

Study Design and Evaluation Issues

Q&A Session: Examples

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Dose Proportionality

- Dose linearity may be evaluated in a two-step procedure

(Chow and Liu, Design and Analysis of Bioavailability and Bioequivalence Studies, Marcel Dekker, New York, pp 367-374 (2nd ed 2000))

- Let \mathbf{y} be the response (AUC, C_{\max}) and \mathbf{x} the dose level. Since the standard deviation of \mathbf{y} increases with the dose, the primary assumption of dose proportionality is that the standard deviation of \mathbf{y} is proportional to \mathbf{x} ; that is,

$$\text{Var}(\mathbf{y}) = \mathbf{x}^2\sigma^2,$$

where σ^2 consists of inter- and intrasubject variabilities.

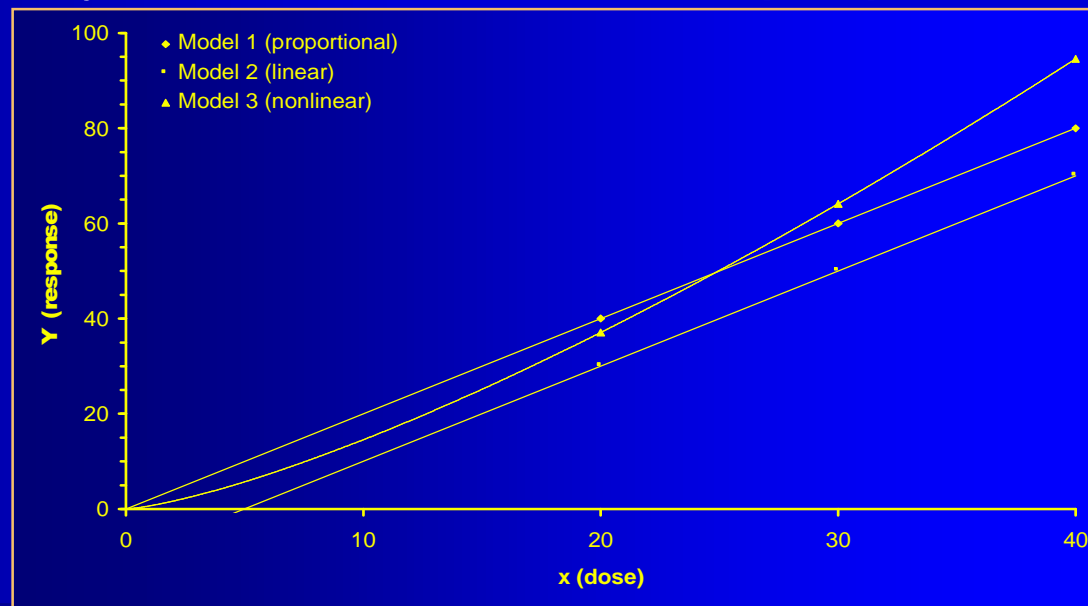


Dose Proportionality

- Two-step procedure
 - Under this assumption, following models are considered to evaluate the relation between response **Y** and dose **x**:
 - Model 1: $(Y | x) = b \cdot x$
 - Model 2: $(Y | x) = a + b \cdot x$, where $a \neq 0$
 - Model 3: $(Y | x) = a \cdot x^b$, where $a > 0$ and $b \neq 0$

Dose Proportionality

- Two-step procedure
 - Model 1 indicates that the relation between response and dose is linear. The dose response curve is a straight line, which passes through the origin. This model is commonly referred to as dose proportionality.



Dose Proportionality

- Two-step procedure
 - Step1 (dose proportionality)

All dose dependent parameters (e.g., AUC, C_{max}) are normalized to the dose of the reference prior to comparative analyses. Multiplicative model as usual in BE: Following hypotheses are evaluated during statistical analysis (given for bioavailability ratios):

