Dose Scale Analysis to Support Bioequivalence Assessment

Statistical Approaches to Establishing Bioequivalence Draft Guidance

March 14, 2023

Meng Hu, PhD

Division of Quantitative Methods and Modeling,
Office of Research and Standards
OGD | CDER | U.S. FDA

Disclaimer

This presentation reflects the views of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration

Outline

- Pharmacodynamic (PD) equivalence studies
- Dose-scale analysis for PD studies
  - What it is and when to use it
  - Recommendations
- Considerations and challenges
  - Model fitting methods
  - Bootstrap implementation

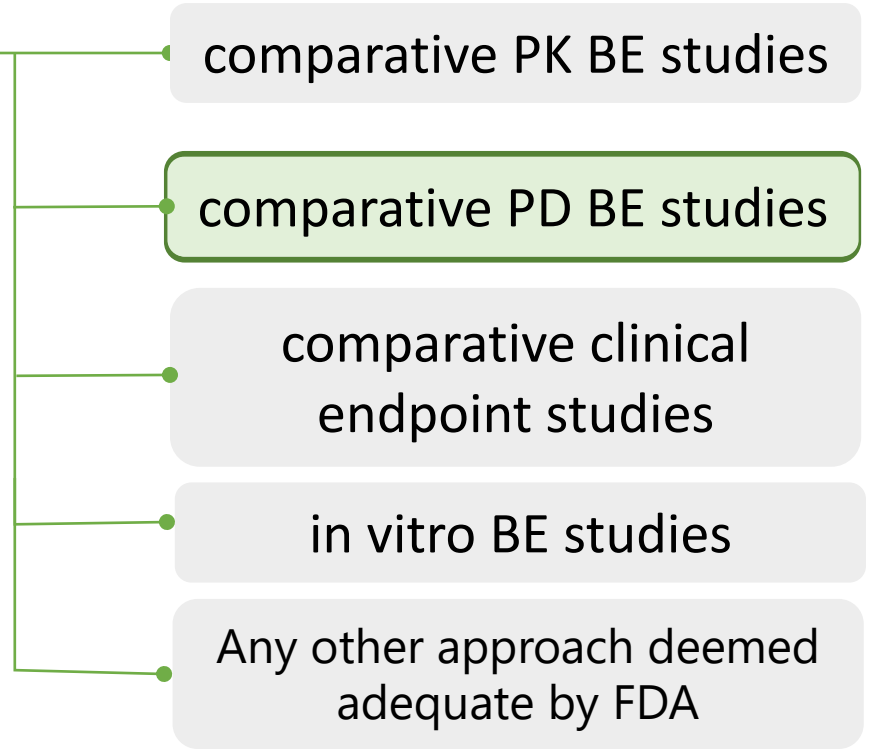
Therapeutic equivalence of generic drugs

PHARMACEUTICAL EQUIVALENCE

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

BIOEQUIVALENCE (BE)

