Incorporating Uncertainty and Variability into Various Types of Simulation: Implementation and Application

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Answers That Matter.

Overview

Attempt to facilitate communication and promote consistency by defining a framework for discussion of common types of simulation.

1. **Background**
2. **Framing the question**
3. **Classification System**
4. **Implementation details (NONMEM/S-PLUS)**
5. **Simple Examples**

Introduction

1. Population models are used to codify what we know about a biological system and the effect(s) of a particular drug, or class of drugs.
   The quality of the model is dependent on the information available, and our understanding of the biological system.

2. Simulations are used to explore the implications of population models under differing assumptions or circumstances.
   The quality of the simulation is dependent on our understanding of the specific drug development question being asked.

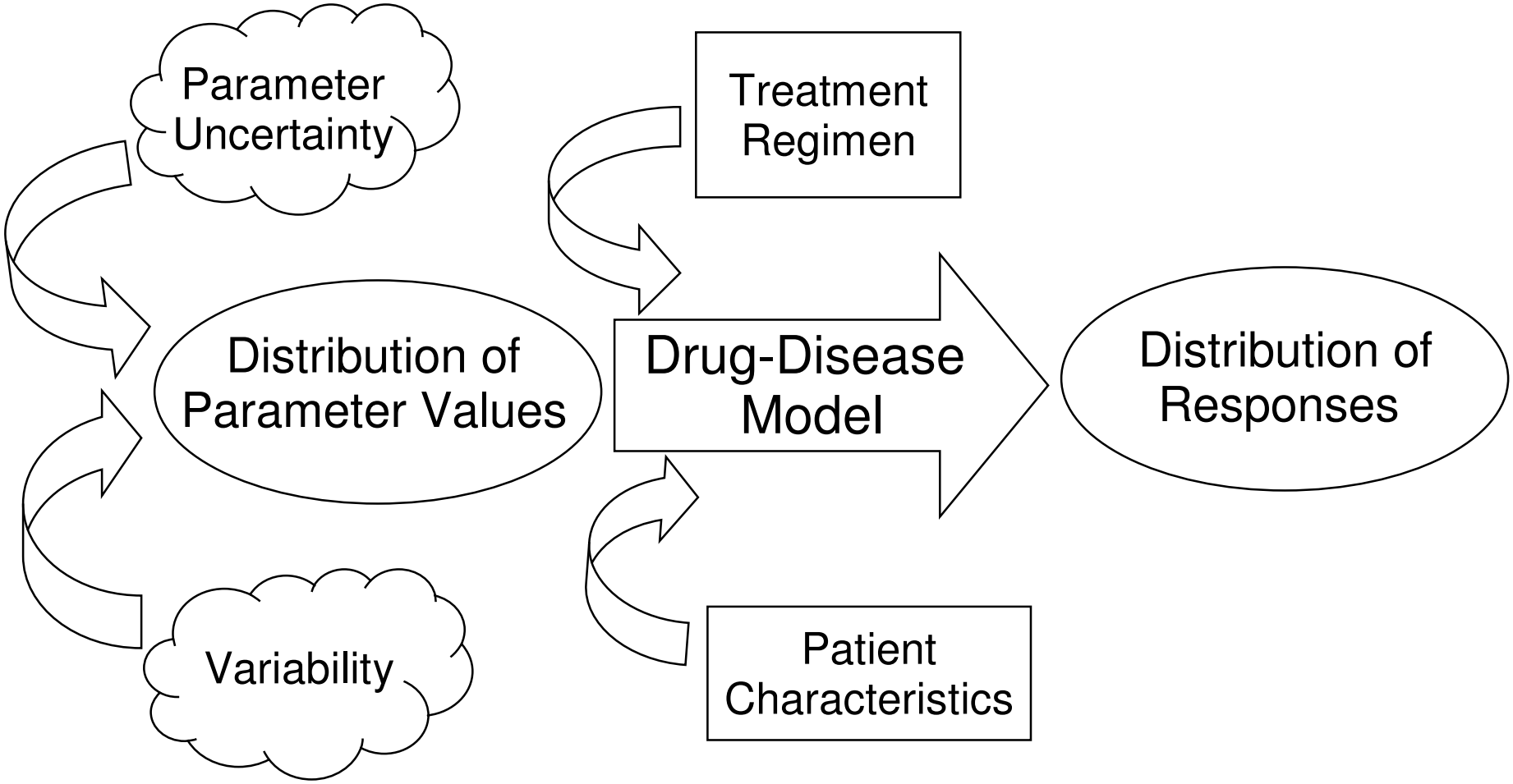
Examples of Simulation Questions

- What dose range should be studied in early clinical trials, given the uncertainty in efficacy and safety?
- What are the probable attributes of the drug in the target patient population?
  - Maximum tolerable dose?
  - Minimum efficacious dose?
  - Margin of safety?
- What is the probability that the intended dose(s) will demonstrate the desired safety and efficacy in the target population?
- Will the proposed trial design unequivocally demonstrate superiority to a comparator in the target population?

Framing the Question

- Understand the question which is being asked.
  - Does the model contain sufficient information? Be aware of your assumptions.
  - Are individual responses important? Study level?
