THE IMPACT OF THE DATA VARIABILITY DUE TO DIFFERENT PATTERNS OF BIOANALYTICAL BIAS – PHARMACOKINETIC ASSESSMENT THROUGH SIMULATION

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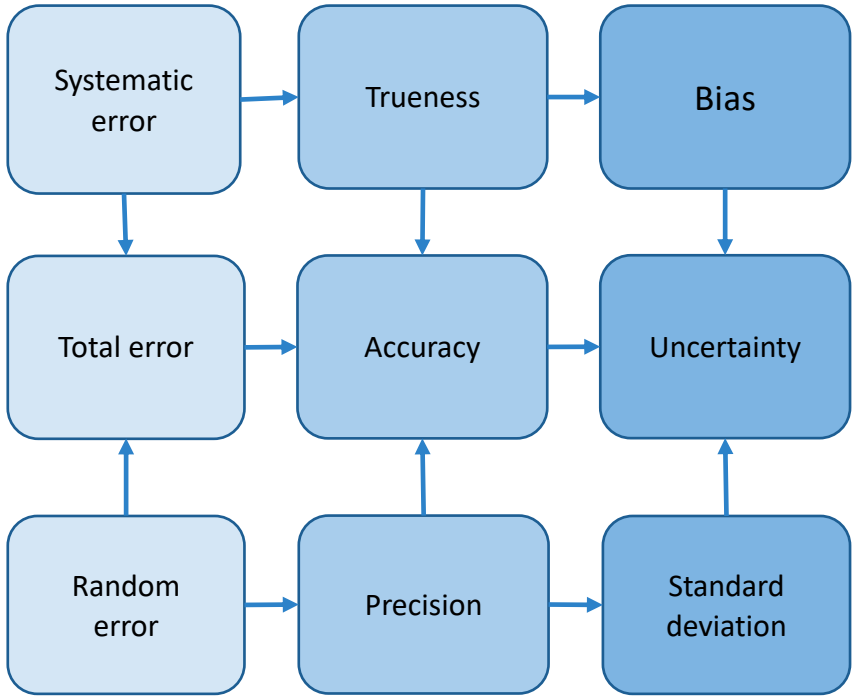
OBJECTIVE

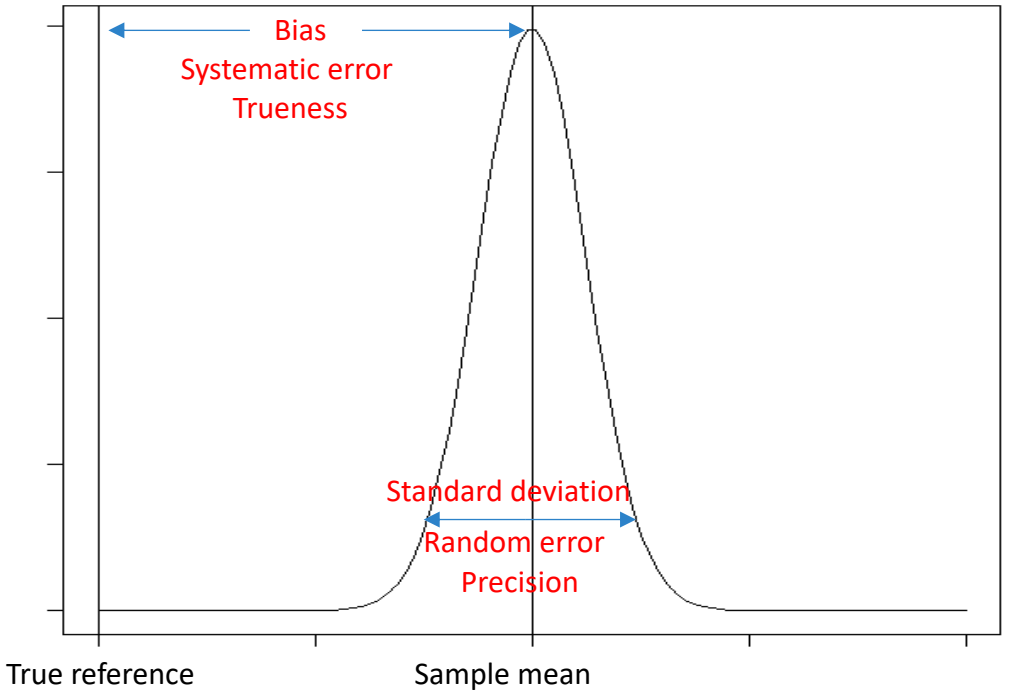
The aim of this presentation is to quantify the impact that different patterns of random and systematic error can have from a PK perspective on the assessment of dose proportionality.

- To simulated concentrations versus time profiles with and without different random error (precision, standard deviation around achieved concentration) and/or systematic error (bias, trueness) patterns.
  - Bias patterns: Increasing, decreasing or constant, each of them with up to 15, 20 and 30% deviation from true result.
  - Precision: 15, 20 and 30% deviation from true (without bias) or achieved result (with bias).
- To calculate AUC and C_{max} values from simulated profiles at 3 different dose levels and to assess whether the dose proportionality criterion was met.
- To simulate the above 1000 times and calculate how many times dose proportionality was met.
- To repeat the above 1000 simulations with increasing sample size, from 5 to 200 subjects/group.
- To repeat the above simulations at different dose levels, with different PK parameters (CL, Vd and ka) and timepoints, …

METHODOLOGY AND CONCEPTS

ACCURACY, PRECISION & TRUENESS





- Accuracy: The closeness of the determined value obtained by the method to the nominal concentration of analyte.
- Precision: The closeness of repeated individual measures of analyte.
- Trueness: The closeness of agreement between the average value obtained from a large series of test results and an accepted reference value.