- No significant difference in the rate and extent of absorption

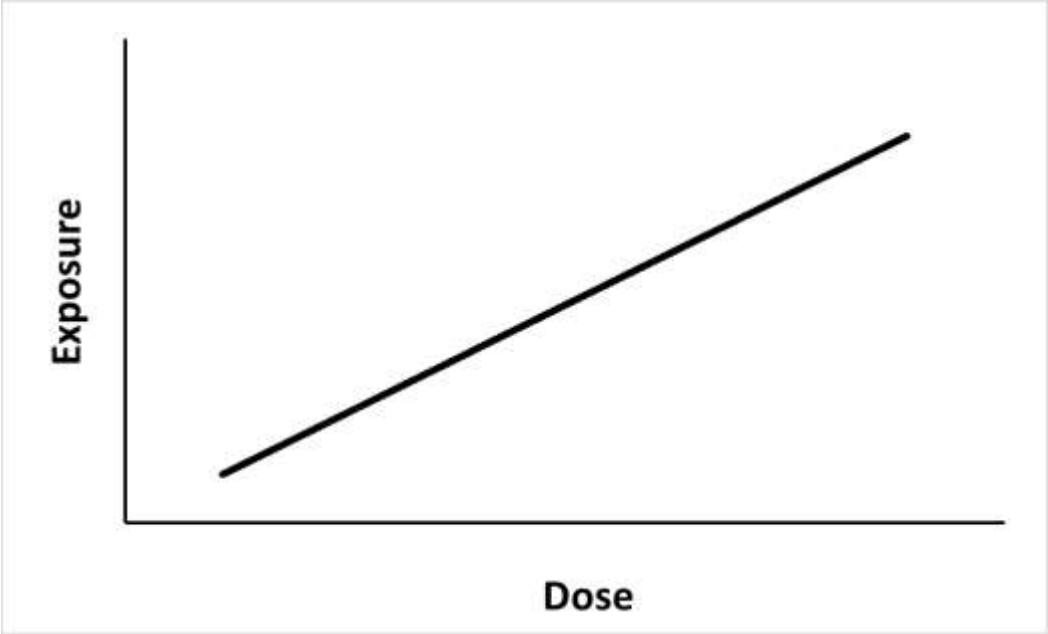


PK: pharmacokinetics

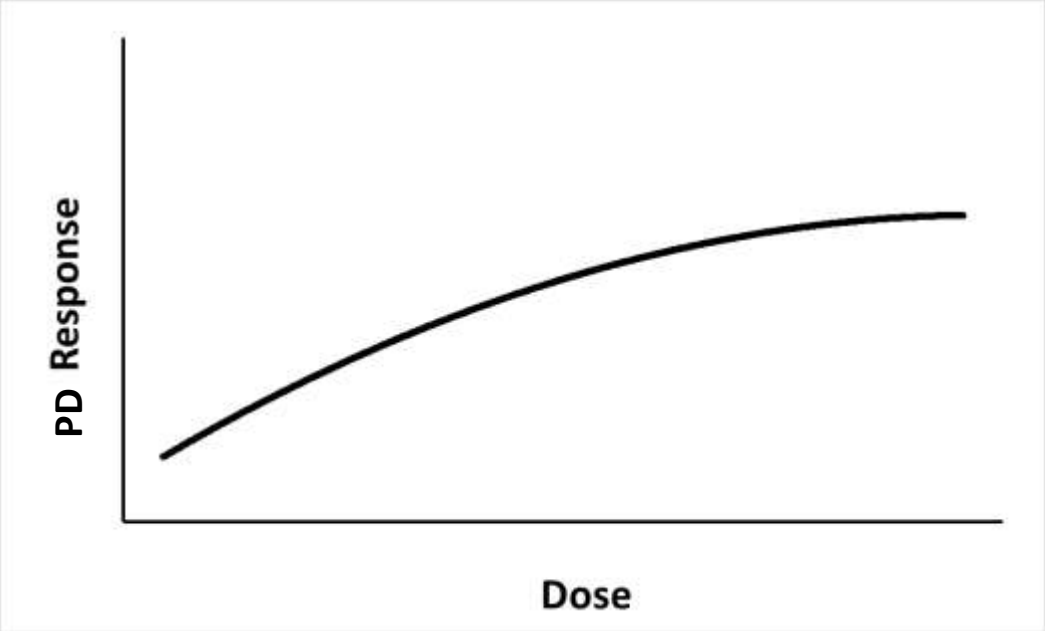
PD studies recommended in product-specific guidance (PSG)

- Oral inhalation drug products
  e.g., albuterol sulfate
- Locally acting gastrointestinal (GI) drug products
  e.g., orlistat, acarbose
- Topical corticosteroid