  - Are we extrapolating beyond the current population?
- Have a focused objective for the simulation exercise.
  - Establishing dose
  - Predicting response
- Define explicit criteria for simulation outcomes.
  - e.g. What dose has a 90% probability of achieving the target response?
  - Distributions are not useful for decision making.

Simulation Process



Types of Simulation

The question being asked determines the structure of the simulation to be performed.

- Are we extrapolating beyond the current population?
  - Parameter uncertainty
- Do we need to understand individual patient responses?
  - Inter-patient variability
  - Residual error
- Do we need to understand summary statistics?

Simulations can be categorized based upon this structure.

Types of Simulation

	Uncertainty	Variability	Nested	Simulation Output
Type 1	No	No	No	Typical response in current population

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Type 3	No	Yes	No	Distribution of individual responses in current population

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Type 4	Yes	Yes	No	Distribution of individual responses in next dosed patient(s)

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Type 3	No	Yes	No	Distribution of individual responses in current population
Type 4	Yes	Yes	No	Distribution of individual responses in next dosed patient(s)
Type 5	Yes	Yes	Yes	Distribution of summary statistics in next dosed population (study)

Example PK/PD Model

$$Y = E_0 + \frac{E_{\max} \bullet Dose^{\gamma}}{ED_{50}{}^{\gamma} + Dose^{\gamma}}$$

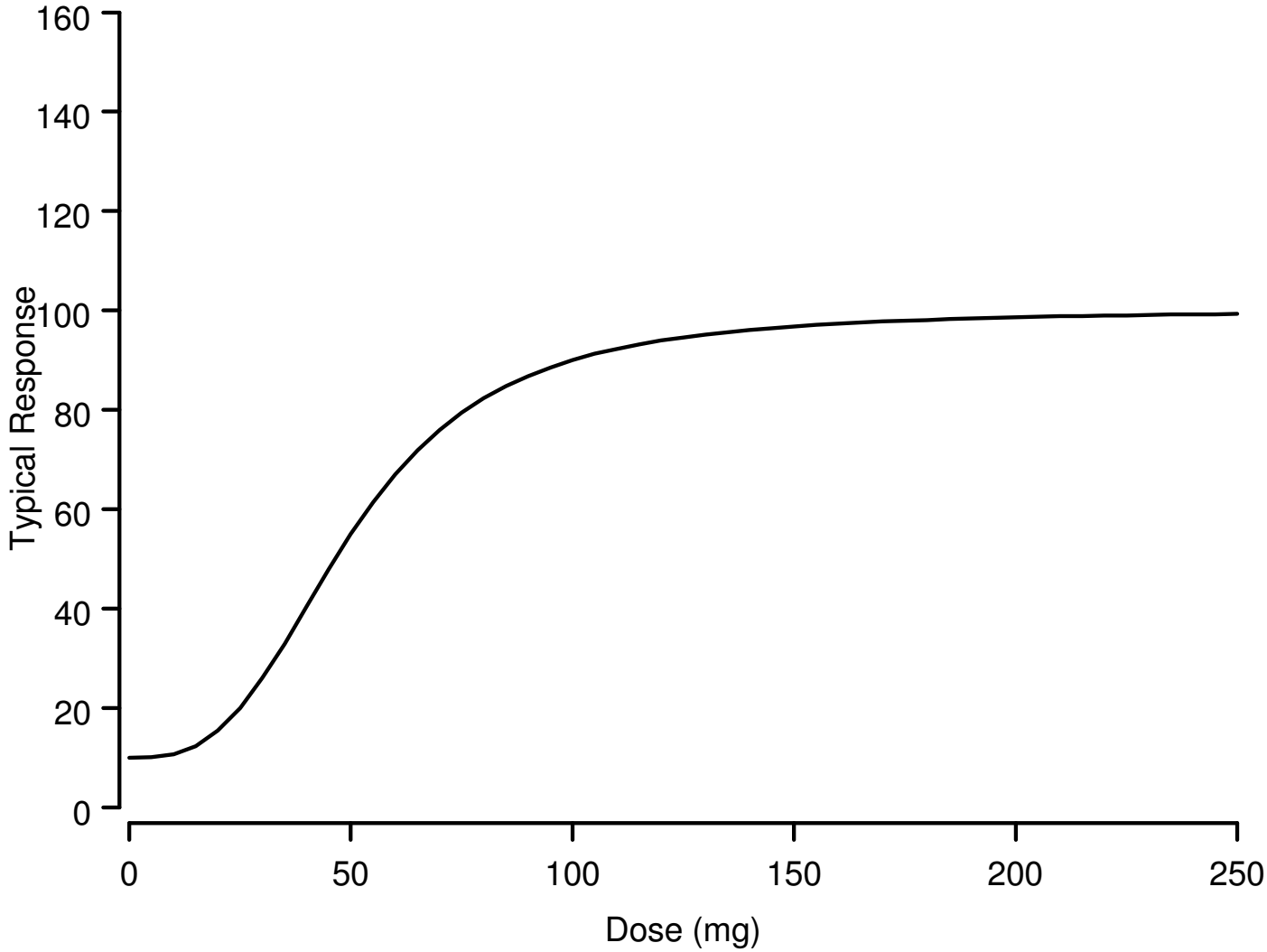
Parameter	Estimate (%SEE)	Inter-Patient Variability (%SEE)
E_0	10 (20%)	0.09 (30%)
E_{max}	90 (10%)	0.09 (40%)
ED_{50}	50 (30%)	0.25 (50%)
Gamma	3 (50%)	---

