Statistical Design and Analysis III

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Dose Proportionality

- Dose proportionality may be evaluated in a two-step procedure
  (Chow and Liu, Design and Analysis of Bioavailability and Bioequivalence Studies, Marcel Dekker, New York, pp 563–573 (3rd ed 2009)
  - 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,

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

    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: $E(Y|x)=b \cdot x$

    Model 2: $E(Y|x)=a+b \cdot x$, where $a \neq 0$

    Model 3: $E(Y|x)=a \cdot x^{b}$, 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
  - Step 1 (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
  - Step 1 (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
  - Step 1 (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 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 of the exponent **b** for departure from one.

Dose Proportionality

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

    The hypotheses of primary interest are given as:
    - H_{30}: **$b=1$** null hypothesis 3 (no departure from dose linearity)
    - H_{31}: **$b \neq 1$** alternative hypothesis 3 (dose response curve follows a power curve)

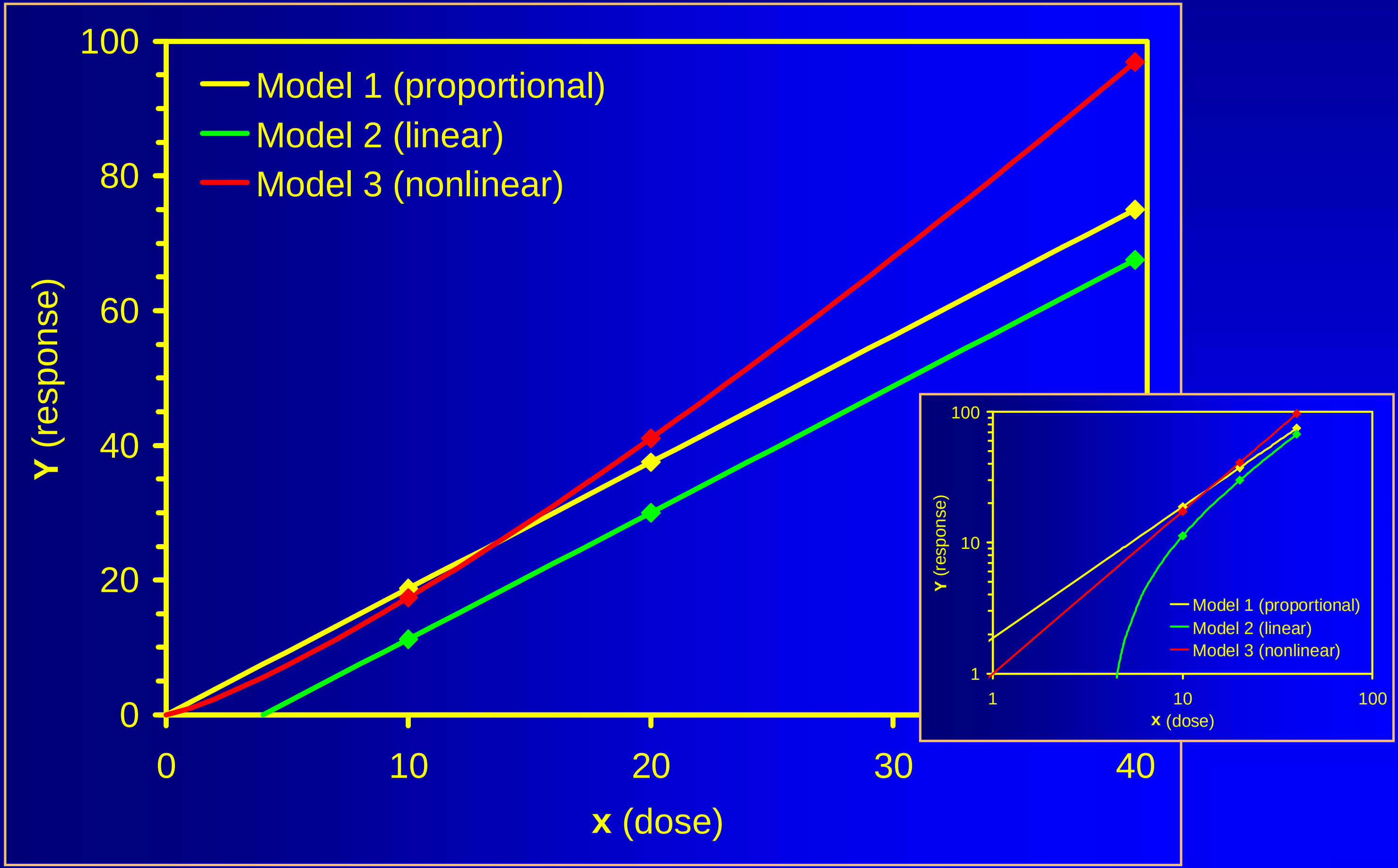
    The departure from dose linearity will be evaluated by the 95% confidence interval (L,U) for **b** according to following decision criteria:

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



Dose Proportionality

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

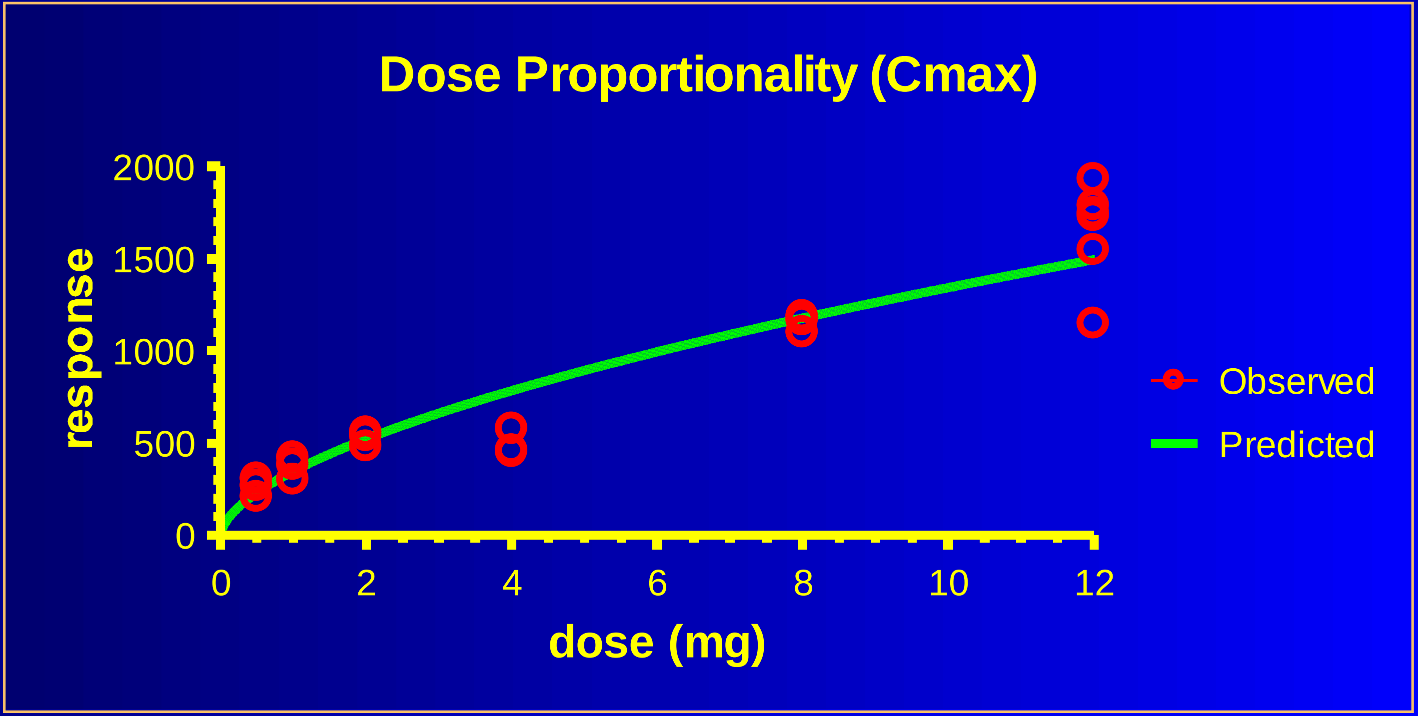
response	**b**	95 % CI (L,U)		CV%	Corr.
C_{max}	0.587	0.471	0.704	7.28	0.9446

$U_b < 0.75$

Model 3 holds (deviation from dose linearity)

Dose Proportionality

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



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Thank You!

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Open Questions?

(WinNonlin User model in your handouts – use at your own risk!)

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Dose Proportionality

- WinNonlin user model

```
remark      DOSE PROPORTIONALITY, Chow/Liu 2009 p 564 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, BEBAC, 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 (Dose Linearity)
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 (Nonlinear PK)
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 (Nonlinear PK)
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
```