Dose Proportionality

- Two-step procedure
 - Step1 (dose proportionality)
 - H_{1a0} : $\mu_{\text{test } 1}/\mu_{\text{ref.}} \leq \theta_1$ or $\mu_{\text{test } 1}/\mu_{\text{ref.}} \geq \theta_2$: null hypothesis 1a ($\mu_{\text{test } 1}$ and $\mu_{\text{ref.}}$ are *not* dose proportional)
 - H_{1a1} : $\theta_1 < \mu_{\text{test } 1}/\mu_{\text{ref.}} < \theta_2$: alternative hypothesis 1a ($\mu_{\text{test } 1}$ and $\mu_{\text{ref.}}$ are dose proportional)
 - H_{2a0} : $\mu_{\text{test } 2}/\mu_{\text{ref.}} \leq \theta_1$ or $\mu_{\text{test } 2}/\mu_{\text{ref.}} \geq \theta_2$: null hypothesis 2a ($\mu_{\text{test } 2}$ and $\mu_{\text{ref.}}$ are *not* dose proportional)
 - H_{2a1} : $\theta_1 < \mu_{\text{test } 2}/\mu_{\text{ref.}} < \theta_2$: alternative hypothesis 1a ($\mu_{\text{test } 2}$ and $\mu_{\text{ref.}}$ are dose proportional)
 - The interval $[\theta_1, \theta_2]$ denotes the acceptance range

Dose Proportionality

- Two-step procedure
 - Step1 (dose proportionality)
 - If the null hypothesis is rejected for a parameter, dose proportionality is proven within the compared dose levels.
 - If, however, the null hypothesis is not rejected, in a second step dose linearity (Model 2), and departure from dose linearity (Model 3) has to be evaluated.



Dose Proportionality

- Two-step procedure

- Step 2 (dose linearity)

Model 2 indicates that the relation between response and the dose follows a straight line with nonzero intercept (**a**). It will be tested using a weighted linear regression with weights equal to x^{-1} with the original (untransformed) data (**x**,**Y**). The hypotheses of primary interest are given as:

- H_{20} : **a=0** null hypothesis 2 (dose response curve pass through the origin)
 - H_{21} : **a≠0** alternative hypothesis 2 (nonzero intercept)



Dose Proportionality

- Two-step procedure

- Step 2 (dose linearity)

Model 3 indicates that the relation between response and the dose follows the form of a power curve with the exponent **b**. It will be tested using a weighted nonlinear regression with weights equal to x^{-1} with the original (untransformed) data (**x**, **Y**).

Model 3 will be evaluated by examining the 95 % confidence interval for the intercept *a* (*i.e.*, the null hypothesis will be rejected if zero is not included).



Dose Proportionality

- Two-step procedure

- Step 2 (dose linearity)

The hypotheses of primary interest are given as:

- $H_{30}: b=0$ null hypothesis 3 (dose response curve follows a power curve)
 - $H_{31}: b \neq 0$ alternative hypothesis 2 (nonzero exponent)

The departure from dose linearity will be evaluated by the 95 % confidence interval (L,U) for b according to the following decision criteria:

Dose Proportionality

- Two-step procedure
 - Step 2 (dose linearity)

if $0.75 < L < 1.0 < 1.25$	no departure from dose linearity (<i>i.e.</i> , Model 2 holds)
if $1.0 < L < U < 1.25$ or $0.75 < L < U < 1.0$	slight departure from dose linearity, but no practical significance from dose linearity
if $L > 1.25$ or $U < 0.75$	reject hypothesis of dose linearity (<i>i.e.</i> , Model 3 holds)

Dose Proportionality

- Two-step procedure
 - Example (FIM biological, 6 dose levels, C_{max})