Type 1: Typical Response

Simulation designed to illustrate typical response in the current analysis population. Purely descriptive.

1. Calculate response from typical parameter values (fixed effects).

Type 1: Typical Response

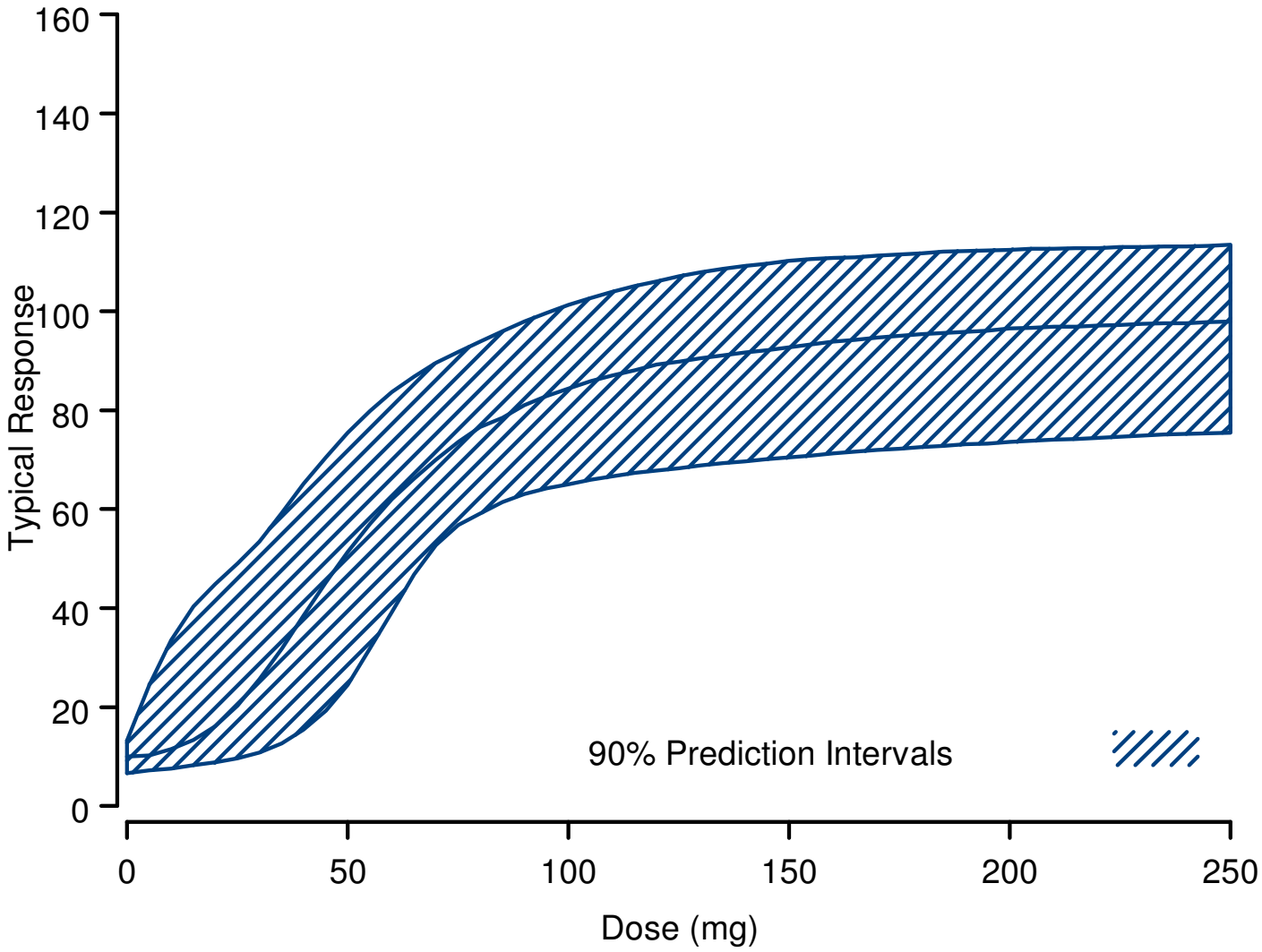


Type 2: Parameter Uncertainty

Simulation designed to explore the distribution of typical responses in future patient populations.

1. Generate N patient populations.
2. Sample from parameter uncertainty to generate a set of parameter values for each population.
3. Calculate responses using N sets of typical parameter values.