BE based on PK or PD endpoints

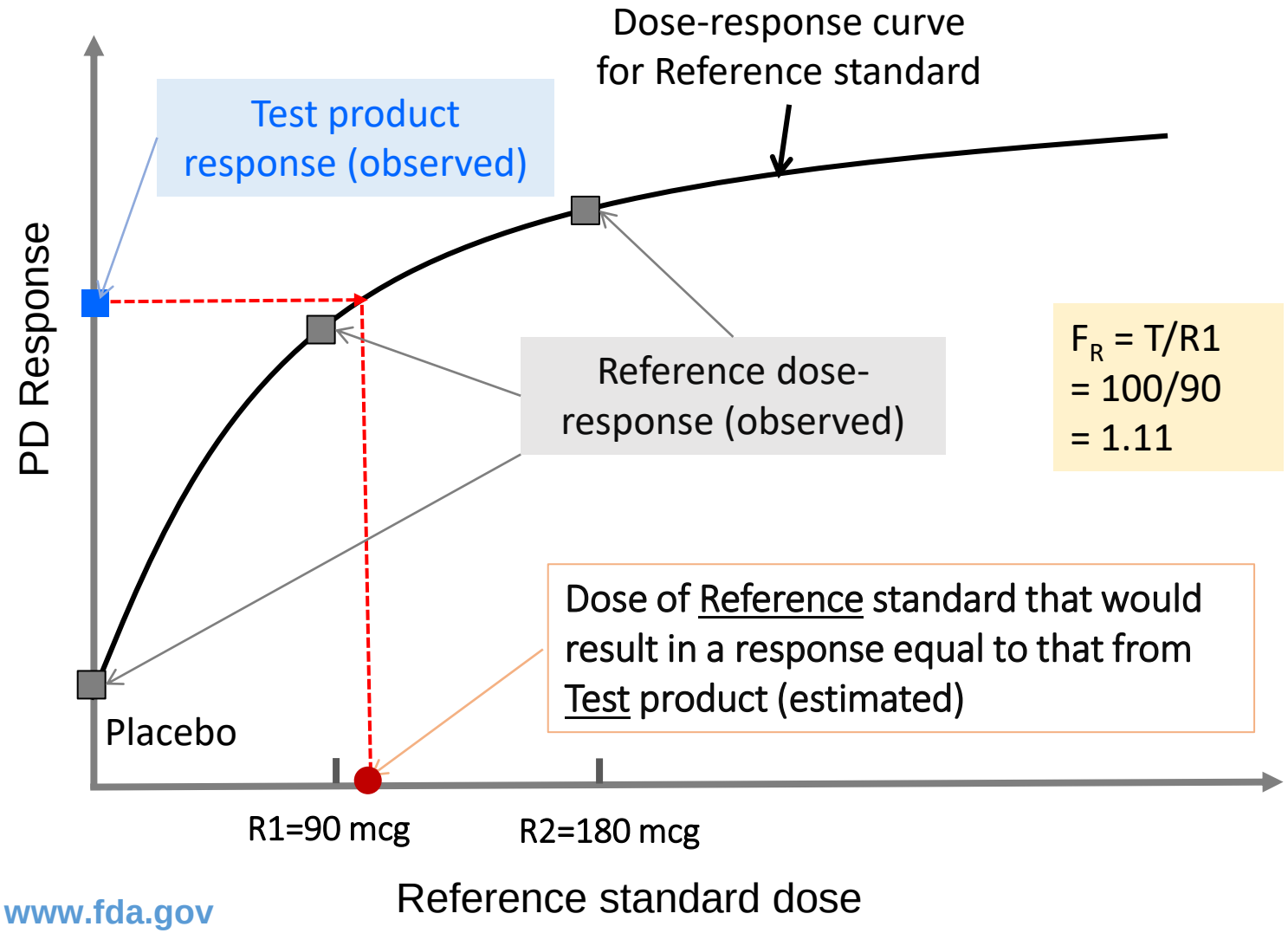


- Exposure is proportional to dose
- No exposure for placebo (or baseline correction)
- 90% CI around exposure ratio can be used for BE



- **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

Dose-scale analysis

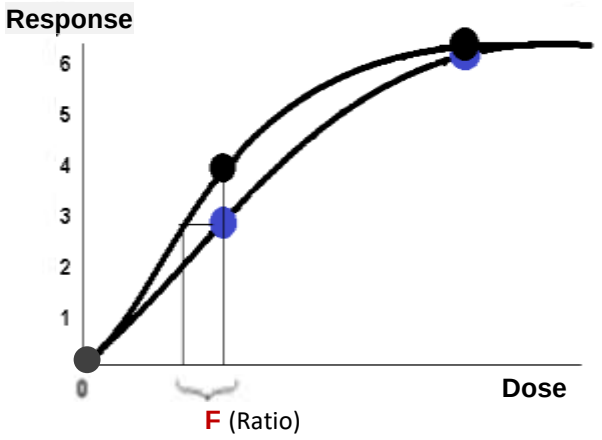


Allow the assessment of relative bioavailability on dose scale, not original scale of PD response

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

Dose-scale analysis: E_{max} model

Fitted curves for T or R using Emax model



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

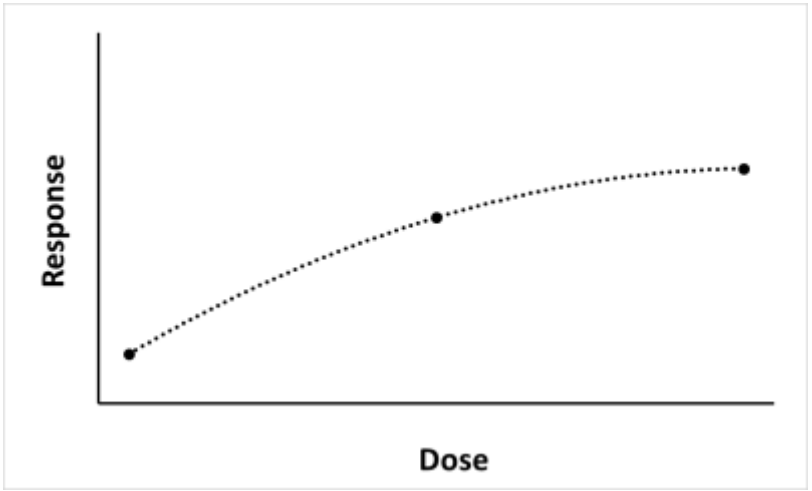
(Ref: $i = 0$; Test: $i = 1$)