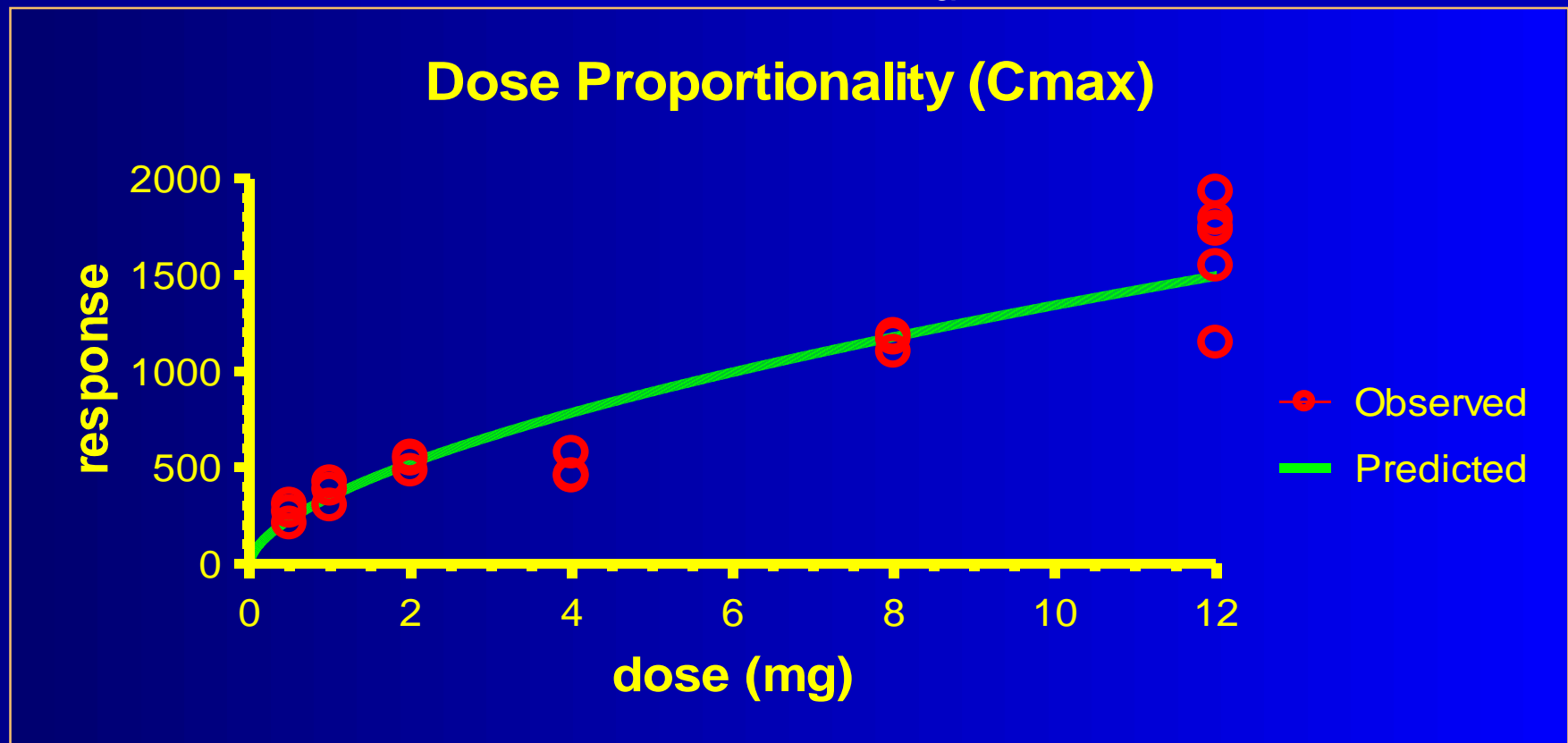
response	b	95 % CI (L,U)		CV%	Corr.
C_{max}	0.587	0.471	0.704	7.28	0.9446

U < 0.75

Model 3 holds (deviation from dose proportionality)

Dose Proportionality

- Two-step procedure
 - Example (FIM, 6 dose levels, C_{max})



Dose Proportionality

● WinNonlin user model

```
remark      DOSE PROPORTIONALITY, Chow/Liu 2000 pp 368 Models 1-4
remark      data in original (untransformed) scale (X/Y)
remark      weight = 1/X, weights must be provided in column 3
remark      (c) Helmut Schuetz, BEBEAC, 1070 Vienna, Austria
model 1
remark      Dose Proportionality
remark      Model 1:  $E(Y)=bX$  (linear through origin)
remark      b1 = slope
remark      weight = 1/X
commands
dnames 'dose' 'response'
npar 1
pname 'b1'
initial 1
nobounds
method 3
weight
end
func 1
f = b1 * x
end
eom
```