Type 2: Parameter Uncertainty

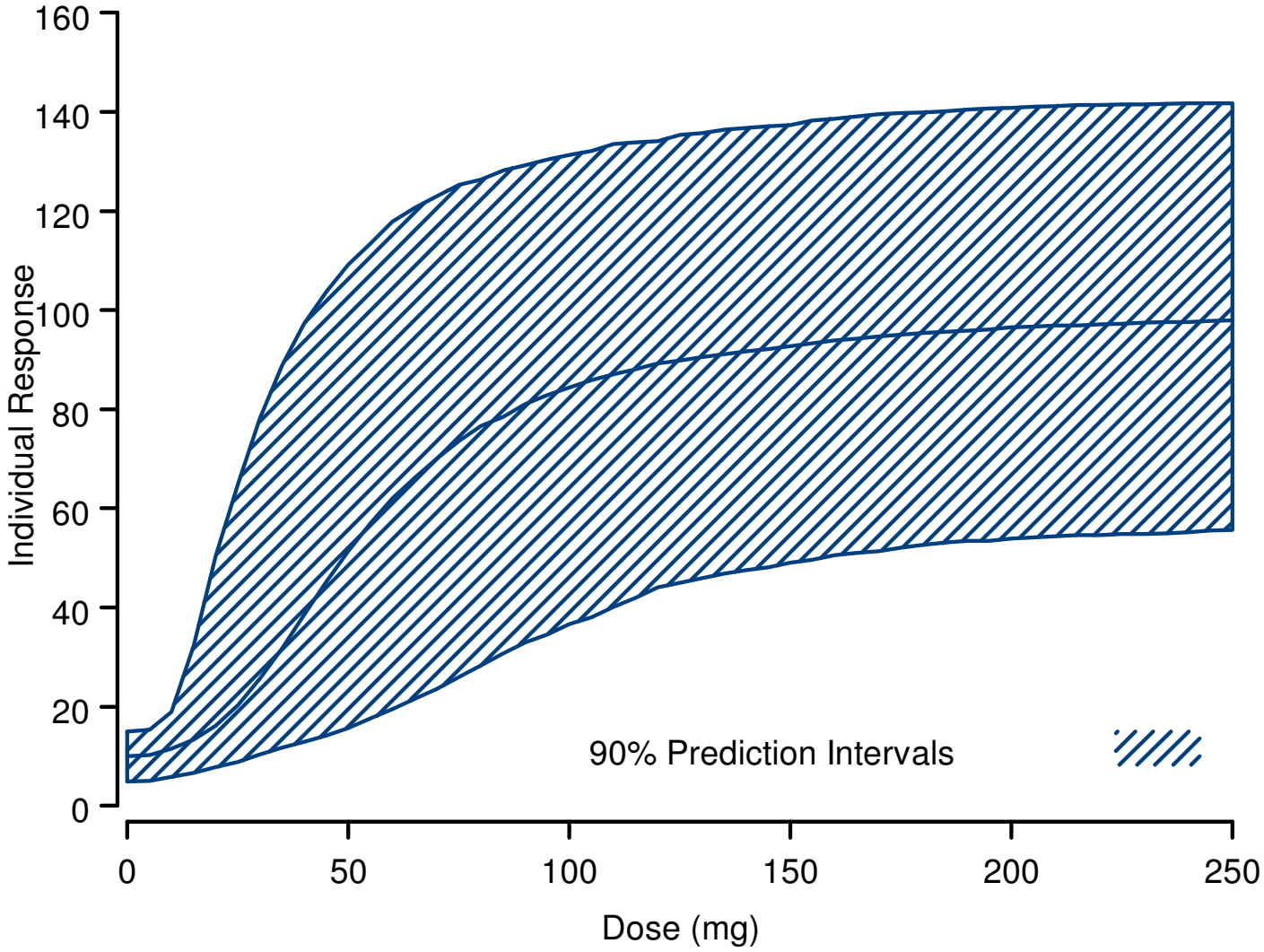


Type 3: Variability of Response

Simulation designed to explore the distribution of individual responses within the current population. Generally descriptive, used for posterior-predictive check.

1. Generate N individual patients.
2. Sample from inter-patient and inter-occasion variability to generate a set of parameter values for each patient/occasion.
3. Calculate responses using N sets of parameter values.
4. Sample from residual error to add random “noise” to observations. [Optional]
   - Yes: Interested in actual observation or measurement.
   - No: Interested in expectation of response.