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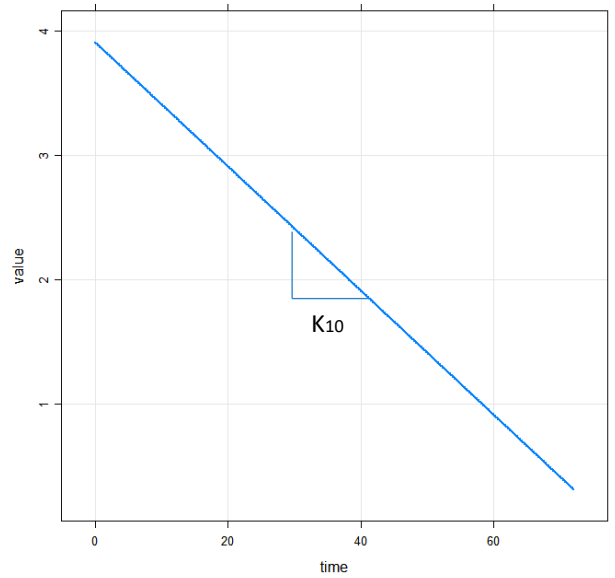
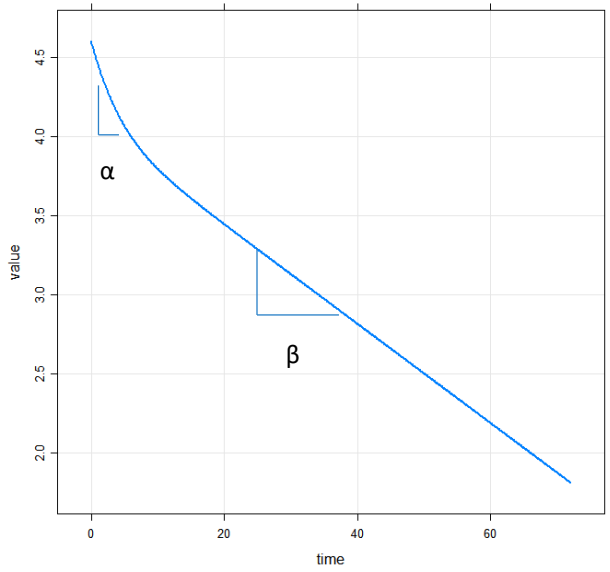
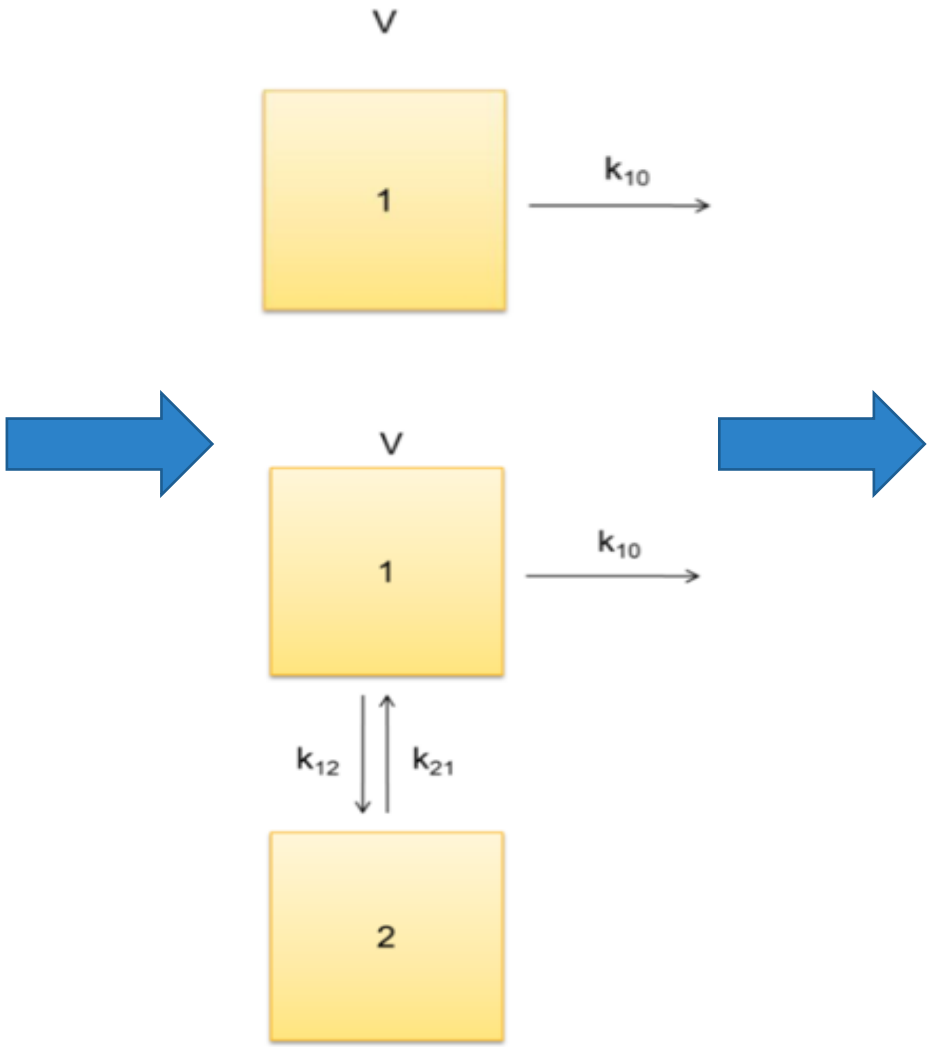
PK COMPARTMENTAL MODELS







$$\frac{dQ}{dt} = -k_{el}Q$$

$$C = C_0 \cdot e^{-k_{el} \cdot t}$$

$$\frac{dQ_1}{dt} = -k_{el}Q_1 - k_{12}Q_1 + k_{21}Q_2$$

$$\frac{dQ_2}{dt} = k_{12}Q_1 - k_{21}Q_2$$

$$C = C_0 \cdot e^{-\alpha \cdot t} - A_0 \cdot e^{\beta \cdot t}$$

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DATA GENERATION

- Concentration vs time profiles were simulated using open source R software and its library mrgsolve, under different scenarios using a 1 compartment extravascular population model.
  - 1 compartment extravascular model: $C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \left(e^{-\frac{CL}{Vd} \cdot t} - e^{-k_a \cdot t} \right)$
  - Pop-PK models allow introducing between subject variability (BSV) and within subject variability (WSV).

$$Cl_i = \exp(\log(Cl) + 0.75 \cdot \log\left({body\ weight}/{70}\right) + e_i$$

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \left(e^{-\frac{CL}{Vd} \cdot t} - e^{-k_a \cdot t} \right)$$

$$Vd_i = \exp(\log(Vd) + \log\left({body\ weight}/{70}\right) + e_i$$

DATA GENERATION

- In this exercise, the only source of WSV is assumed to be the bioanalytical method.

Pop. Model specifications for BSV and WSV

```
$MAIN
double CL = exp(log(TVCL) + 0.75*log(WT/70) + ECL);
double V  = exp(log(TVV)  +      log(WT/70) + EV );
double KA = exp(log(TVKA)                   + EKA);

$OMEGA @labels ECL EV EKA
0.3 0.1 0.5

$SIGMA 0

$TABLE
capture IPRED = CENT/V;
capture DV1 = IPRED*(1+0.15*((CENT/V-0)/(500-0)));
capture DV2 = DV1*exp(EPS(1));
capture DV3 = IPRED*exp(EPS(1));

$CAPTURE CL V ECL
```

BSV
- Upper part: Parameter variability
  - depends on body weight (WT)
  - Depends on random residual variability
- Bottom part: Random effect - var-covar matrix
  - Assigns random BSV to each profile

WSV (Precision around true subject profile)
- Bottom part: Var-covar matrix
  - Assigns random WSV to each timepoint

IPRED = Data with BSV only
DV3 = Data with BSV + WSV
DV1 = Data with BSV + 15% increasing bias
DV2 = Data with BSV + 15% increasing bias + WSV

BIAS PATTERNS

- Increasing bias

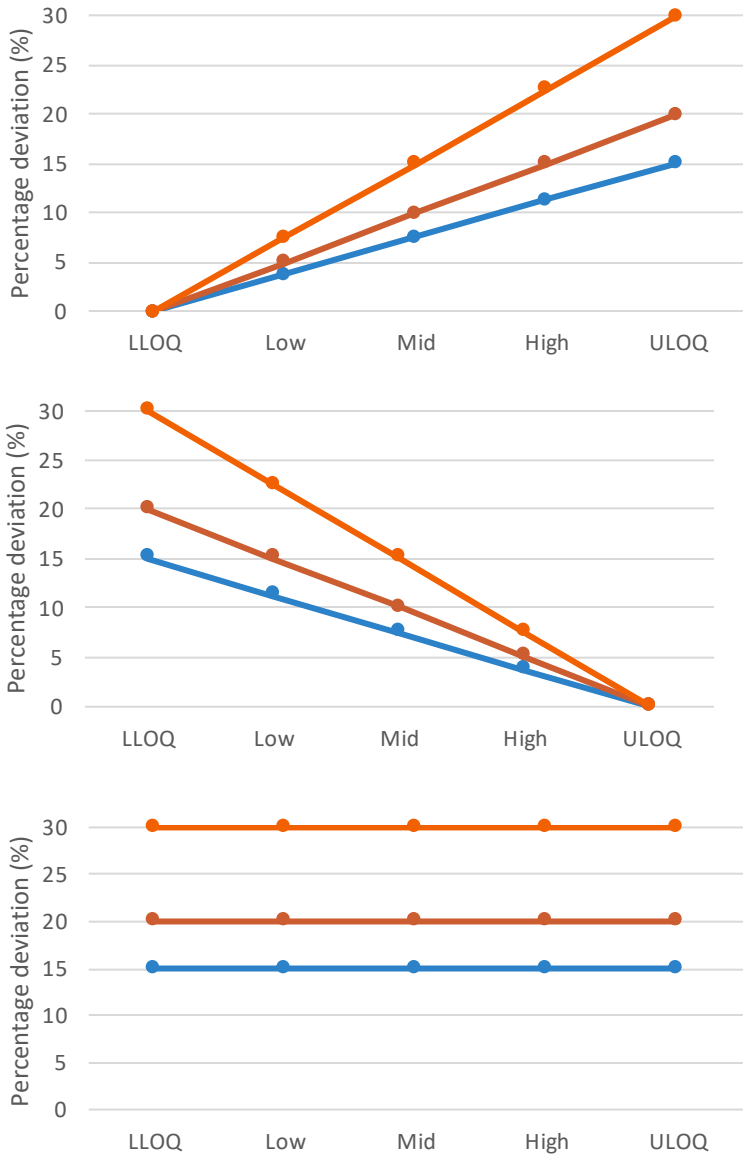
$$Bias_{incr} = (pCt - LLOQ)/((ULOQ - LLOQ)$$
$$Ct = pCt \cdot bias_{incr}$$

