Regulatory Considerations on Dose-Scale Analysis in Assessing Pharmacodynamic Equivalence

Complex Generic Drug Product Development Workshop

Session 7: Quantitative Methods and Modeling-Informed Regulatory Decision Making

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Disclaimer

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Outline

- Pharmacodynamic (PD) equivalence studies
- Dose-scale analysis for PD studies
  - What it is and when to use it
  - Product-specific guidance recommendation
- Considerations and challenges
  - Model fitting methods
  - Bootstrap implementation
  - Missing data
  - Study
- Case examples

Therapeutic equivalence of generic drugs

PHARMACEUTICAL EQUIVALENCE

- Same active ingredient(s), strength, dosage form, route of administration

BIOEQUIVALENCE (BE)

- No significant difference in the rate and extent of absorption at the site of action

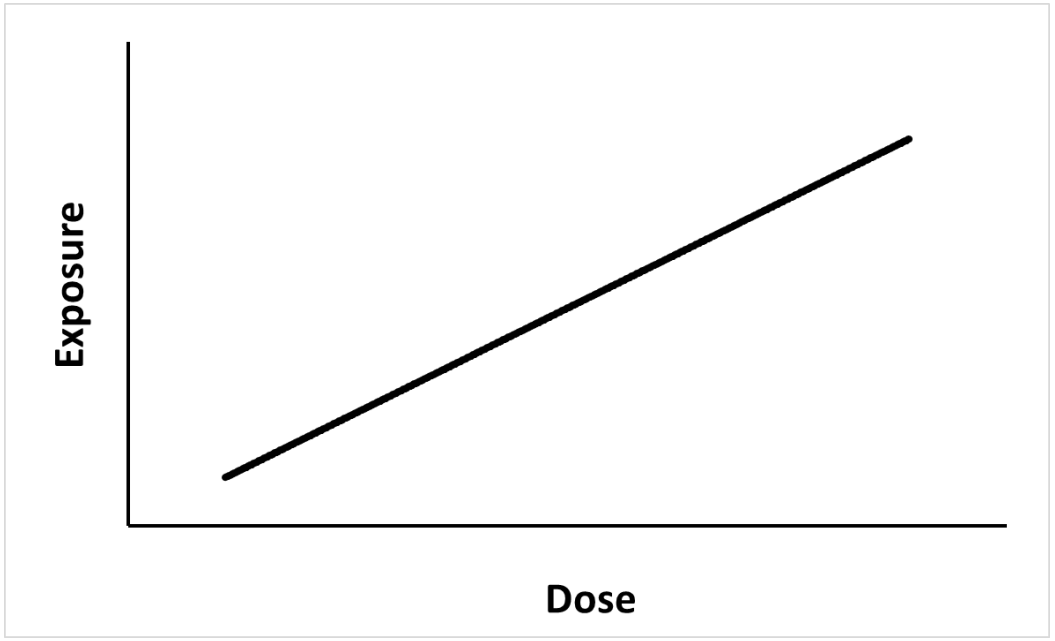
- in vitro BE studies
- comparative PK BE studies
- comparative PD studies
- comparative clinical endpoint studies