Type 3: Variability of Response

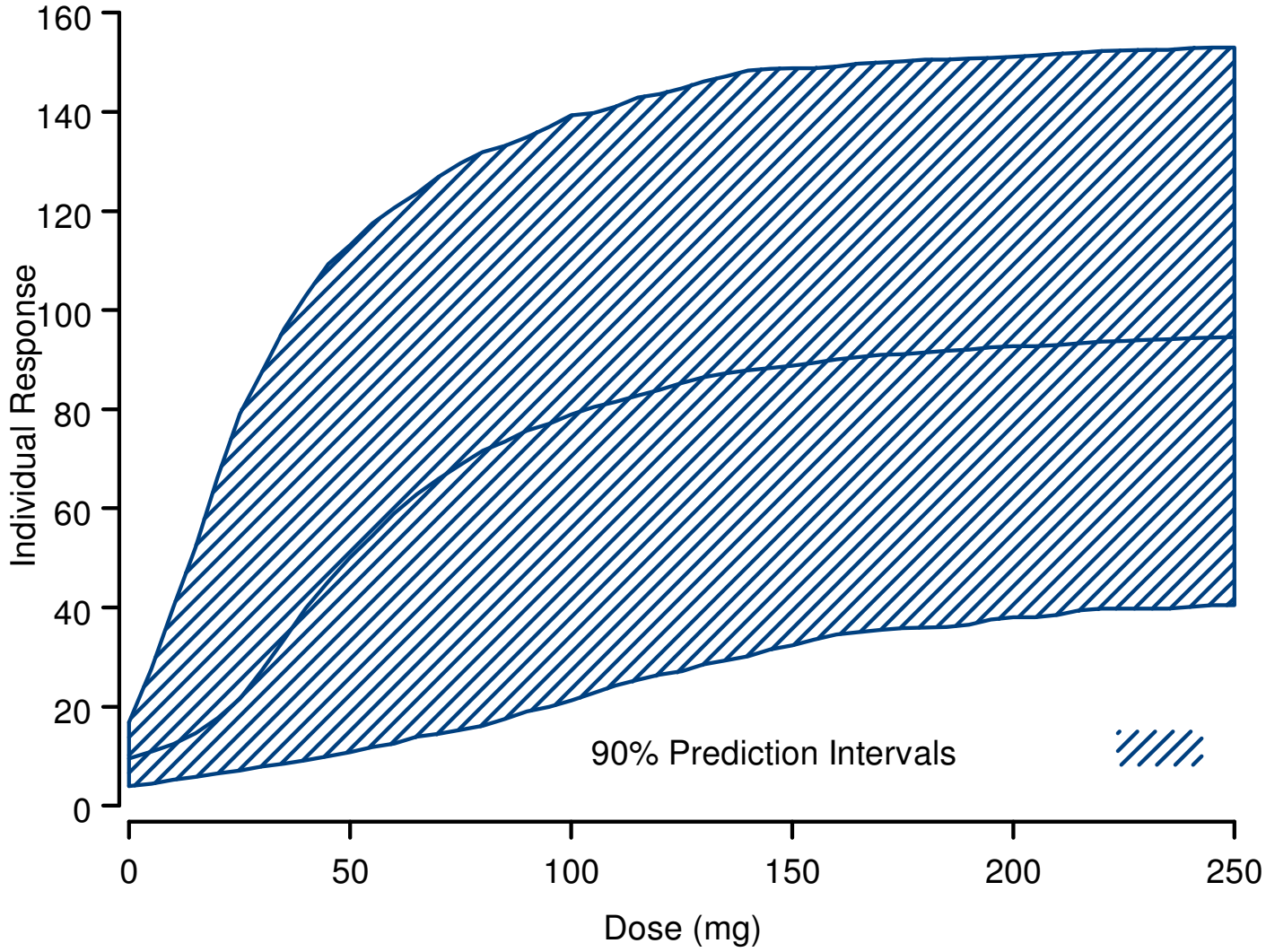


Type 4: Uncertainty and Variability "Next Dosed Patient"

Simulation designed to explore the distribution of individual responses within future patient populations.

1. Generate N patient populations, sampling from parameter uncertainty to generate a set of parameter values for each population.
2. Sample from inter-patient and inter-occasion variability, to generate individual parameter values for 1 patient in each population.
3. Calculate responses using N sets of individual parameter values.
4. Sample from residual error to add random "noise" to observations. [Optional]

Type 4: Uncertainty and Variability "Next Dosed Patient"