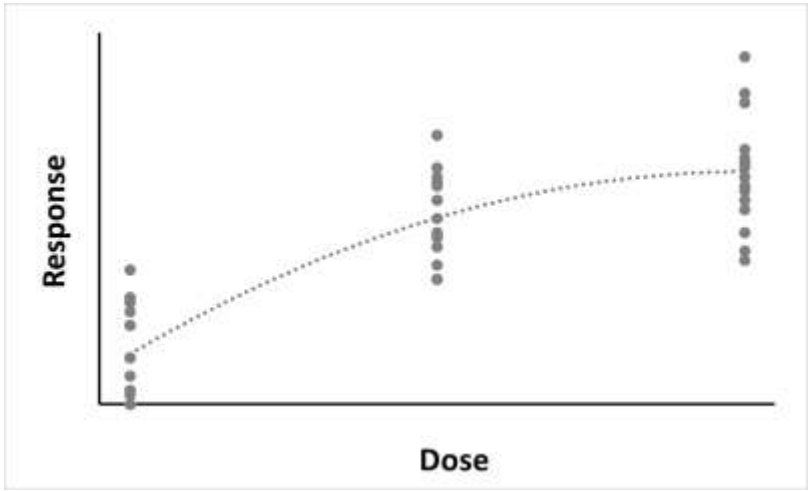
Where y = Response, Dose = Administered dose, E_0 = Baseline response in the absence of the drug, E_{max} = Fitted maximum drug effect, ED_{50} = Dose required to produce 50% the fitted maximum effect, and i = Treatment indicator (0 = Ref, 1 = Test), with the understanding that $F^0 = 1$ and that F^1 is the relative potency used to evaluate bioequivalence.

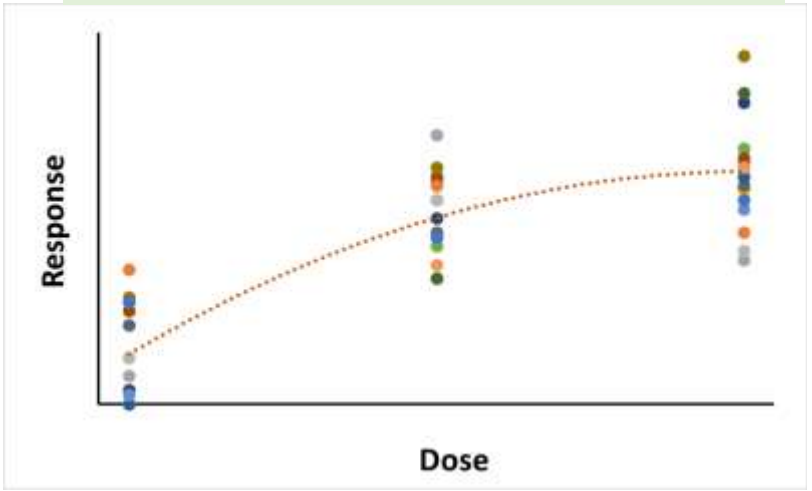
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020766.pdf

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

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

- Data from all individuals pooled as if coming from one single individual

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

- All individual data

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

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

E_{max} model fitting: available statistical methods

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

BSV = between subject variability

NLME

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

✓ **Recommended for E_{max} model fitting**

Calculating 90% CI for F

Directly from NLME	Bootstrap procedure
• Directly from the point estimate of logF and its standard error calculated using NLME modeling	• 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

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 using bootstrap

- 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

Summary

- The dose-scale analysis has been used to demonstrate PD equivalence for locally acting drug products with a nonlinear dose-response relationship
- When finalized, the guidance will reflect 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 guidance (e.g., using BE trial simulations)
- Applicants are encouraged to discuss significant differences or alternative approaches with OGD


FDA
U.S. FOOD & DRUG
ADMINISTRATION