

Dose-Response and Related Mathematical Considerations

International Conference
*European Equivalence Considerations for Orally
Inhaled Products (OIPs) for Local Action*
(Frankfurt, Germany, 12-14 October 2010)

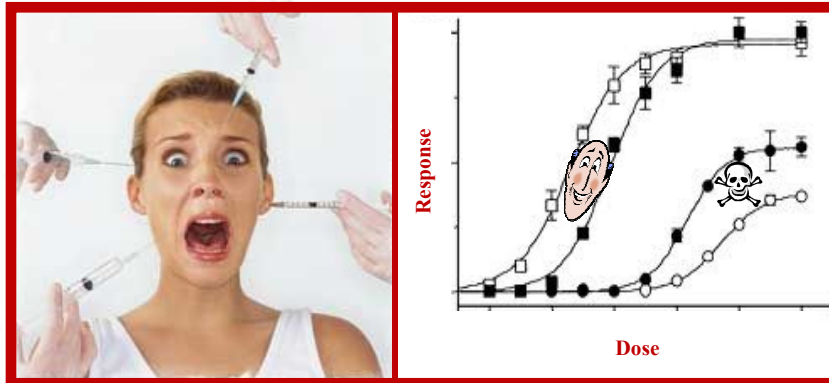
Gur Jai Pal Singh, Ph.D.
Axar Pharmaceuticals, Irvine, California

*This presentation represents the personal opinions of the speaker and does not reflect the views
of any regulatory agency or the organizations of the speaker's past or current affiliations*

Outline

- **Relevant Fundamentals**
- **Regulatory Considerations**
- **What Constitutes Acceptable Dose-Response?**
- **Types of Dose-Response Relationships and Related
Mathematical Considerations**
- **Dose-Response Dependency on the In Vivo Model**
- **Implications for Determination of Bioequivalence(BE)
of OIPs:“Response” versus “Dose” Scale Evaluation**
- **Mathematical Underpinning of the “Dose Scale”
Evaluation of Equivalence in Local Delivery**

Relevant Fundamentals



3

GJPS 12 October 2010

Relevant Fundamentals (Definitions)

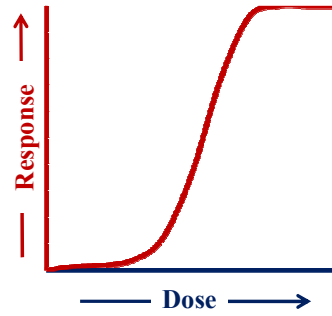
- **Dose**
 - Drug input to the body or a biological system
- **Response**
 - A direct measure of the pharmacologic effect of the drug, based on a variety of clinically relevant endpoints/biomarkers or clinical effects related to either efficacy or safety

4

GJPS 12 October 2010

Relevant Fundamentals (Pharmacological Considerations)

- Response originates from drug –receptor interactions
- Absence of (or baseline) response in the absence of drug
- Increase in response with increase in dose over certain range
- Plateau beyond certain dose levels due to finite number of receptors – existence of maximum effect



5

GJPS 12 October 2010

Relevant Fundamentals (Factors Affecting Dose-Response)

- **Disease severity**
- ***In vivo* model**
 - Pharmacodynamic/clinical measure(s) of activity
- **Dose range**
- **Dosing interval**
- **Variability in the observed response**
 - **Intrinsic variability**
 - **Experimental variability**
 - **Within-site**
 - Within-operator (inter-occasion WRT dose administration and response measurements)
 - Between operators
 - **Between sites**
 - The above within-site + between-site differences in quality/precision

6

GJPS 12 October 2010

Regulatory Considerations



7

GJPS 12 October 2010

Regulatory Considerations (Dose-Response in Determination of BE)

➤ EMEA 2009

Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma In Children and Adolescents.