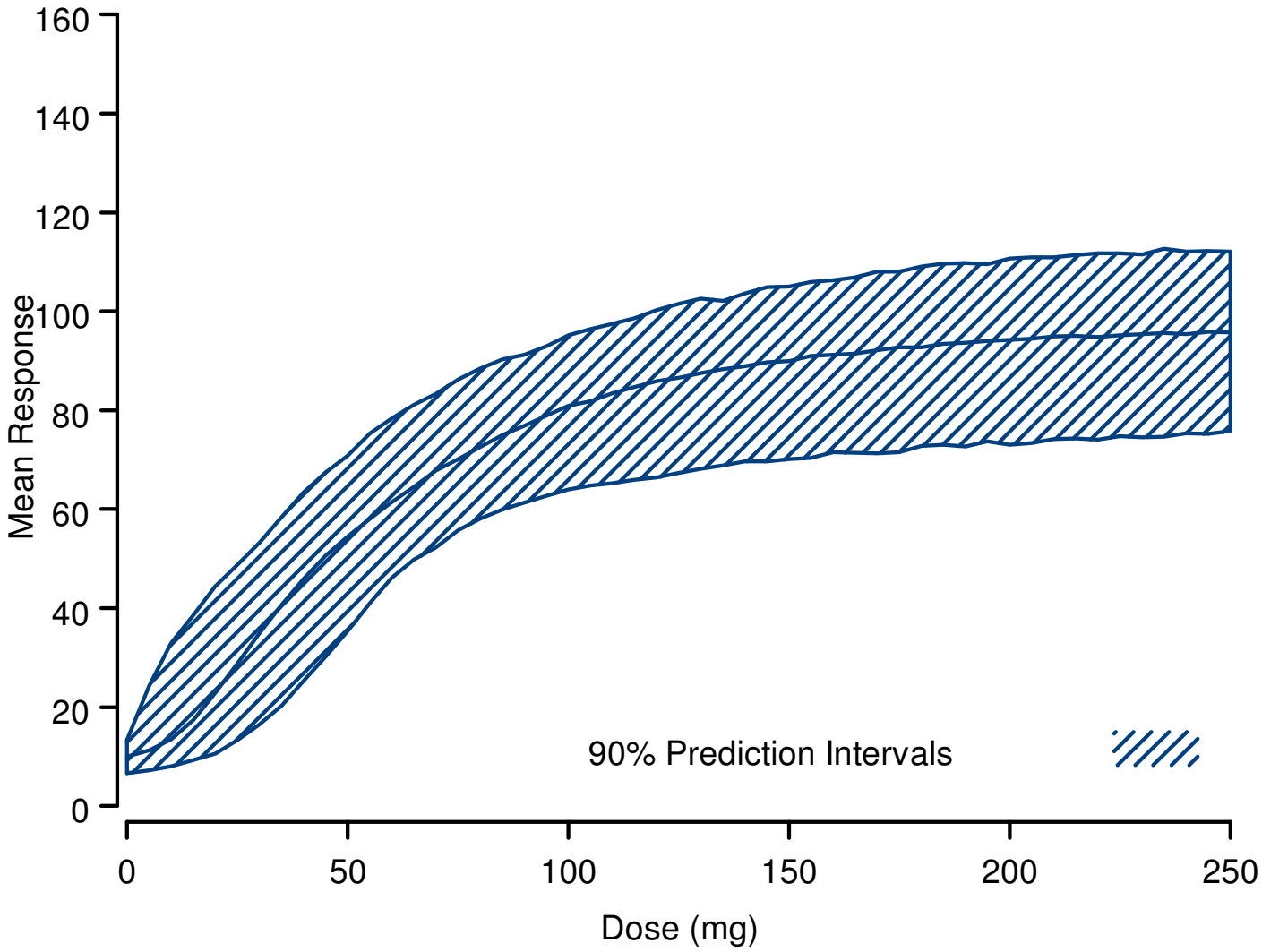


Type 5: Nested Simulation

Simulation designed to explore the distribution of a statistic which is calculated from a patient population, such as mean response.

1. Generate N patient populations, sampling from parameter uncertainty to generate N sets of parameter values.
2. Sample from inter-patient and inter-occasion variability to generate individual parameter values for M patients within each population.
3. Calculate individual responses from M x N sets of individual parameter values.
4. Sample from residual error to add “noise” to individual responses. [Optional]
5. Summarize the M patient responses for each of the N populations.

Type 5: Nested Simulation



Implementing Variability

Inter-Patient Variability:

Sample from normal distribution of ETA values, using NONMEM variance estimate.

```
cl <- tvcl*exp(rnorm(Nrep,mean=0,sd=sqrt(omega)))
```

OMEGA BLOCK requires multivariate normal

```
omega.cov <- rbind(c(omega[1],omega[2]),c(omega[2],omega[3]))

eta <- rmvnorm(Nrep,mean=c(0,0),sd=sqrt(omega.cov))

cl <- tvcl*exp(eta[1])

v <- tvv*exp(eta[2])
```

Implementing Variability

Inter-Occasion Variability:

As with inter-patient variability, sample from random normal distribution. Generate separate random value for each occasion rather than each patient.

