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

    $\mathrm{Var}(\mathbf{Y}) = \mathbf{x}^2\sigma^2$,

    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**:

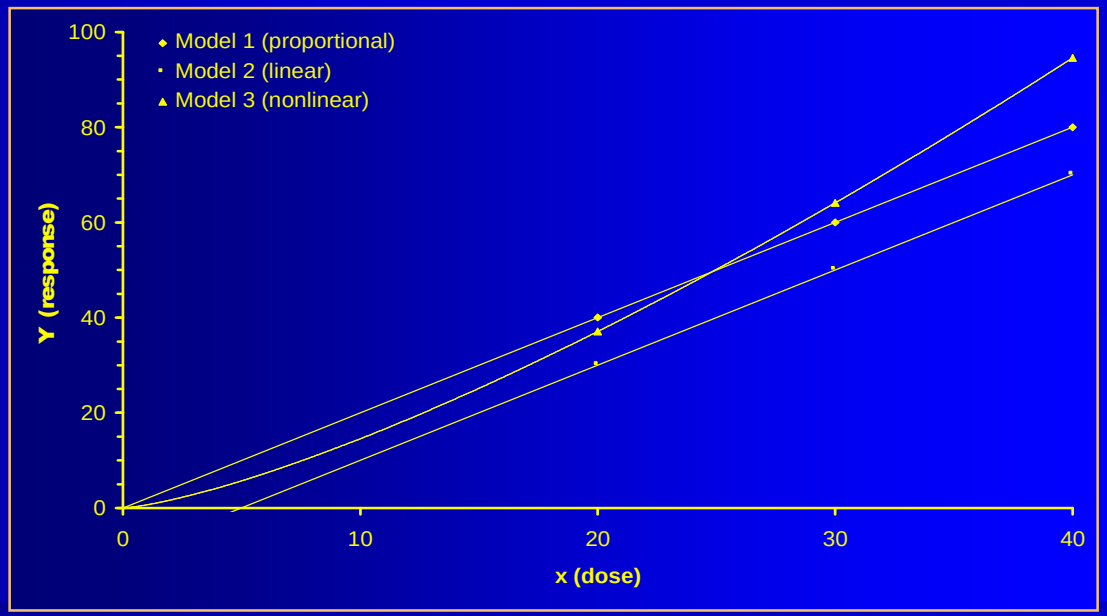
    Model 1: $(Y|x)=b \cdot x$

    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}: $\mu_{test\ 1}/\mu_{ref.} \leq \theta_1$ or $\mu_{test\ 1}/\mu_{ref.} \geq \theta_2$: null hypothesis 1a ($\mu_{test\ 1}$ and $\mu_{ref.}$ are *not* dose proportional)
    - H_{1a1}: $\theta_1 < \mu_{test\ 1}/\mu_{ref.} < \theta_2$: alternative hypothesis 1a ($\mu_{test\ 1}$ and $\mu_{ref.}$ *are* dose proportional)
    - H_{2a0}: $\mu_{test\ 2}/\mu_{ref.} \leq \theta_1$ or $\mu_{test\ 2}/\mu_{ref.} \geq \theta_2$: null hypothesis 2a ($\mu_{test\ 2}$ and $\mu_{ref.}$ are *not* dose proportional)
    - H_{2a1}: $\theta_1 < \mu_{test\ 2}/\mu_{ref.} < \theta_2$: alternative hypothesis 1a ($\mu_{test\ 2}$ and $\mu_{ref.}$ *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 $\mathbf{x^{-1}}$ 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 passess 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 $\mathbf{x}^{-1}$ 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≠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.e.*, 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.e.*, Model 3 holds)