- Decreasing bias

$$Bias_{decr} = (ULOQ - pCt)/((ULOQ - LLOQ)$$
$$Ct = pCt \cdot bias_{decr}$$

- Constant bias

$$Bias_{const} = Fixed\ \%$$
$$Ct = pCt \cdot bias_{const}$$



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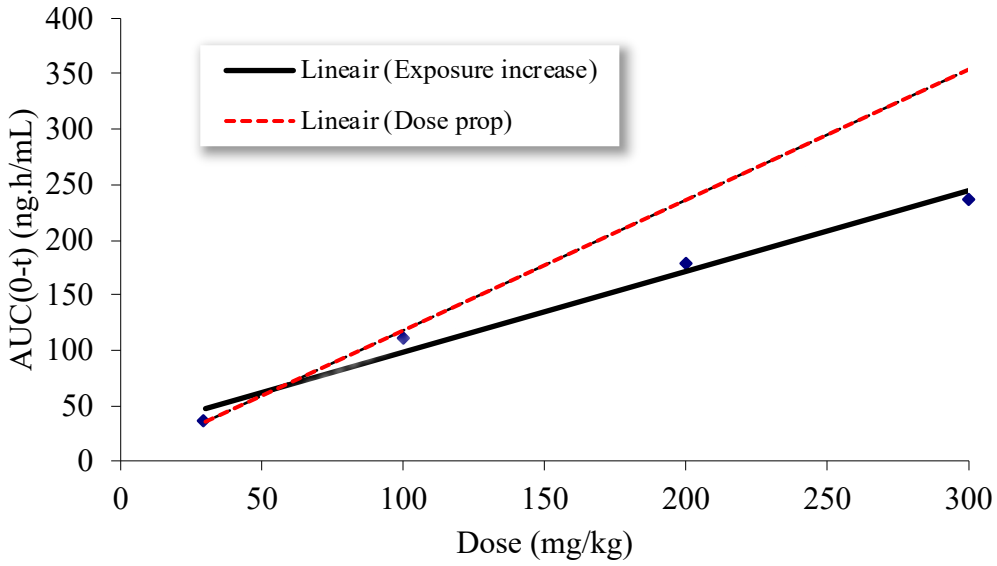
DOSE PROPORTIONALITY ASSESSMENT

- Power model
- $AUC = \alpha \cdot Dose^{\beta}$
- $\log(AUC) = \alpha + \beta \cdot \log(Dose)$
- $1 + \frac{Ln(0.8)}{Ln(\frac{h}{l})} < LLCI90\% < slope > ULCI90\% > 1 + \frac{Ln(1.25)}{Ln(\frac{h}{l})}$

- Where
  - h = high dose
  - l = low dose
- Therefore, to declare dose proportionality, the slope β an its 90% confidence interval (CI) obtained by means of a linear model has to be within the specified range.
- The wider the dose range is, the narrower the interval to declare dose proportionality will be.



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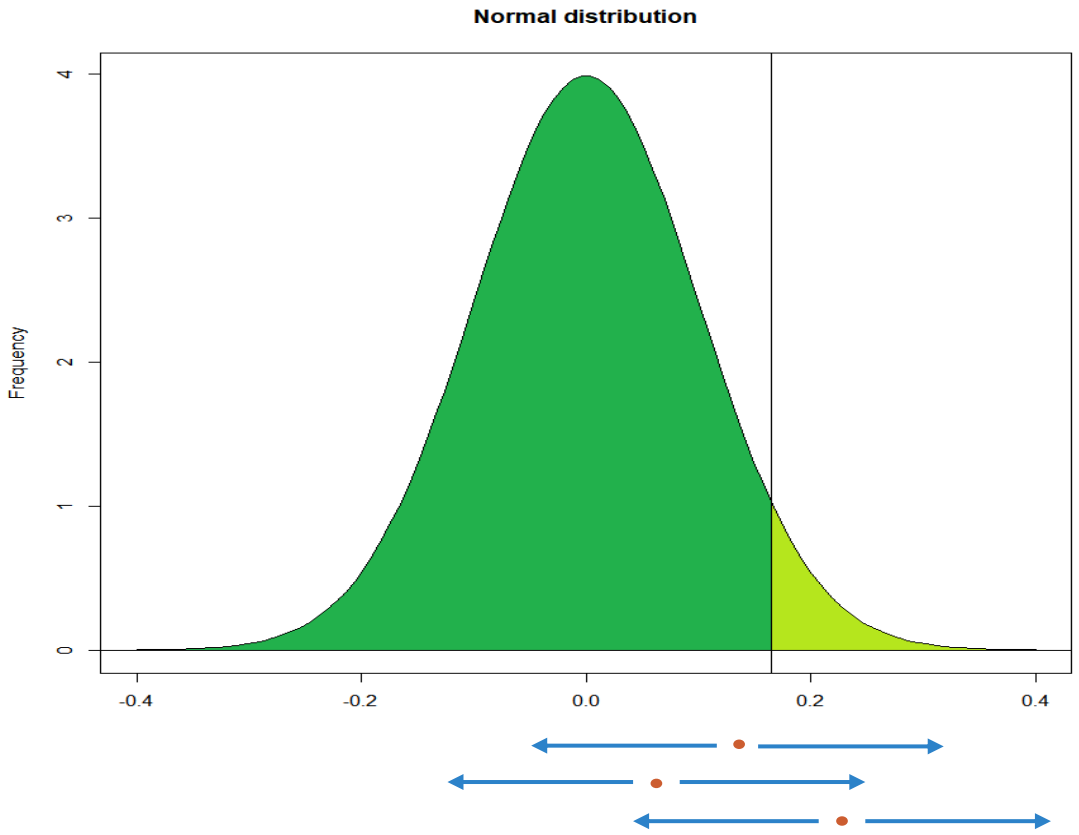
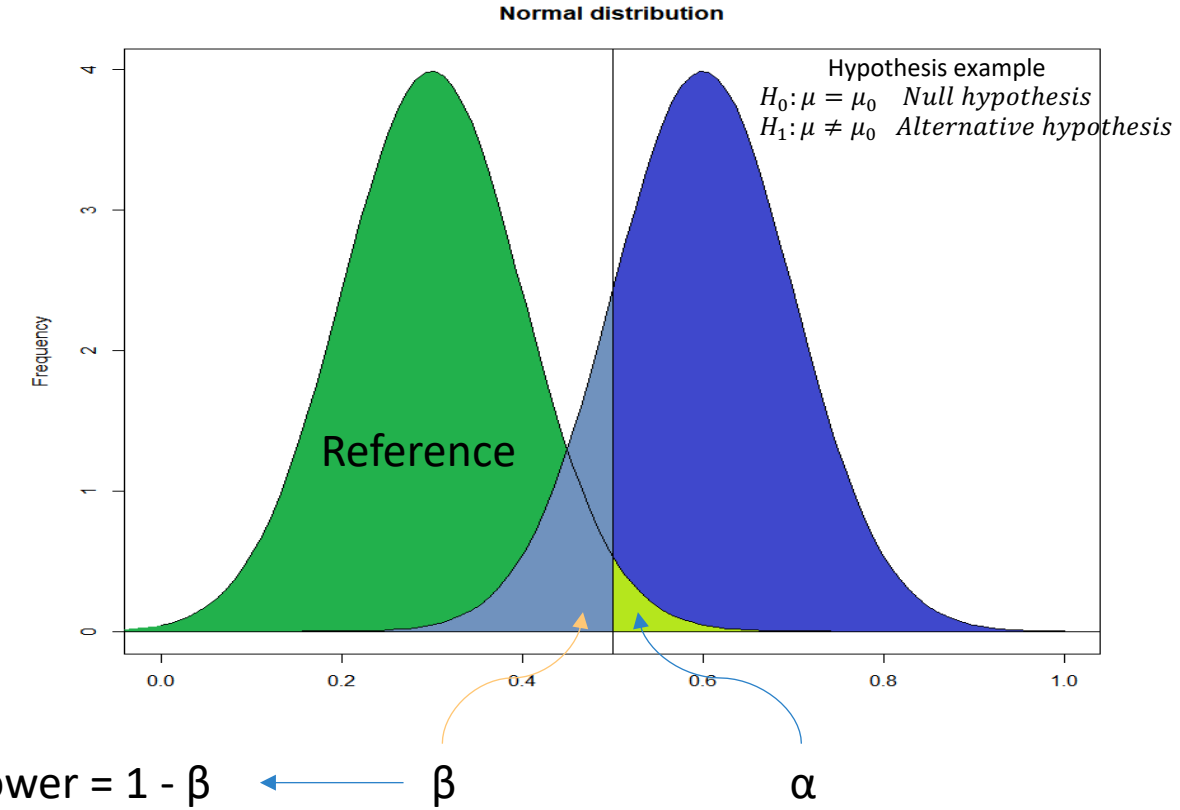
STATISTICAL CONCEPTS