PK: pharmacokinetics

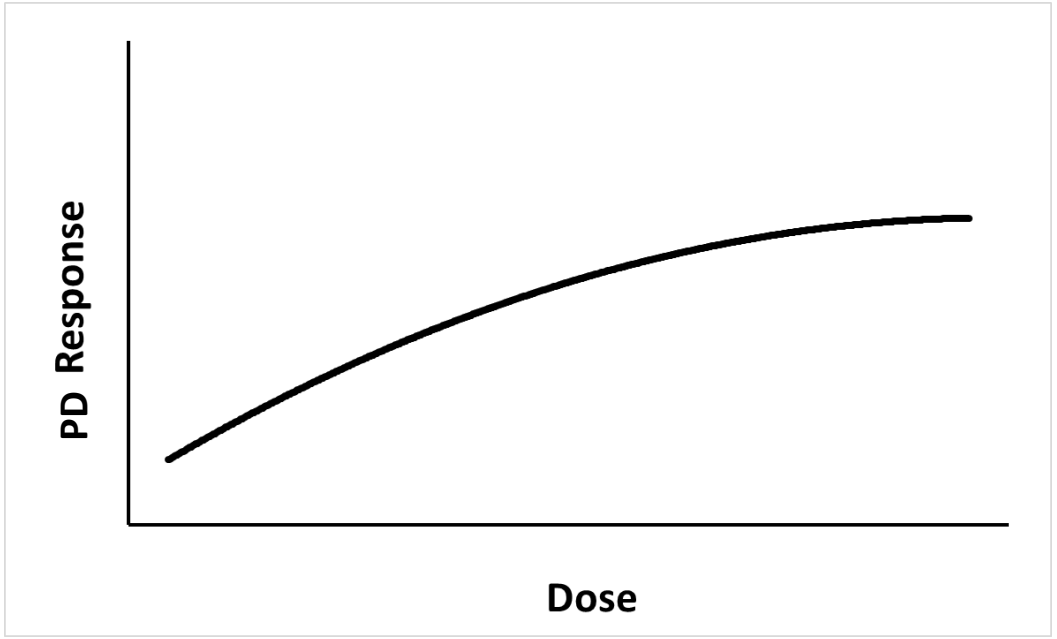
PD studies recommended in product-specific guidance (PSG)

- Oral inhalation drug products
  - Short-acting beta2 agonist (e.g., albuterol sulfate)
  - Long-acting beta2 agonist (e.g., salmeterol xinafoate)
  - Corticosteroids (e.g., ciclesonide)
- Locally acting gastrointestinal (GI) drug products
  e.g., orlistat, acarbose
- Topical corticosteroid
- Low molecular weight heparin injectables

BE based on PK or PD endpoints



- Exposure is proportional to dose
- No exposure for placebo (or baseline correction)
- 90% CI around exposure ratio can be used for BE



- Nonlinear dose-response: response does not increase proportionally with dose
- Placebo effect can be large
- 90% CI around PD response ratio often should not be used for BE