➤ US FDA 1994

In vivo bioequivalence of albuterol inhalation aerosols
(*Withdrawn*)

➤ Health Canada 1999

Guidance to Establish Equivalence or Relative Potency of Safety and Efficacy of a Second Entry Short-acting Beta₂-agonist Metered Dose Inhaler

8

GJPS 12 October 2010

Regulatory Considerations (Dose-Response in Determination of BE)

➤ EMEA 2009

- **A minimum requirement is for the study to have assay sensitivity**
 - Ability of a clinical trial to distinguish an effective treatment from a less effective treatment or ineffective treatment.
- **At least two non-zero doses; one dose level needs to be shown to be superior to the other.**
- **It is essential that doses on *the steep part of the dose response curve* are studied.**
- **For ICS: A successful efficacy equivalence study requires demonstration of**
 - **A *significant dose response relationship*** with the study of at least two doses of the test compared with two doses of the reference product.
 - The doses studied should be on *the steep part* of the dose response curve

9

GJPS 12 October 2010

Regulatory Considerations (Dose-Response in Determination of BE)

➤ FDA 1994: Dose response demonstration - as an Inclusion Criterion [Section IV(B)(8)] for Bronchoprovocation Studies

“One and two actuations of the listed reference drug dosed on separate days. Subjects be randomly assigned to one of two sequences: Ventolin[®], 2 actuations; Ventolin[®] 1 actuation or Ventolin[®] 1 actuation; Ventolin[®], 2 actuations.

A minimum two-fold ratio of response to two actuations relative to one actuation of Ventolin[®] Inhalation Aerosol”

$$\frac{PC_{20} \text{ or } PD_{20} \text{ of Ventolin, 2 actuations}}{PC_{20} \text{ or } PD_{20} \text{ of Ventolin, 1 actuation}} \geq 2.0$$

10

GJPS 12 October 2010

Regulatory Considerations (Dose-Response in Determination of BE)

➤ Health Canada 1999

- Measurement of the magnitude and duration of effect of 1 and 2 puffs for each of the test and reference products.
- Relative potency estimated from a 4 point parallel line assay (2 formulations at 2 doses) within a 4 sequence, 4 period crossover design.

$$R = (\text{form}_t - \text{form}_s) / b$$

where

R is the estimate of log(relative potency),

form_t is the estimated overall form effect due to the test formulation,

form_s is the estimated overall form effect due to the standard formulation, and

b is the estimate of the overall common *slope*

11

GJPS 12 October 2010

What Constitutes Acceptable Dose-Response?



12

GJPS 12 October 2010

Acceptable Dose-Response?

- **Significant difference in response**
 - Between the placebo (zero dose) and active (1 actuation)
 - Between 1 and 2 actuations of active, or 1 and 3 actuations
 - Does significant mean statistically significant?
- **Slope**
 - Positive (Upward)
 - Steepness
 - Statistically significant?
- **A ratio of responses to 2 and 1 actuation determined *a priori***

13

GJPS 12 October 2010

Acceptable Dose-Response (Regulatory Stipulations)

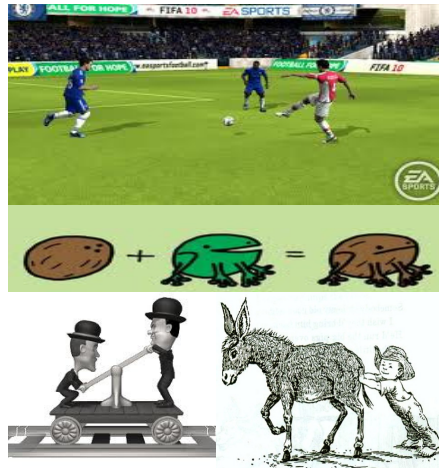
- **ICH TRIPARTITE GUIDELINE - 1994**
Dose-Response Information to Support Drug Registration (E4)
- **FDA 2003 :Guidance for Industry: Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications.**
 - A *positive slope* provides evidence of a drug effect.
 - Ability to detect *a statistically significant difference in pairwise comparisons between doses is not necessary* if a *statistically significant trend (upward slope)* across doses can be established using all the data.
 - Population (group)-average dose-response vs. individual dose-response relationships.
- **EMA 2009 Guideline**
 - Significant dose response relationship
 - Doses on the steep part of the dose response curve – “convincing evidence” of this will be required”