Power = 1 - β ← β α

- Confidence interval: A range of values so defined that there is a specified probability that the value of a parameter lies within it.

Null hypothesis is …	True	False
Rejected	Type I error False positive Probability = α	Correct decision True positive Probability = 1 - β
Not rejected	Correct decision True negative Probability = 1 – α	Type II error False negative Probability = β

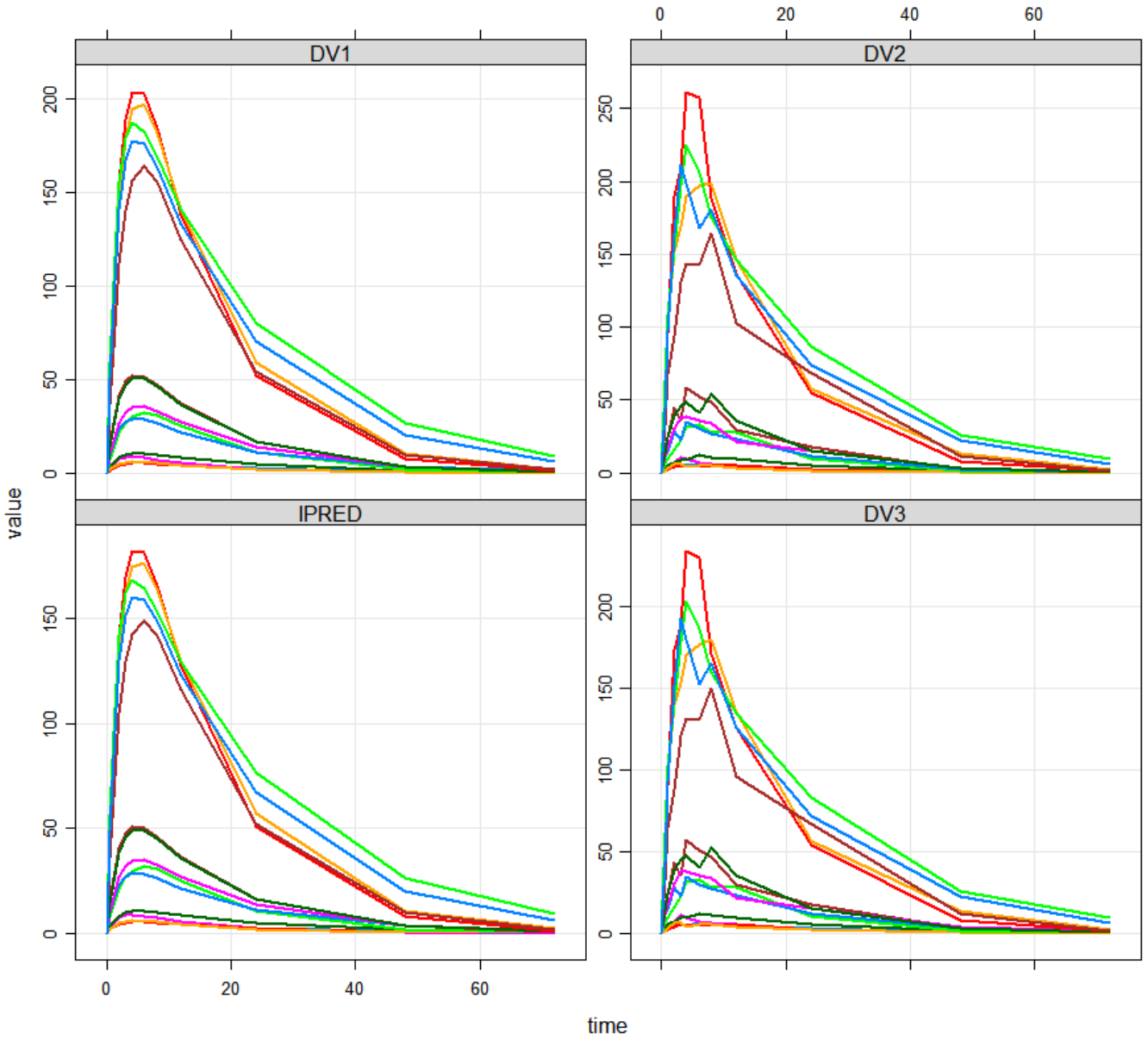
RESULTS

SIMULATED DATA (EXAMPLES)

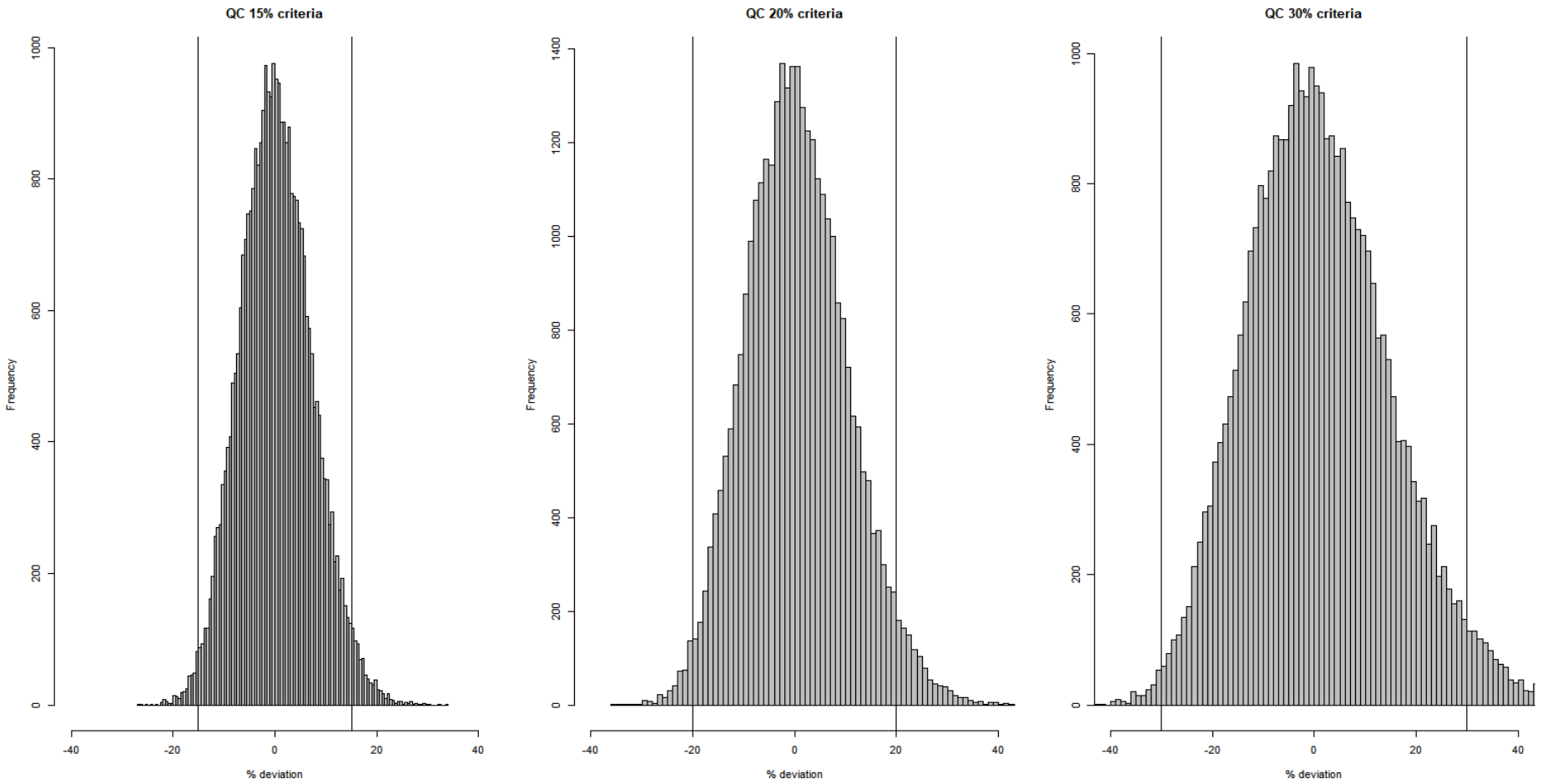
- Data simulated at 3 different dose levels with and without random error (precision around achieved or true concentration) and/or systematic error (bias).

