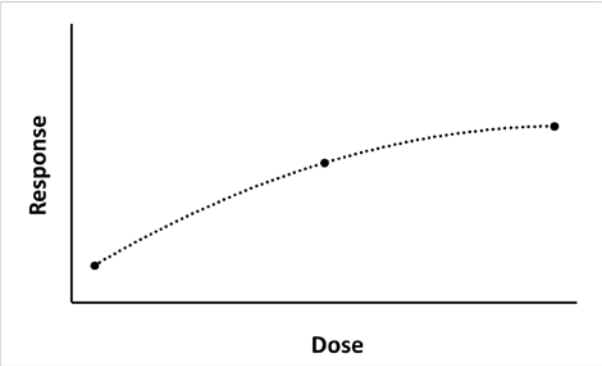
# Comparative PD studies with dose-scale analysis

| Product | Orlistat oral capsule | Albuterol/levalbuterol MDIs | |
|---|---|---|---|
| **Study** | Fecal fat excretion study | Bronchoprovocation study[a] | Bronchodilatation study |
| **Design** | Multiple-dose crossover study in healthy subjects | Single-dose, double-blind, double dummy, randomized, crossover study in subjects with asthma | |
| **Treatment arm** | • Baseline/placebo<br>• Reference product: 2 dose levels R1, R2<br>• Test product: 1 dose level T1, second dose level optional (T2) | | |
| **Endpoint** | %fecal fat excretion (FFE)[b] | post-dose $PC_{20}$ or $PD_{20}$[c] | $FEV_{1max}$, $AUEC_{0-4h}$, $AUEC_{0-6h}$[d] |
| **90% CI of F** | 80.00-125.00% | 67.00-150.00% | |

a, a Bio-IND is required prior to conduct of the bronchoprovocation study; b, expressed as a ratio of the mount of fat excretion over a 24-h period at steady-state relative to the amount of daily ingested fat; c, dose or concentration of methacholine required to reduce forced expiratory volume in one second ($FEV_1$) by 20% following a dose of albuterol sulfate; d, endpoints are adjusted using the pre-dose $FEV_1$

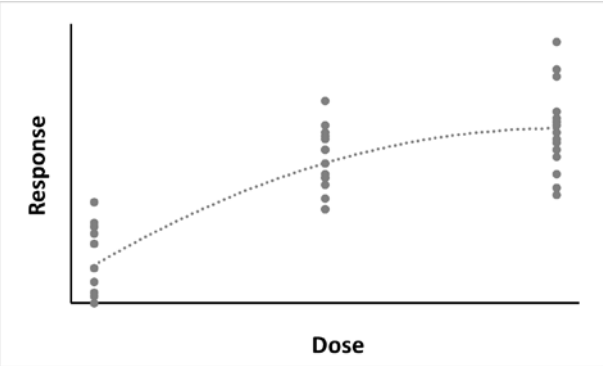
# Pre-market submission challenges for dose-scale analysis – modeling approach perspective

Naïve average data (NAD)



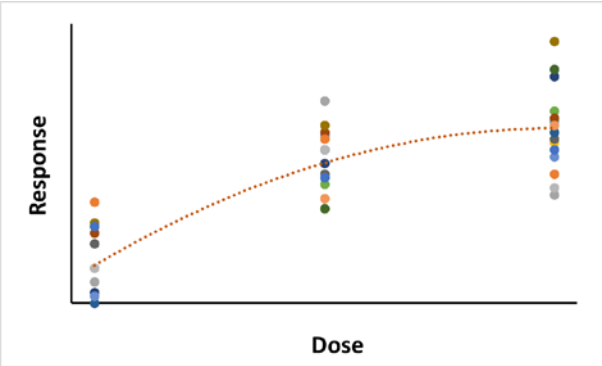

- Mean data only
- One data point/dose

Naïve pooled data (NPD)




- Treating all data as if they are from the same individual

Nonlinear mixed effect modeling (NLME)