14

GJPS 12 October 2010

Types of Dose-Response Relationships and Related Mathematical Considerations



15

GJPS 12 October 2010

Dose-Response Relationship (Mathematical Consideration)

➤ Simple Linear Relationship

- (i) $E = D \cdot S$, or
- (ii) $E = E_0 + D \cdot S$ or $E - E_0 = D \cdot S$

Where:

“E” is intensity of effect

“D” is dose and

“S” is a slope parameter

“E₀” is the effect without drug



**Dose not allow
determination of
maximum effect**

16

GJPS 12 October 2010

Dose-Response Relationship (Mathematical Consideration)

➤ Log-linear relationship

$$E = \text{Log } D \cdot S + I$$

Where:

“E”, “D” and “S” are same as in
the previous slide
“I” is a constant



Dose not allow determination of
(i) E when D is zero, and
(ii) maximum effect



17

GJPS 12 October 2010

Dose Response Relationships (Mathematical Consideration)

➤ Curvilinear Relationship

➤ The “Emax” Model

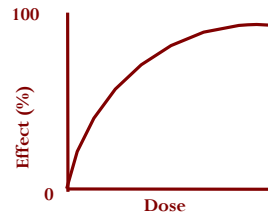
$$E = \frac{E_{\text{max}} \cdot \text{Dose}}{\text{Dose} + ED_{50}}$$

Where:

E = Pharmacodynamic effect

E_{max} = Maximum fitted value of “E”,

ED_{50} = Dose required to achieve 50% of the E_{max} value



- Predicts the maximum achievable effect.
- Estimates no effect in the absence of drug.
- Conforms to simple theories, relating dose or concentration to receptor binding and the observed effect.

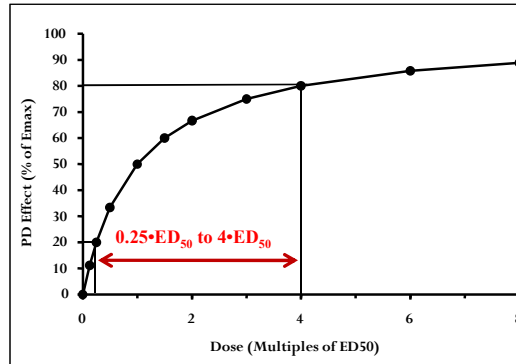


18

GJPS 12 October 2010

Sensitive Region of the Dose Response Curve (Mathematical Consideration)

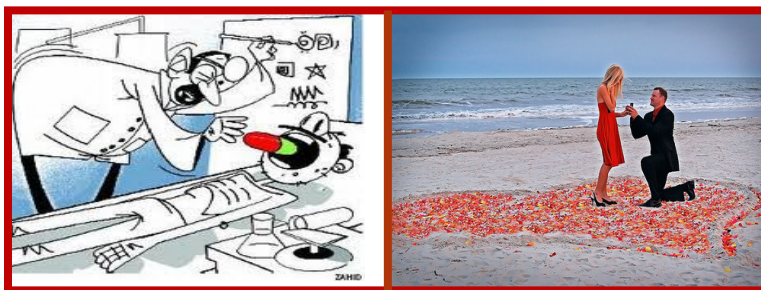
Multiples Of ED_{50}	PD Effect (% of E_{max})
0	0
0.125	11.1
0.25	20.0
0.5	33.3
1	50.0
1.5	60.0
2	66.7
3	75.0
4	80.0
6	85.7
8	88.9
16	94.1