Courtesy slide from Dr. Lanyan (Lucy) Fang

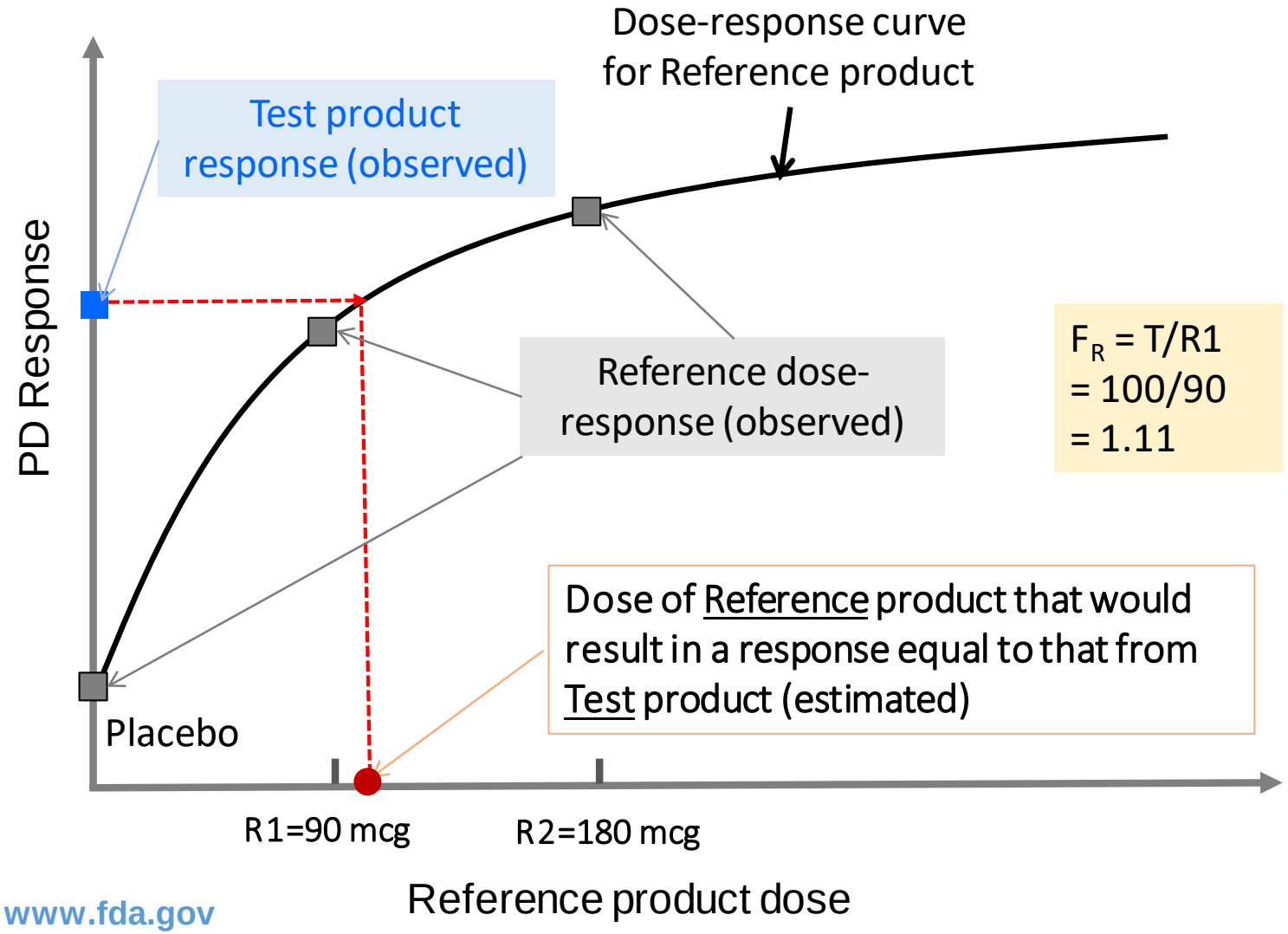
Orlistat capsule

- Intestinal lipase inhibitor
- Systemic absorption of orlistat is negligible
- Comparative clinical endpoint (e.g., weight loss) study is lengthy
- Nonlinear dose-PD response
  PD response (fecal fat excretion) plateaus at higher doses

Albuterol sulfate MDI

- Drug is delivered to the lung where bronchodilator effect occurs
- Limited relevance of systemic exposure to the amount of drug delivery to the site of action
- Nonlinear dose-PD response
  from bronchoprovocation or bronchodilatation study

Dose-scale analysis

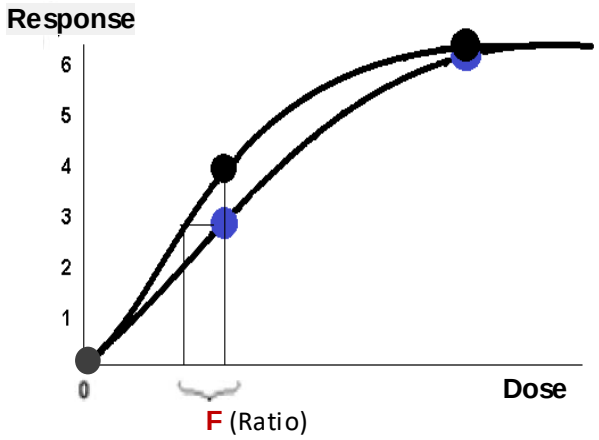


Allow the assessment of relative bioavailability on dose scale, not original scale of PD response

Suggest equivalence of the amount of drug reaching the site of action

Dose-scale analysis: E_{max} model fitting

Fitted curves for T or R using Emax model



Method 1

one dose level of Test

1) Using **Reference** data to fit Emax model, estimate E0R, EmaxR, and ED50R

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

2) Using **Test** data to estimate F

$$\phi_R^{-1}(E_T) = \frac{(E_T - E_{0R}) * ED_{50R}}{E_{max\ R} - (E_T - E_{0R})}$$

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

Method 2

two dose levels of Test

Simultaneously fit **Reference** and **Test**

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

(Ref: $i = 0$; Test: $i = 1$)

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Orlistat_cap_21887_20766_RC2-10.pdf

Dose-scale analysis: calculating 90% CI for F

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

PD BE studies with dose-scale analysis

When to use it?