- All individual data

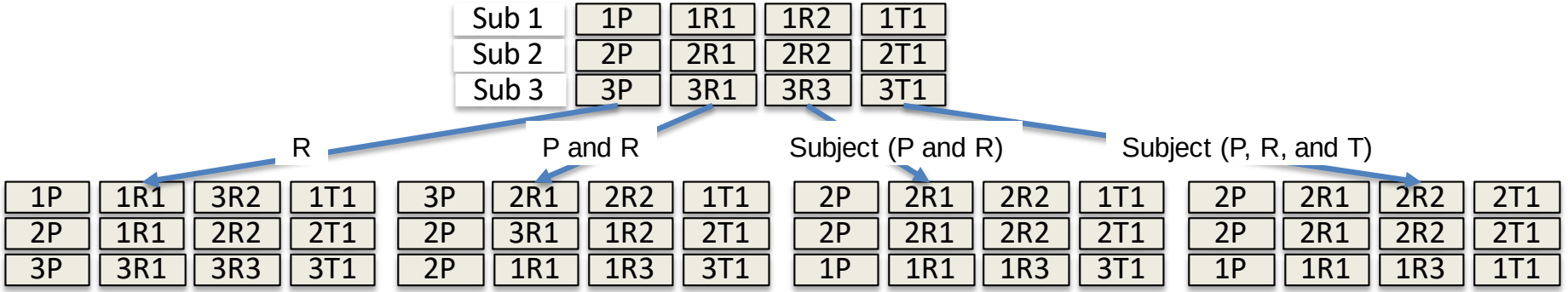
# Compare model fitting approaches

| | NAD | NPD | NLME |
|---|---|---|---|
| Data | Mean data | Pooled data | Pooled individual data |
| Model | $Y_{mean} = E_0 + \frac{E_{max} * Dose * Fi}{ED_{50} + Dose * Fi}$ | $Y = E_0 + \frac{E_{max} * Dose * Fi}{ED_{50} + Dose * Fi}$ | $E_{0,s} = E_0 + \eta_s$<br>$Y_{s,j} = E_{0,s} + \frac{E_{max} * Dose * Fi}{ED_{50} + Dose * Fi} + \varepsilon_{s,j}$ |
| Pros | • Easy to implement<br>• Short running time | • Easy to implement<br>• Short running time | • Handle rich or sparse data with missing value<br>• Characterize BSV, WSV, and residual variability |
| Cons | • No estimation of variability<br>• Average model may not be representative of some subjects when between-subject variability (BSV) is high<br>• Potential bias if individuals have different amount of data | • Cannot separate BSV from within-subject variability (WSV)<br>• Potential bias resulting from ignoring individual differences in response | • Complex algorithms<br>• Relatively longer running time |

**Tip:** NLME approach has been routinely used for $E_{max}$ model fitting

# Challenges associated with calculation of 90% CI for F

- Generating "sample dose-response dataset"
  - Multiple resample ways for crossover studies




  - Number of "sample dose-response dataset"
- **Tips:**
  - Resample by subjects (including data from all treatment arms)
  - Prefer large number of resampled dataset (e.g., 10,000 sets)

# Challenges associated with calculation of 90% CI for F

- Estimating F by fitting the $E_{max}$ model to each "sample dose-response dataset"
  - Data for the test arm to be used in NPD or NLME approach: mean or individual data?
  - Modeling software: NONMEM, SAS, R, or others?
- Computing 90% CI of F
  - Implementation of BCA method
- **Tips**:
  - Use individual data for the test arm in NPD or NLME approach
  - Prespecify modeling software and computation method for 90% CI

# Case example: missing $PC_{20}$ data in bronchoprovocation study

- $PC_{20}$ is the concentration of methacholine required to achieve a 20% reduction in $FEV_1$ following a dose of albuterol (or placebo)
- $PC_{20}$ data in some subjects/treatment arms may be missing
  - Missing completely at random (MCAR)
    - Missing data occur independent of both observable and unobservable variables of interest
    - e.g., subject dropout due to relocation
  - Missing at random (MAR)
    - Missing data are related to factors other than study variables of interest
    - e.g., technique or equipment issues
  - Missing not at random (MNAR)
    - Missing data are related to study variables of interest
    - e.g., fail to complete a treatment due to unfavorable treatment effect
- Missing data may impact the F estimation

# Case example: simulations with missing $PC_{20}$ data

- Simulate a 5-way, 5-treatment crossover study with assumed model parameters
  - Scenario 1: F = 0.96
  - Scenario 2: F = 0.80
- Missing data imputation by deletion (~10% for each treatment arm)
  - MAR: deletion at random
  - MNAR: deletion only occurs at lower end
- Analyze the data using the NAD and NLME approaches
- Comparison of these two approaches is based on which one can recover the assumed true F



Slide courtesy of Lanyan (Lucy) Fang, Ph.D.