19

GJPS 12 October 2010

Dose-Response Dependency on the In Vivo Model

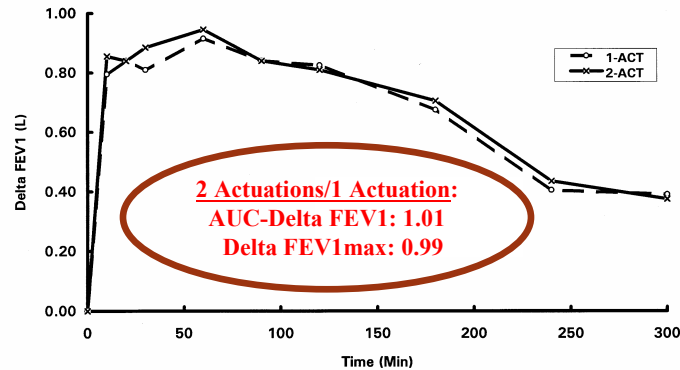


20

GJPS 12 October 2010

DR Dependency on the In Vivo Model

- In 1989 the Office of Generic Drugs (US FDA) Issued a guidance “*In Vivo Bioequivalence Studies of Metaproterenol Sulfate and Albuterol Inhalation Aerosols(Metered Dose Inhalers)*”



21

GJPS 12 October 2010

DR Dependency on the In Vivo Model (FDA Exploratory Pilot Studies of Albuterol Dose-Response)*

➤ Study 1

- **Design:** Single Dose/Separate Days, Bronchodilation, N = 10
- **Treatments:** Placebo 1, 2 and 4 actuations, Active: 9 – 576 µg.
- Measure:** FEV₁ at 0, 15, 30, 45 60 min ... 3 hrs

➤ Study 2

- **Design:** Cumulative Dose/Single Day, Bronchodilation, N = 10
- **Treatments:** Active: 9 – 576 µg (Cumulative) . **Measure:** FEV₁

➤ Study 3

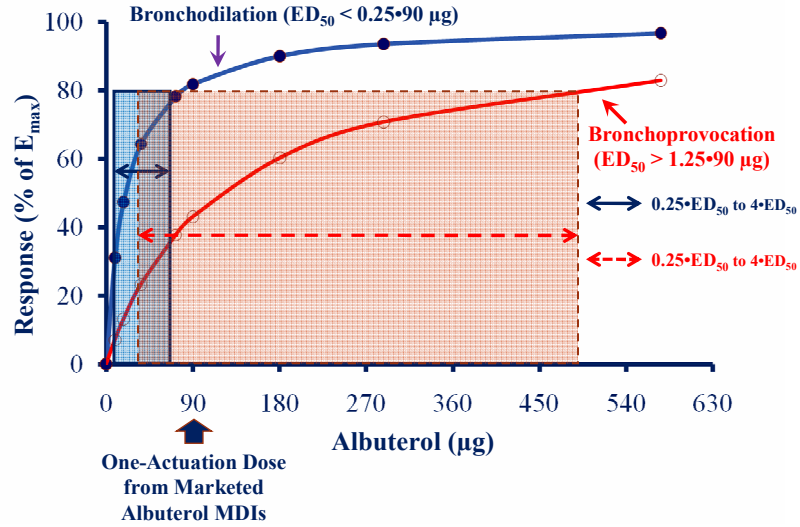
- **Design:** Cumulative Dose/Single Day, Methacholine Challenge N = 15
- **Treatments:** Placebo 1, 2 and 4 actuations, Active: 9 – 576 µg.
- Measure:** PD₂₀
- **Results Published** (*J. Allergy Clin. Immunol.* 2002;110:713-20.)

22

*For study details, see *Drug Information Journal* 1995;29:935-40

GJPS 12 October 2010

DR Dependency on the In Vivo Model (FDA Exploratory Pilot Studies of Albuterol Dose Response)



23

DR Dependency on the In Vivo Model Inhaled Corticosteroids(Flovent-HFA*)