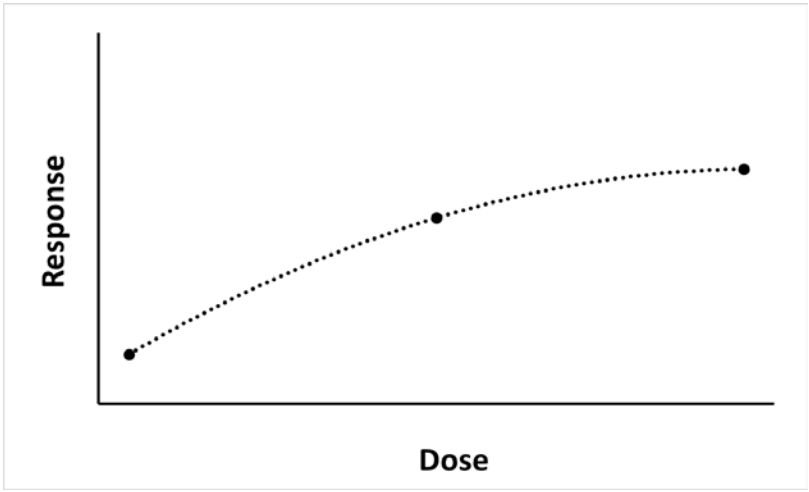
Product	 Orlistat oral capsule	 Albuterol/Levalbuterol MDIs	
Study	Fecal fat excretion study	Bronchoprovocation study [a]	Bronchodilatation study
Design	Multiple-dose, crossover study in healthy subjects	Single-dose, double-blind, double dummy, randomized, crossover study in subjects with asthma	
Treatment arm	• Baseline • Reference: 2 dose levels • Test: at least 1 dose		
Endpoint	% fecal fat excretion (FFE) [b]	post-dose PC_{20} or PD_{20} [c]	$FEV1_{max}$, $AUEC_{0-4h}$, $AUEC_{0-6h}$ [d]
90% CI of F	80.00-125.00%	67.00-150.00%	

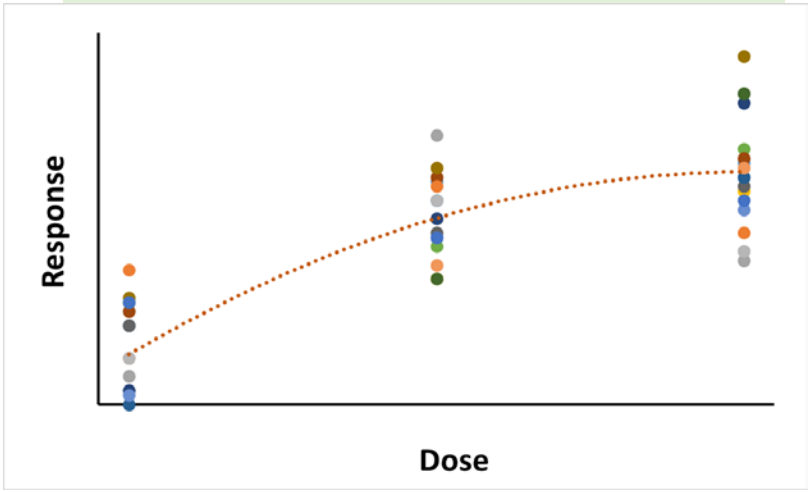
a. Bio-IND is required prior to conduct of the bronchoprovocation study
b. expressed as a ratio of the amount of fat excretion over a 24-h period at steady-state relative to the amount of daily ingested fat
c. dose or concentration of methacholine required to reduce forced expiratory volume in one second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

Adapted from courtesy slide of Dr. Zhichuan (Matt) Li

E_{max} model fitting: available statistical methods

Naïve average data (NAD)	Naïve pooled data (NPD)	Nonlinear mixed effect modeling (NLME)





- Mean data → one data point per dose for each formulation
- Data from all individuals pooled as if coming from one single individual
- All individual data

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

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

$$E_{0,i} = E_0 + \eta_i$$

$$Y_{obs,i,j} = E_{0,i} + \frac{E_{max} * Dose * Fi}{ED_{50} + Dose * Fi} + \varepsilon_{i,j}$$

E_{max} model fitting: available statistical methods

NLME

- Characterize between-subject variability (BSV) and residual unexplained variability (RUV)
- Handle rich or sparse data with missing value

✓ Routinely used for E_{max} model fitting

NAD

- Actively reduces available observation
- No direct estimate of variability
- Biased if BSV is large
- Potential bias if individuals have different amount of data, or aberrant observation