- IPRED: Data with BSV only
- DV3 = Data with BSV + WSV
- DV1 = Data with BSV + 15% increasing bias
- DV2 = Data with BSV + 15% increasing bias + WSV

- WSV: Within subject variability; related to precision around the true or achieved concentration.
- BSV: Between subject variability; related to the physiology of the subject.



SAMPLE VARIABILITY AROUND TRUE ESTIMATE (WSV)



- Example for ±15,20 and 30% variability around the true estimate.
- Less than 5% of samples deviate more than allowable in all cases.

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DOSE PROPORTIONALITY ASSESSMENT FOR AUC

- Number of times (%) the data could not be declare dose proportional

N/group	IPRED	IPRED+WSV15	IPRED+B15	IPRED+B15+WSV15
5	94.8	94.8	95.7	95.0
10	58.6	59.0	67.0	68.0
15	31	31.4	37.1	38.0
20	15.5	15.5	22.7	23.3
25	8.7	8.5	16.2	16.4
30	8.6	9.1	16.9	16.6
35	10.5	9.5	19.8	19.1
40	11.5	11.3	20.6	20.8
45	8.5	8.0	20.6	20.0
50	11.4	11.0	22.0	20.8
55	10.1	9.4	24.1	24.4
60	8.5	8.5	22.2	21.9
65	10.1	10.4	22.4	22.8
70	10.3	10.2	25.5	25.3
75	8.9	9.9	29.5	29.4
80	9.5	9.0	27.4	27.1
85	10.7	11.4	27.7	27.3
90	9.6	10.1	33.2	32.7
95	12	12.2	33.4	33.1
100	9.4	9.9	30.5	29.4
150	10.6	10.5	40.3	39.7
175	8.7	8.4	48.1	46.7
200	10.1	9.7	54.6	53.7

N/group	IPRED	IPRED+WSV20	IPRED+B20	IPRED+B20+WSV20
5	94.8	95.3	95.7	95.6
10	58.6	61.5	69.7	71.5
15	31	32.4	42.5	43.7
20	15.5	16.0	27.1	28.9
25	8.7	9.1	20.9	20.7
30	8.6	9.2	20.9	21.4
35	10.5	9.3	25.8	24.9
40	11.5	11.2	27.3	26.9
45	8.5	7.8	27.1	25.5
50	11.4	11.3	30.2	28.1
55	10.1	9.9	32.3	32.6
60	8.5	8.3	31.9	31.0
65	10.1	10.1	32.7	31.6
70	10.3	9.8	37.9	36.9
75	8.9	9.9	40.3	39.6
80	9.5	8.9	38.5	37.1
85	10.7	11.0	40.3	39.3
90	9.6	9.7	46.9	44.8
95	12	12.2	46.2	45.6
100	9.4	9.7	46.0	43.3
150	10.6	10.8	60.1	58.9
175	8.7	8.6	66.2	65.3
200	10.1	10.0	70.6	69.6

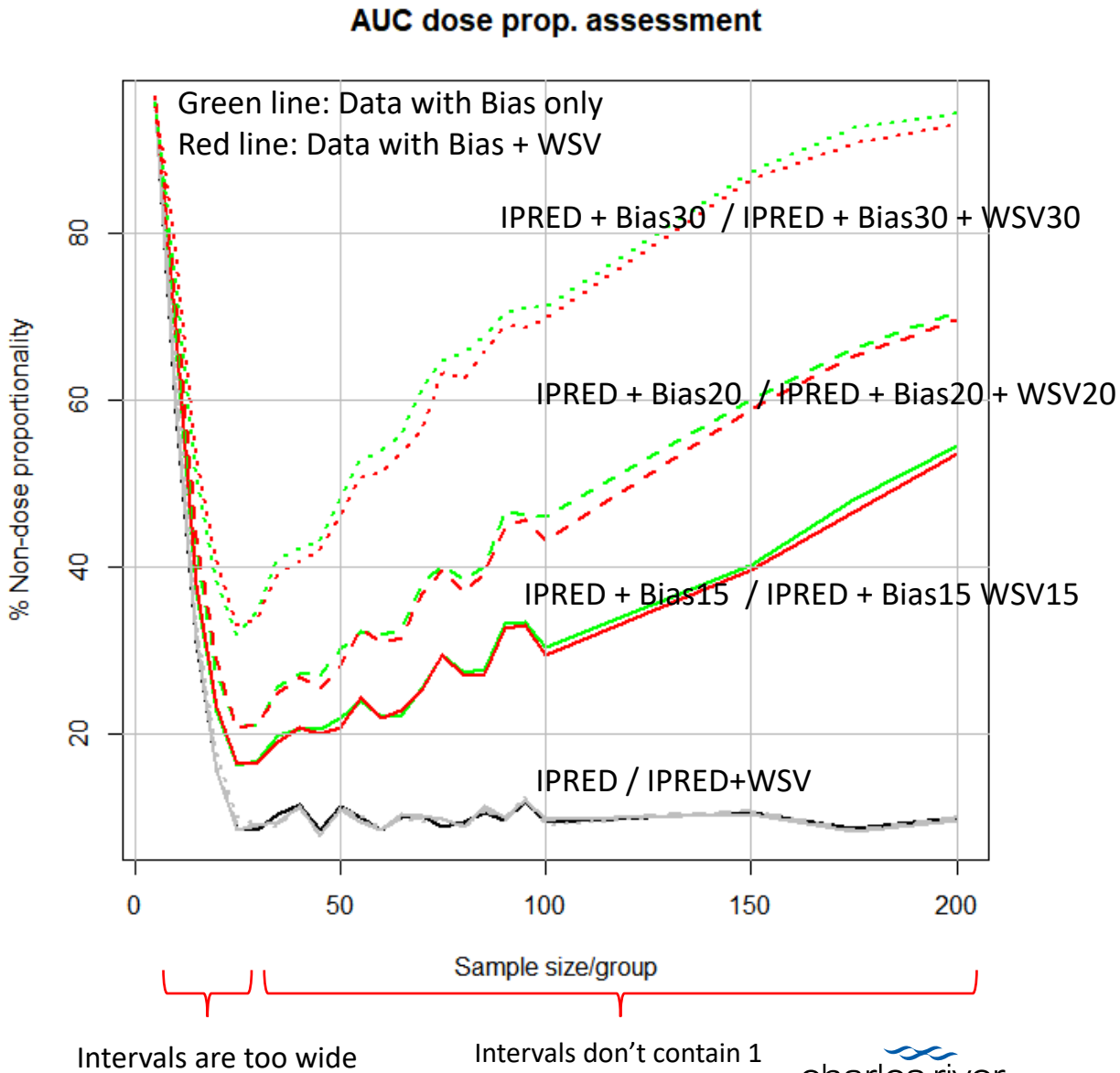
N/group	IPRED	IPRED+WSV30	IPRED+B30	IPRED+B30+WSV30
5	94.8	96.0	95.7	96.5
10	58.6	64.9	74.1	78.0
15	31.0	33.9	51.0	53.5
20	15.5	17.7	38.4	40.7
25	8.7	10.0	32.0	33.0
30	8.6	9.2	34.8	33.8
35	10.5	8.9	40.9	39.2
40	11.5	11.3	42.3	40.8
45	8.5	7.9	43.2	42.1
50	11.4	11.2	48.1	46.2
55	10.1	10.3	52.8	50.8
60	8.5	8.7	54.0	51.3
65	10.1	10.0	55.8	53.8
70	10.3	9.4	61.3	56.4
75	8.9	9.6	64.8	63.2
80	9.5	9.1	65.6	62.7
85	10.7	10.8	67.8	65.9
90	9.6	10.1	70.4	68.9
95	12.0	12.5	71.1	68.7
100	9.4	9.1	71.1	69.8
150	10.6	10.9	87.4	86.5
175	8.7	8.3	92.6	90.8
200	10.1	10.1	94.4	93.0