# Case example: impact of missing $PC_{20}$ data on F estimation

| F | Modeling | MAR | | MNAR | |
|---|---|---|---|---|---|
| | | P.E. | 90% CI | P.E. | 90% CI |
| 0.96 | NAD | 0.99 | (0.73, 1.28) | 1.14 | (0.81, 1.84) |
| | NLME | 0.99 | (0.77, 1.24) | 1.05 | (0.78, 1.40) |
| 0.80 | NAD | 0.91 | (0.64, 1.11) | 0.93 | (0.70, 1.31) |
| | NLME | 0.83 | (0.61, 1.07) | 0.88 | (0.64, 1.09) |

P.E., point estimate; equivalence criteria on 90% CI: 0.67-1.50

**Tip:** When there are missing values not at random, NLME model is less sensitive to missing values.



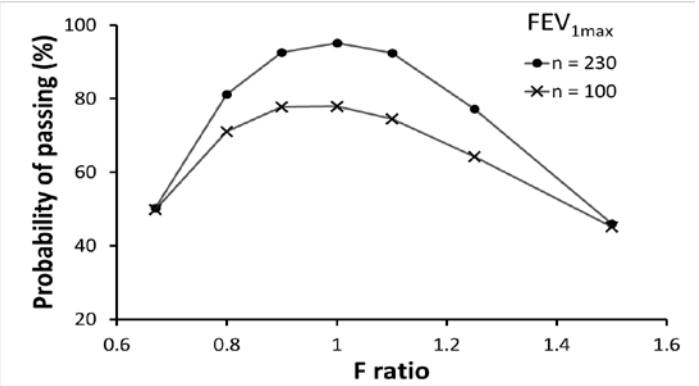
Slide courtesy of Lanyan (Lucy) Fang, Ph.D.

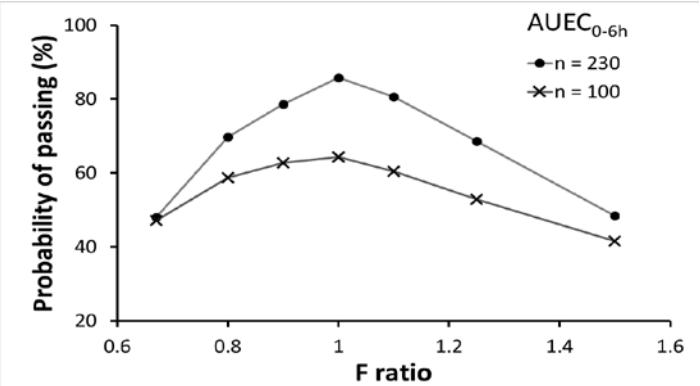
# Case example: imputation of missing $PC_{20}$ data

- Subjects receiving the maximum concentration of methacholine may not achieve 20% drop in $FEV_1$
- Imputation the "null" value using the maximum concentration of methacholine can influence the F estimation
- **Tips**:
  - The imputation of missing data should be specified in statistical analysis plan
  - The impact of missing data should be evaluated
  - NLME model is less sensitive to missing values

# Case example: issues associated with bronchodilatation studies

- High variability in response data ($FEV_{1max}$, $AUEC_{0-4h}$, $AUEC_{0-6h}$)
- Negative values in response data as a result of baseline-correction
- Depending on the study proposal and data, dose-scale approach for bronchodilatation studies may be insensitive to difference in relative bioavailability
  - Modeling and simulations




- **Tip**: A bronchoprovocation study may provide more sensitive means of demonstrating BE between a test and reference albuterol/levalbuterol MDI product.

# Closing remarks

- Dose-scale modeling is a viable approach to demonstrate PD equivalence for locally acting drug products with a nonlinear dose-response relationship
- The PSG reflects the Agency's current thinking and recommendations
- Encourage industry to
  - Submit a protocol to the FDA for evaluating prior to initiating the pivotal BE studies for orlistat oral capsule
  - Consider the conduct of a pilot study to refine the study design (e.g., inclusion and exclusion criteria) and estimate the study power based on BSV, WSV and the dose-response curve for albuterol/levalbuterol MDIs
- Discuss significant differences and/or alternative approaches with OGD
- Provide sufficient justification for alternative approaches and/or differences from PSG (e.g., BE trial simulations to compare the proposed alternative approaches to the current recommendation)

# Acknowledgements

**DQMM/ORS**

- Lanyan (Lucy) Fang, Ph.D.
- Xiajing Gong, Ph.D.
- Gab-Jin Park, M.D.
- Jia Chen, Ph.D.
- Meng Hu, Ph.D.
- Myong-Jin Kim, Pharm.D.
- Liang Zhao, Ph.D.

**DTP/ORS**

- Kimberley Witzmann, M.D.

**ORS**

- Robert Lionberger, Ph.D.

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