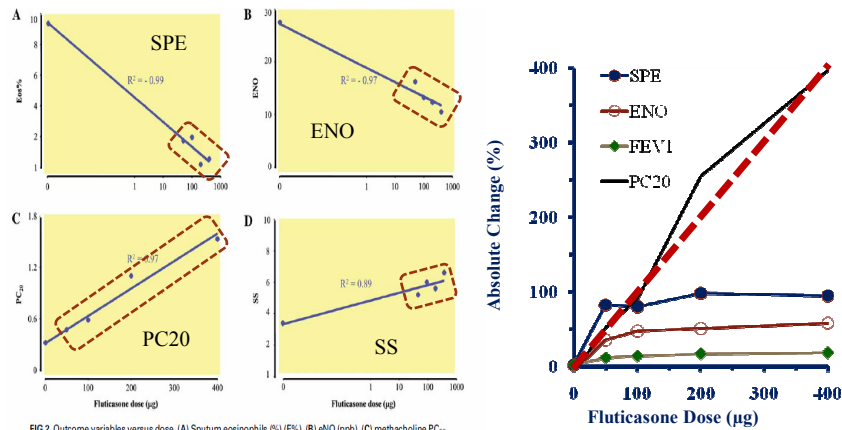


FIG 2. Outcome variables versus dose. (A) Sputum eosinophils (%), (B) eNO (ppb), (C) methacholine PC₂₀ (mg/mL; expressed as geometric mean), and (D) symptom score (SS).

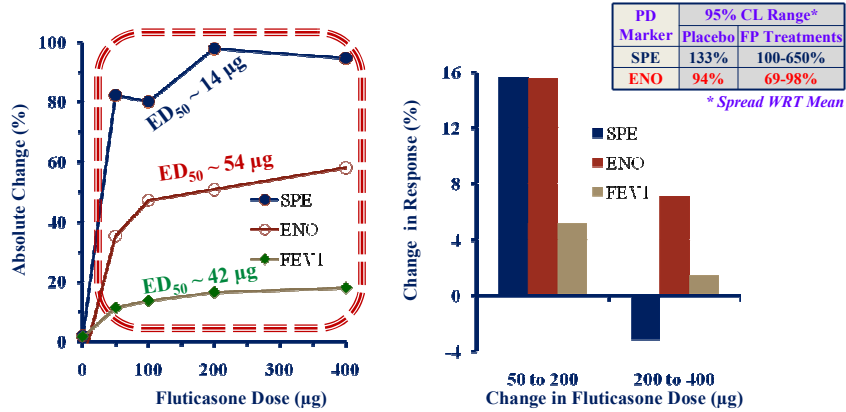
**J. Allergy Clin. Immunol.* 2006;117:989-94

SPE = Sputum Eosinophils, ENO = Exhaled Nitric Oxide, SS= Symptom Scores

24

GJPS 12 October 2010

DR Dependency on the In Vivo Model Inhaled Corticosteroids(Flovent-HFA*)

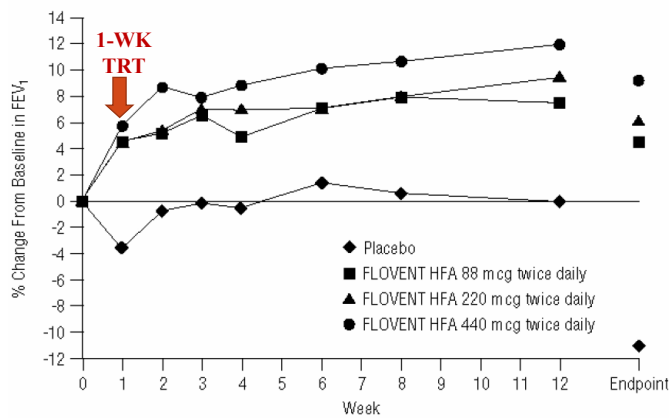


SPE = Sputum eosinophils ENO = Exhaled Nitric Oxide
 *Data based on *J Allergy Clin Immunol* 2006;117:989-94

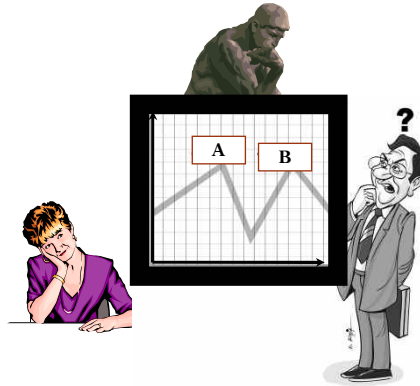
Flovent-HFA Dose Response

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021433s0111bl.pdf

Figure 2. A 12-Week Clinical Trial in Patients ≥12 Years of Age Already Receiving Daily Inhaled Corticosteroids: Mean Percent Change From Baseline in FEV₁ Prior to AM Dose (Study 2)