- Model specifications:
  - PK param.: Ka = 0.5; CL = 0.03; V = 0.5
  - Dose: 5, 25, 125
  - Timepoints: n=12, up to 72h
  - BSV: AUC CV% ≈ 20-25%
  - Bias: Increasing

- Table legend:
  - IPRED: Data with BSW only; no differences in data
  - WSV: Allowed Within subject variability
  - B: Allowed % of increasing bias

DOSE PROPORTIONALITY ASSESSMENT FOR AUC

- Data with only BSV (IPRED) should be declared dose proportional (black/grey lines).
- Under the specifications of this model, 25 subjects were needed to detect no differences in IPRED (up to 25 patients, warm up period).
- The data in models with bias should be intrinsically different.
- From 25 patients onwards, we start detecting differences and the % of non dose prop increases.
- From 25 patients onwards, the percentage of non dose prop is equivalent to the power of your study to detect differences.



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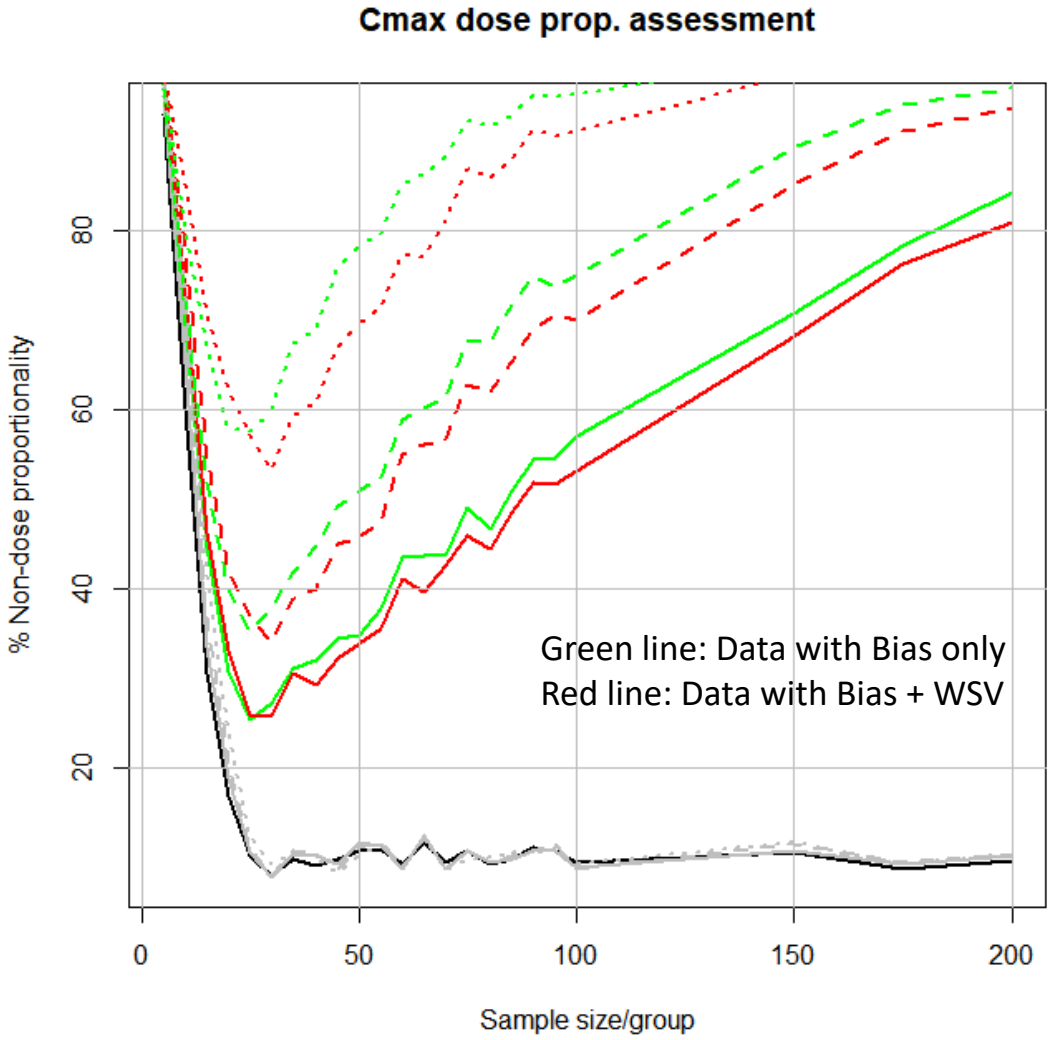
DOSE PROPORTIONALITY ASSESSMENT FOR CMAX

- Same model for Cmax.
- WSV played a more important role in the assessment of Cmax.
- Where confidence intervals were just above 1, the addition of WSV to bias made some of those intervals to contain 1 and therefore dose prop was declared.
- Less subjects needed to detect true differences in the presence of bias.
- Overall, the trends were the same as for AUC.