Residual Error:

Sample from random normal distribution, using NONMEM variance estimate.

```
conc.err <- conc*(1 + rnorm(length(conc),mean=0,sd=sqrt(SIGMA)))
```

```
conc.err <- conc + rnorm(length(conc),mean=0,sd=sqrt(SIGMA))
```

Parameter Uncertainty

The precision of our parameter estimates is limited by our current knowledge and the information content of the data.

Can be quantified using:

- NONMEM Covariance Matrix
  - Assumes uncertainty is normally distributed
- Bootstrap Analysis
  - Non-parametric Bootstrap (Large N)
  - Parametric Bootstrap
- Educated Guess

Implementing Parameter Uncertainty

NONMEM Covariance Matrix:

1. Output into file (INFN routine)
2. Import into S-PLUS (or R)
   - Separate parameter estimates from covariance matrix
   - Remove entries for fixed parameters and off-diagonal variance parameters which are not estimated
3. Generate parameter distributions
   parms <- rmvnorm(Nrep,mean=estimates,cov=covariance)
4. If necessary, screen out unrealistic parameter values e.g. negative variance values

Implementing Parameter Uncertainty

Bootstrap Analysis:

1. Summarize bootstrap parameter estimates
2. Import into S-PLUS (or R)
   - Remove non-convergent runs
3. Sample parameter values

No assumptions about distribution of uncertainty.