NPD

- Preferable to NAD approach
- Biased if BSV is large
- Potential bias as data coming from non-standard designs can be pooled together

Calculating of 90% CI for F: bootstrap sample

Various ways to generating "sample dose-response dataset" for crossover study with multiple dose-response observations per subject

Original data

Subj 1	P	R1	R2	T
Subj 2	P	R1	R2	T
Subj 3	P	R1	R2	T

Resample observations

P	R1	R2	T
P	R1	R2	T
P	R1	R2	T

Resample subjects but Reference data only

P	R1	R2	T
P	R1	R2	T
P	R1	R2	T

Resample subjects

Subj 2	P	R1	R2	T
Subj 1	P	R1	R2	T
Subj 1	P	R1	R2	T

✓ Bootstrap sampling unit should be the ***subject*** (remaining all the data from T and R), in order to maintain the correlation of observations within subject

Practical Considerations

Fitting E_{max} model

- NLME approach is preferred
  - Incorporates BSV, less sensitive to aberrant observation
  - NLME has been routinely used in ANDA submission and assessment
- Modeling software: NONMEM, SAS, R, etc.
  - Results are generally consistent with the same model structure and parameter settings

Computing 90% CI of F

- Resample original dose-response observations at subject level
- Minimum of 1000 bootstraps are typically needed
- Recommend following the bootstrap procedure in the PSG
- Prespecify modeling software and computation method for 90% CI

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)
- Missing mechanism
  - Missing completely at random (MCAR)
    e.g., dropout due to relocation
  - Missing at random (MAR)
    e.g., technique or equipment issues (unrelated to treatment)
  - Missing not at random (MNAR)
    e.g., discontinuation of a treatment due to adverse reaction

- Almost impossible to justify whether these missing data are truly MCAR or MAR due to potential confounds
- Crossover study design can be sensitive to missing data
- 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

Courtesy slide from Dr. Lanyan (Lucy) Fang

Case Example

Impact of missing PC_{20} data on F estimation

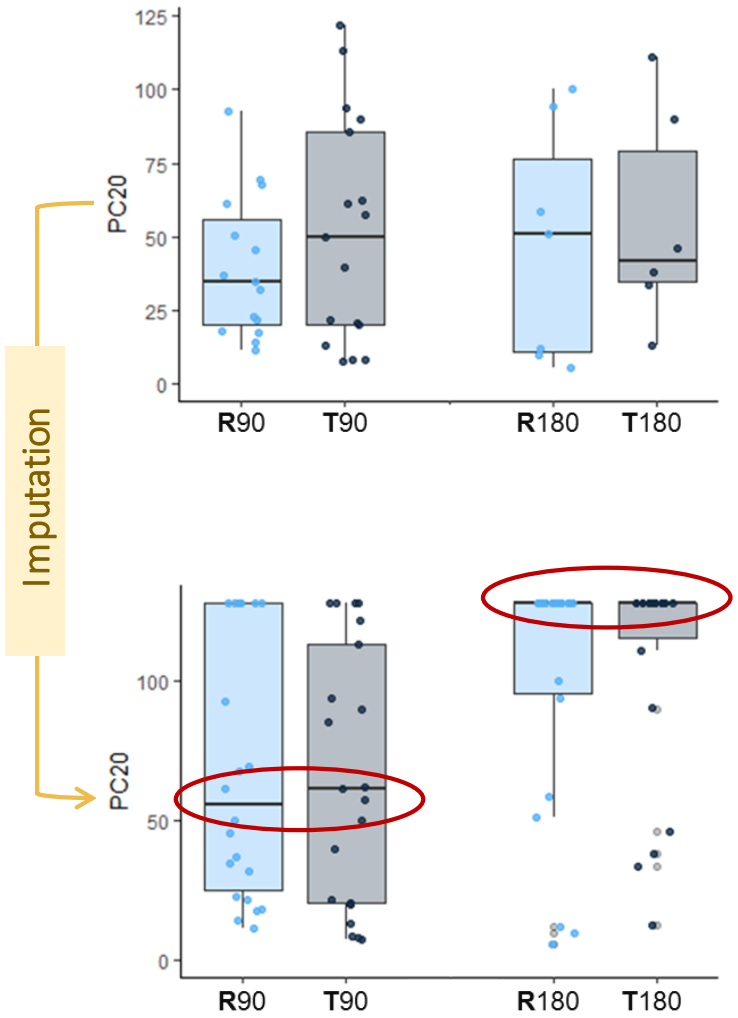
F	Modeling	MAR		MNAR	
		P.E.	90% CI	P.E.	90% CI
0.96	NAD	0.99	(0.73, 1.28)	1.14	(0.81, 1.84)
	NLME	0.99	(0.77, 1.24)	1.05	(0.78, 1.40)
0.80	NAD	0.91	(0.64, 1.11)	0.93	(0.70, 1.31)
	NLME	0.83	(0.61, 1.07)	0.88	(0.64, 1.09)