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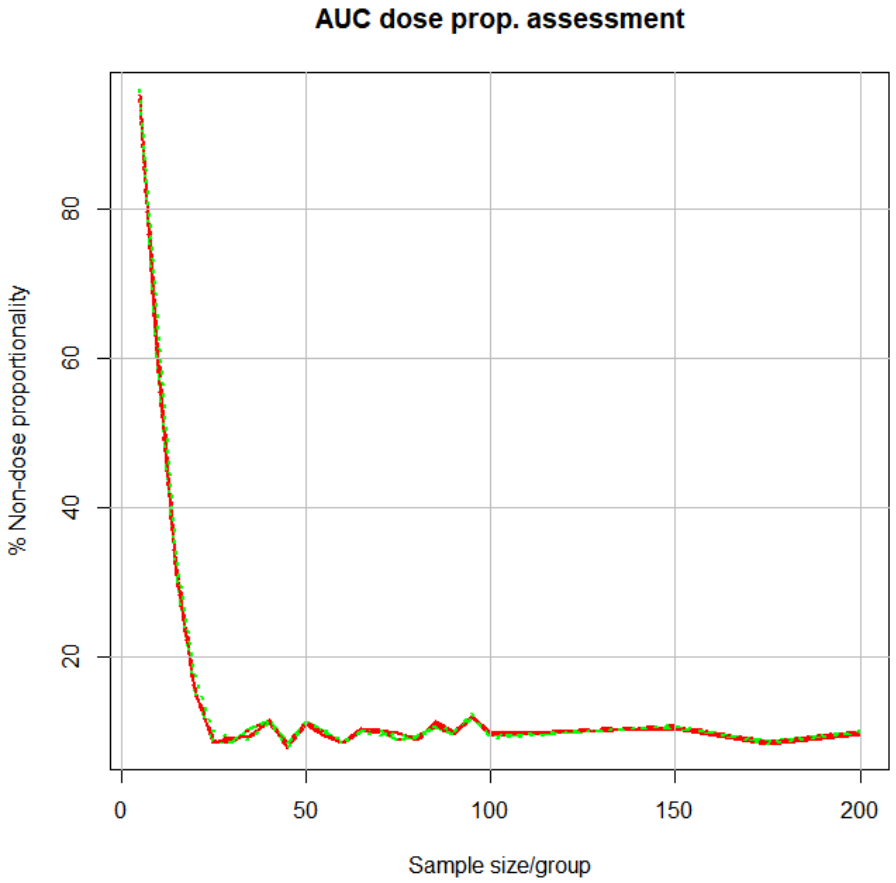
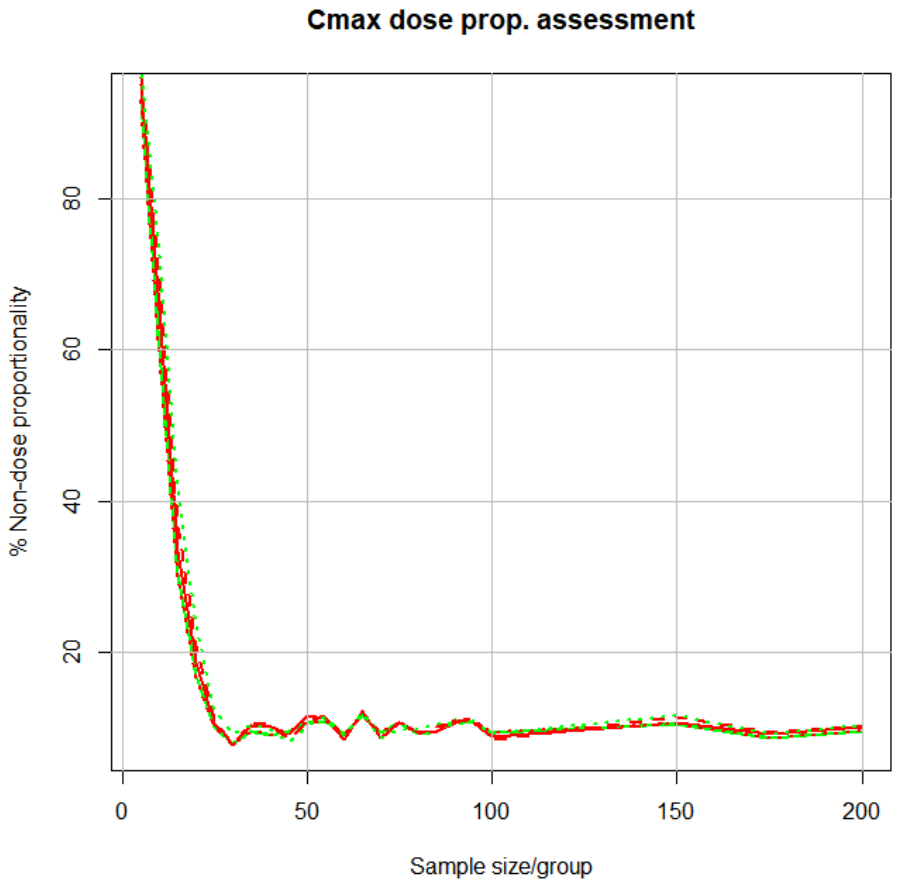
DOSE PROPORTIONALITY ASSESSMENT





- Model specifications:
  - PK param.: Ka = 0.5; CL = 0.03; V = 0.5
  - Dose: 5, 25, 125
  - Timepoints: n=12, up to 72h
  - BSV: AUC CV% ≈ 20-25%
  - Bias: **Constant**

- Trends for decreasing bias with this model specifications were the same as for increasing bias so they have not been plotted.

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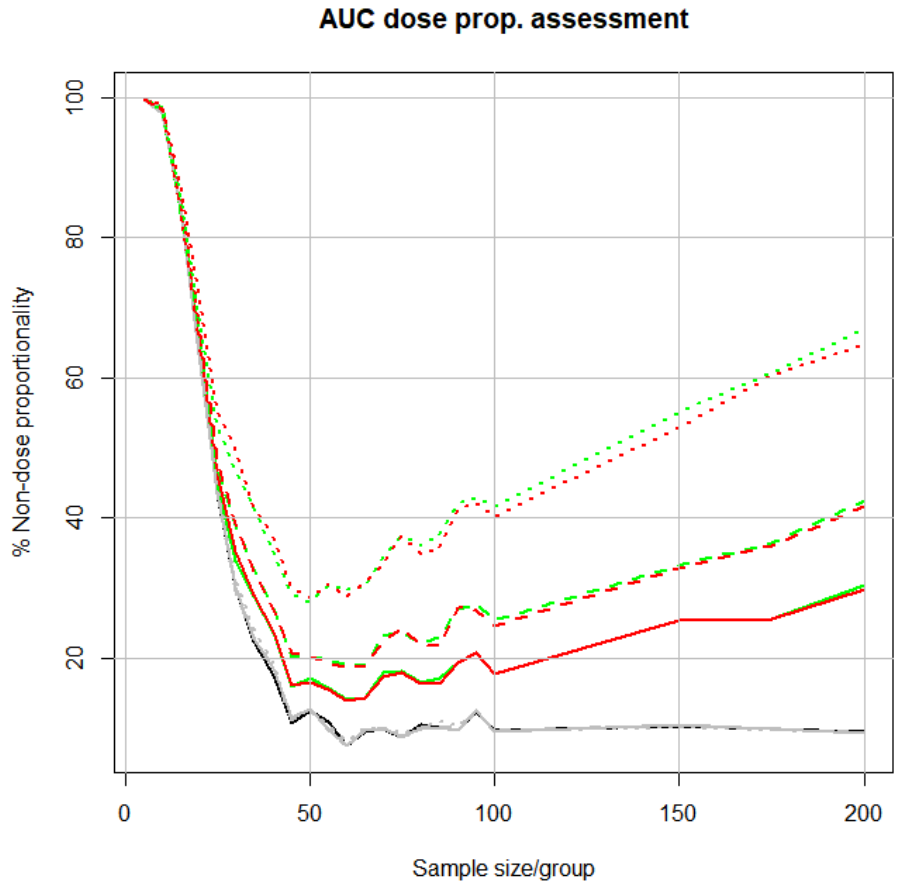
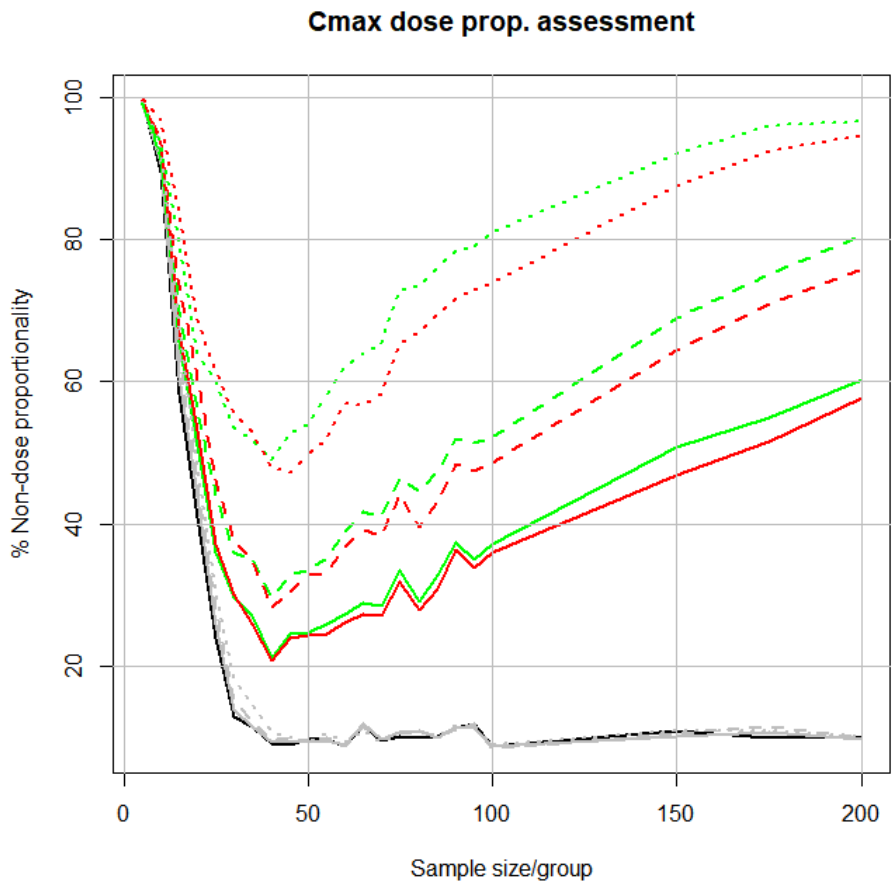
DOSE PROPORTIONALITY ASSESSMENT