Implications for Determination of Bioequivalence (BE) of OIPs: "Response" versus "Dose" Scale Evaluation of BE

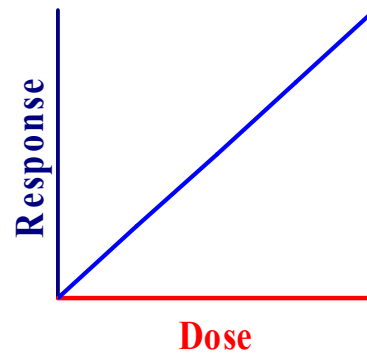


27

GJPS 12 October 2010

Assessment of Bioequivalence

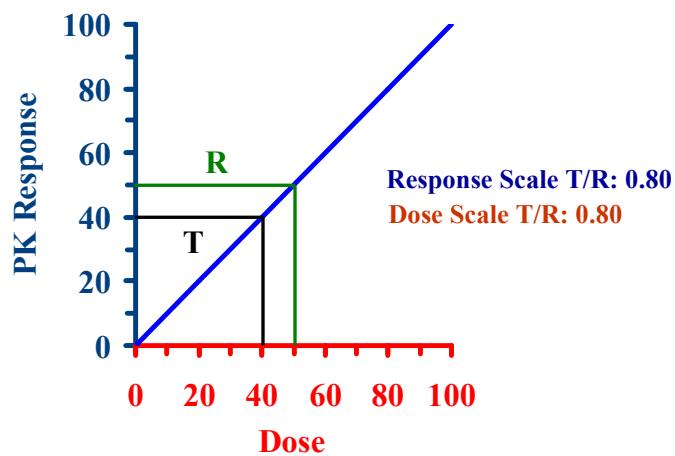
Based on:
"Response Scale"
or
"Dose Scale"