Dose Proportionality

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

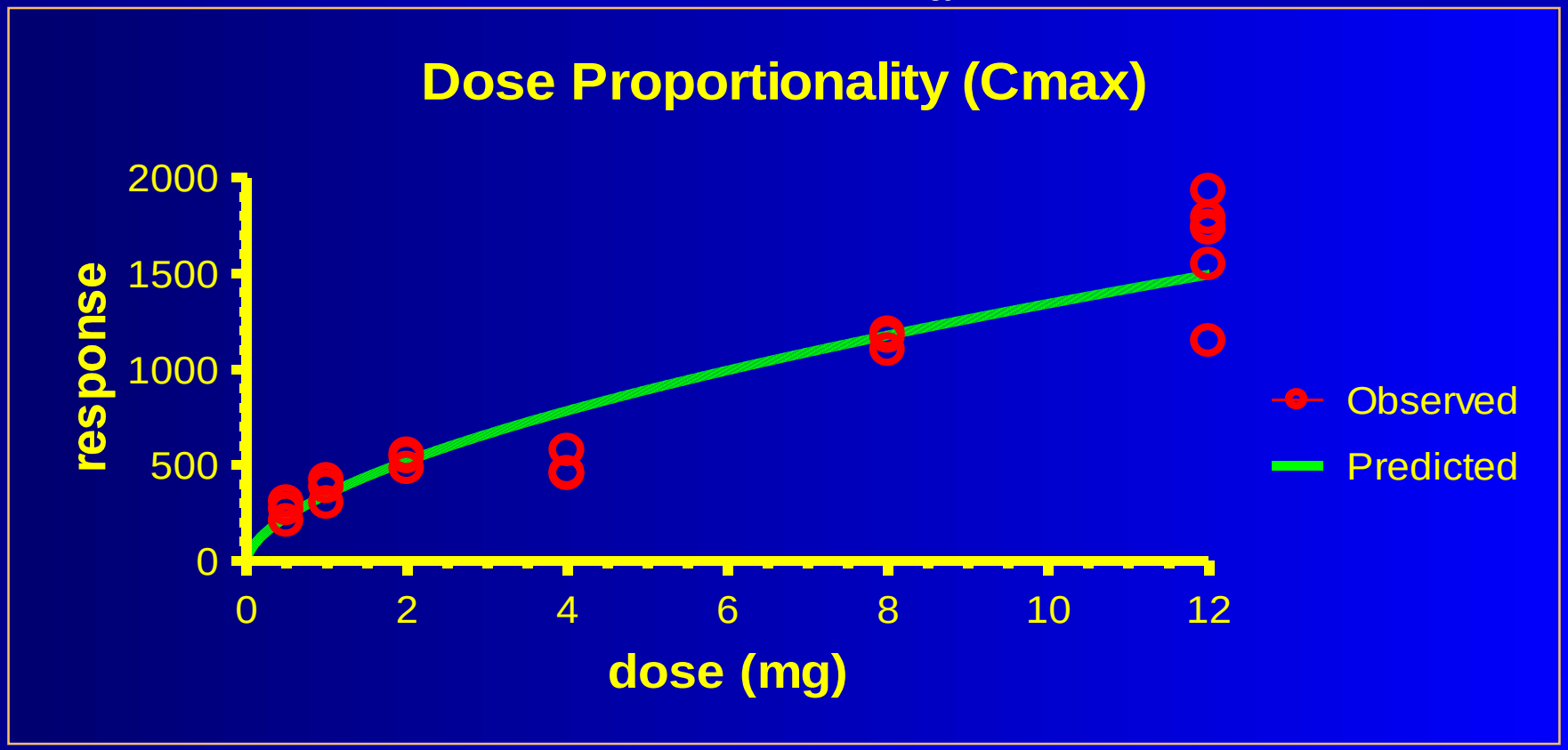
response	b	95 % CI (L,U)		CV%	Corr.
C_{max}	0.587	0.471	0.704	7.28	0.9446

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#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#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#0 and/or b#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 acccording 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 α=0.20)

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

Pooling of CV%

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

studies	N
2	24

df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
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
2	36

df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
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
2	36

df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
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