- Model specifications:
  - PK param.: Ka = 0.5; CL = 0.03; V = 0.5
  - Dose: 5, 25, 125
  - Timepoints: n=12, up to 72h
  - BSV: AUC CV% ≈ **30-35%**
  - Bias: Increasing

- With increased BSV and this model specifications the trends were the same but more sample size was needed to detect differences

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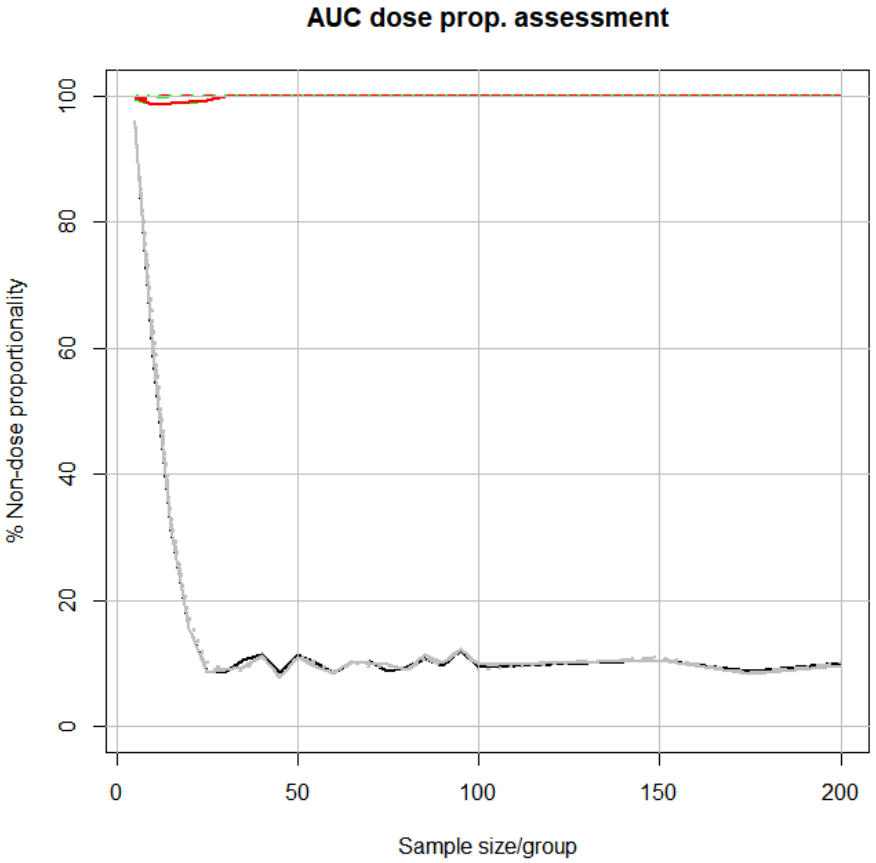
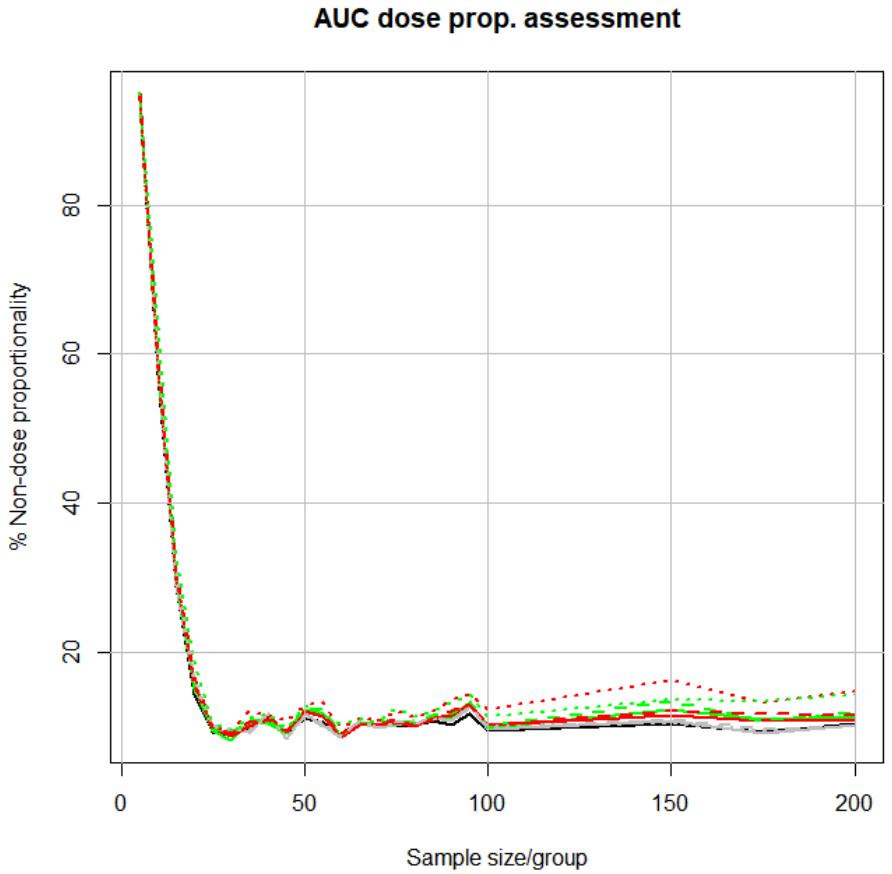
DOSE PROPORTIONALITY ASSESSMENT (AUC)



- Model specifications:
  - PK param.: Ka = 0.5; CL = 0.03; V = 0.5
  - Dose: **10, 100, 1000**
  - Timepoints: n=12, up to 72h
  - BSV: AUC CV% ≈ 20-25%
  - Bias: Increasing



- Model specifications:
  - PK param.: Ka = 0.5; CL = 0.03; V = 0.5
  - Dose: **5, 15, 25**
  - Timepoints: n=12, up to 72h
  - BSV: AUC CV% ≈ 20-25%
  - Bias: Increasing

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CONCLUSIONS

- In the absence of bias, bioanalytical variability (WSV) around the true estimate (up to 30% deviation from target) did not have an impact on the assessment of dose proportionality for AUC or Cmax (using power model method), when compared with the assessment using predicted results from the model without WSV.
- When increasing or decreasing bias patterns were introduced, the test was able to detect the difference as the sample size increased.
- When bias was introduced, the addition of WSV made some of the intervals to contain 1 for the β coefficient of the model and therefore, dose proportionality was declared more times with bias + WSV than with bias alone. This effect was more pronounced for Cmax.
- The impact of bias depended on several factors:
  - The degree of BSV (physiological variability) the model introduced.
  - The tested dose range (fold increase between low and high dose levels).
  - The sample size.