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

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

Courtesy slide from Dr. Lanyan (Lucy) Fang

Case Example Impact of PC_{20} data imputation



Subjects receiving maximum concentration of methacholine may not achieve 20% drop in FEV1

Example: imputation the unmeasurable value using the maximum concentration of methacholine at both T and R treatment arms

→ decreases PC_{20} difference between T and R

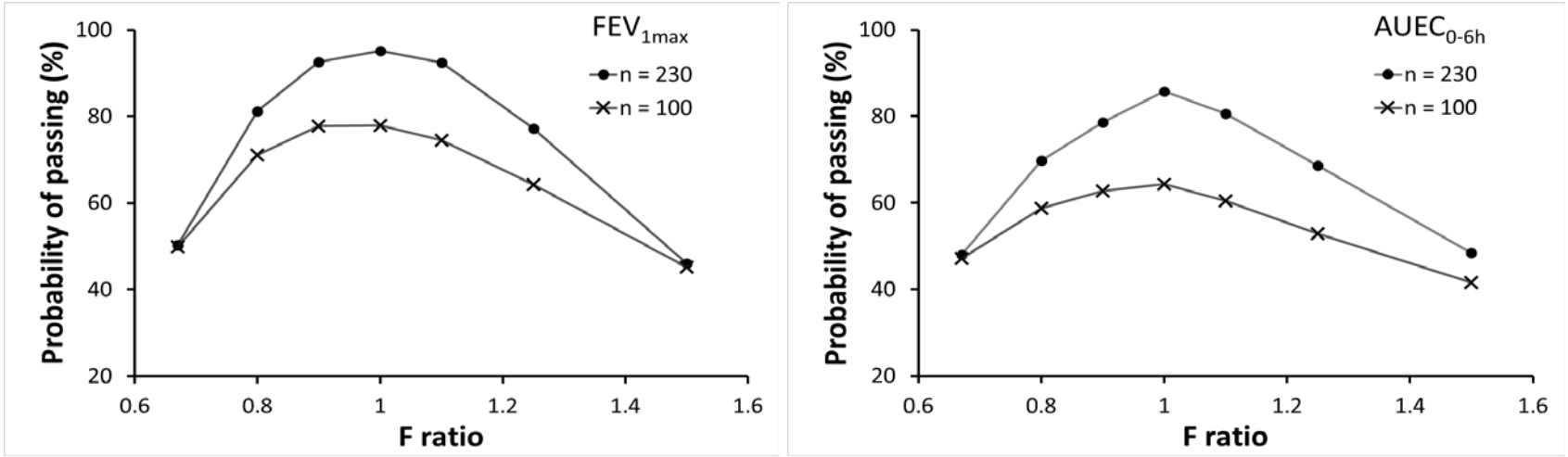
→ potentially bias the BE evaluation

✓ Specify imputation strategy in statistical analysis plan, supported by justification

✓ Evaluate whether the chosen imputation is valid and sensitive in detecting product differences

Issues associated with bronchodilatation study

- 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



✓ A bronchoprovocation study may provide more sensitive means of demonstrating BE between a test and reference albuterol/levalbuterol MDI product

Courtesy slide from Dr. Zhichuan (Matt) Li

Summary

- Utility of the dose-scale analysis 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
- Towards reliable dose-scale analysis:

  Study: appropriate planning, pilot study

  Data: state how missing data will be handled in protocol

  Model: provide sufficient justification for alternative approaches that are not in the PSG (e.g., using BE trial simulations)
- Applicants are encouraged to discuss significant differences or alternative approaches with OGD

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