28

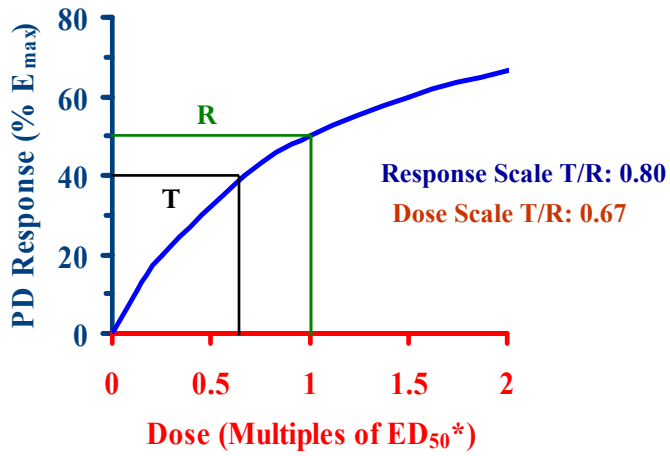
GJPS 12 October 2010

Pharmacokinetic Studies



Pharmacodynamic Studies

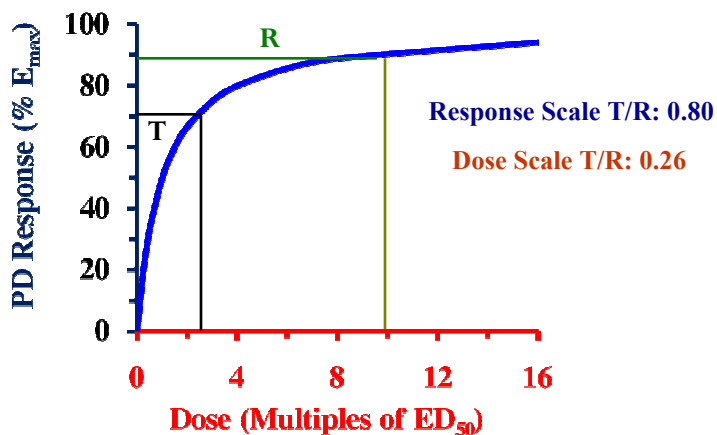
Reference Product Dose = ED_{50}



* Dose required to produce 50% of the maximum achievable effect

Pharmacodynamic Studies

Reference Product Dose $>ED_{50}$

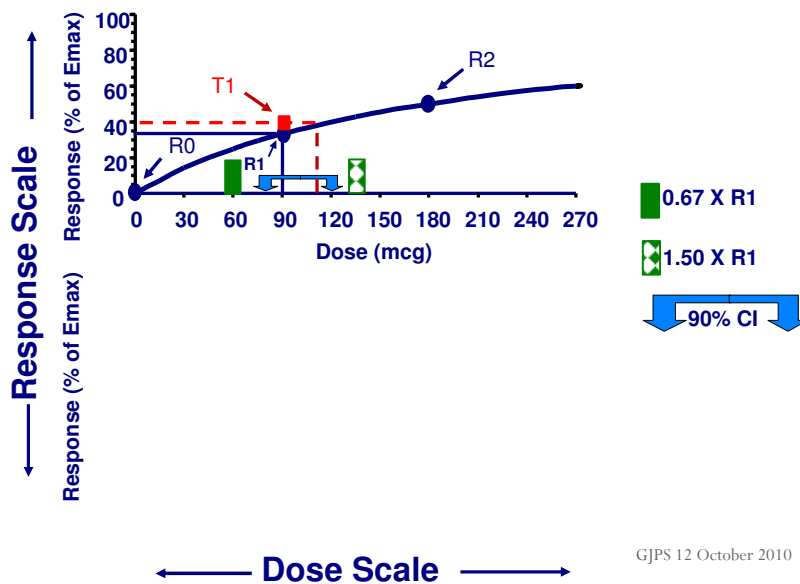


31

GJPS 12 October 2010

Effect of Dose-Response Relationship

on 90% Confidence Intervals



32

GJPS 12 October 2010

Mathematical Underpinning of “Dose Scale” Analysis of Equivalence in Local Delivery



33

GJPS 12 October 2010

“Dose Scale” Analysis (Mathematical Basis)

$$E = \phi(D)$$

D = Dose E= Effect

R= Response

$$E_R = \phi_R(D_R)$$

34

GJPS 12 October 2010

“Dose Scale” Analysis (Mathematical Basis)

➤ Application to Determination of BE of OIP

- Requires an *a priori* determination of the dose-response function ϕ .
- When the dose-response relationship is described using the E_{\max} model, then ϕ_R for the reference product(R) can be described as follows:

$$\phi_R = E_{0R} + \frac{E_{\max R} \cdot \text{Dose}_R}{ED_{50R} + \text{Dose}_R}$$

Dose Scale” Analysis (Mathematical Basis)

➤ Application to Determination of BE of OIP

The relative bioavailability “F” of a dose of the test product relative to that of the reference product can be calculated by applying the inverse of ϕ_R to the response data for the test product as follows:

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

E_T = Response of the test product to its ex-actuator dose (D_T)

Dose Scale” Analysis (Mathematical Basis)

The basic PD BE study designs require multiple doses (e.g., 0, 1 and 2 actuations) of the reference product and 1 actuation of the test product. For such studies the relative bioavailability of the test product can be estimated as follows:

$$F = \phi_R^{-1}(E_{T1})/D_{T1}$$

E_{T1} = Response to the single ex-actuator dose (D_{T1}) of the test product.

Conclusions

In evaluation of PD BE studies, establishment of dose-response and an understanding of its influence on the outcome of BE evaluations is an important consideration.

PD measures used for establishing dose-response should be relevant to the pharmacological basis/mode of drug action.

Dose-response relationships may vary with the *in vivo* models and study designs. Observations based on cumulative-dose studies may not represent actual proportionality between dose and response.

Due to nonlinearity in dose-response relationships, assessment of BE on the "Response Scale" can be misleading, because it may not accurately reflect differences in relative bioavailability (local) of T & R.

The "Dose Scale" assessment of BE incorporates the dose-response information and provides appropriate estimates of relative BA. Application of the "Dose Scale" method to PD BE studies is independent of the *in vivo* PD model/endpoint as well as quantitative aspects of dose-response relationships.