Dose Proportionality

- WinNonlin user model

```
model 2
remark      Dose Proportionality
remark      Model 2:  $E(Y)=a+bX$  (linear)
remark      where  $a \neq 0$ 
remark      a = intercept
remark      b = slope
remark      weight =  $1/X$ 
commands
dnames 'dose' 'response'
npar 2
pname 'a2' 'b2'
initial 0 1
nobounds
method 3
weight
end
func 1
f = a2 + b2 * x
end
eom
```



Dose Proportionality

- WinNonlin user model

```
model 3
remark      Dose Proportionality
remark      Model 3:  $E(Y)=a*X^b$  (power function)
remark      where  $a>0$  and  $b\neq 0$ 
remark      a = coefficient
remark      b = exponent ('curvature')
remark      weight =  $1/X$ 
commands
dnames 'dose' 'response'
npar 2
pname 'a3' 'b3'
initial 1 1
nobounds
weight
end
func 1
f = a3 * x ** b3
end
eom
```



Dose Proportionality

- WinNonlin user model

```
model 4
remark      Dose Proportionality
remark      Model 4:  $E(Y)=a+c*X^b$  (power function with intercept)
remark      where  $a \neq 0$  and/or  $b \neq 1$ 
remark      a = intercept
remark      b = exponent ('curvature')
remark      c = coefficient
remark      weight = 1/X
commands
dnames 'dose' 'response'
npar 3
pname 'a4' 'b4' 'c4'
initial 0 1 1
nobounds
weight
end
func 1
f = a4 + c4 * x ** b4
end
eom
```



Pooling of CV%

- Intra-subject CV from different studies can be pooled
 - Don't use the arithmetic mean – or the geometric mean either – of CVs
 - Before pooling CVs must be weighted according to the sample size
 - In the parametric model of log-transformed data, additivity of variances (not of CVs) apply
 - Calculate the variance from CV

$$\sigma_W^2 = \ln(CV^2 + 1)$$

Pooling of CV%

- Intra-subject CV from different studies
 - Calculate the total variance weighted by degrees of freedom

$$\sum \sigma_w^2 df$$

- Calculate the pooled CV from total variance

$$CV = \sqrt{e^{\sum \sigma_w^2 df / \sum df} - 1}$$

- Optionally calculate an upper (1- α) % confidence limit on the pooled CV (recommended $\alpha=0.20$)

$$CL_{CV} = \sqrt{e^{\sum \sigma_w^2 df / \chi_{1-\alpha, \sum df}^2} - 1}$$

Pooling of CV%

- Example 1: $n_1 = n_2$;
 $CV_{Study1} < CV_{Study2}$

studies	N	df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
2	24	20	0.2	0.8	1.2540	0.254	0.245
				$\chi^2_{(1-\alpha, df)}$	14.578	0.300	+17.8%

CV_{intra}	n	seq.	df (mj)	σ_w	σ^2_w	$\sigma^2_w \times df$	$CV_{intra} / pooled$	$>CL_{upper}$
0.200	12	2	10	0.198	0.0392	0.3922	78.6%	no
0.300	12	2	10	0.294	0.0862	0.8618	117.9%	yes

Pooling of CV%

- Example 2: $n_1 < n_2$;
 $CV_{Study1} < CV_{Study2}$

studies	N	df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}	
2	36	32	0.2	0.8	2.2881	0.272	0.245	
					$\chi^2_{(1-\alpha, df)}$	25.148	0.309	+13.4%

CV_{intra}	n	seq.	df (mj)	σ_w	σ^2_w	$\sigma^2_w \times df$	$CV_{intra} / pooled$	$>CL_{upper}$
0.200	12	2	10	0.198	0.0392	0.3922	73.5%	no
0.300	24	2	22	0.294	0.0862	1.8959	110.2%	no

Pooling of CV%

- Example 3: $n_1 > n_2$;
 $CV_{Study1} < CV_{Study2}$

studies	N	df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
2	36	32	0.2	0.8	1.7246	0.235	0.245
				$\chi^2_{(1-\alpha, df)}$	25.148	0.266	+13.2%

CV_{intra}	n	seq.	df (mj)	σ_w	σ^2_w	$\sigma^2_w \times df$	$CV_{intra} / pooled$	$>CL_{upper}$
0.200	24	2	22	0.198	0.0392	0.8629	85.0%	no
0.300	12	2	10	0.294	0.0862	0.8618	127.5%	yes