Should not encounter unrealistic parameter values

Making Inferences About Drug Attributes

Phase 1 Example

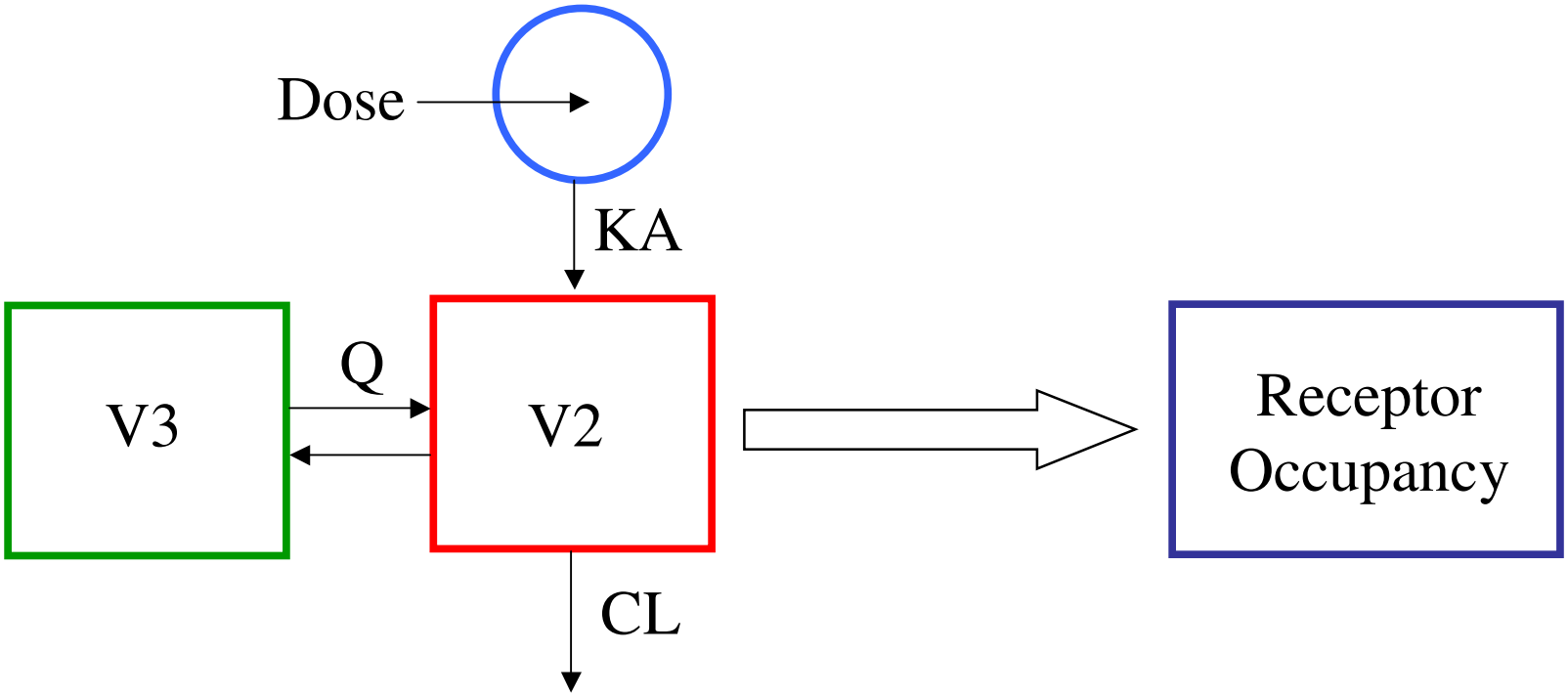
Compound X is an investigational drug which targets the Z receptor. Plasma concentration and receptor occupancy data are available from the first study in humans.

Design upcoming proof-of-concept study:

1. Toxicology data indicate that peak plasma concentrations should not exceed 500 ng/mL in any patient.
2. Would like to maintain receptor occupancy (RO) above 75% for the duration of the steady-state dosing interval.

Question: What dosing regimens should be studied?

Population PK/PD Model



$$RO(\%) = E_0 + (E_{\max} - E_0) \cdot \frac{Conc}{Conc + EC_{50}}$$

Parameter Estimates

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Rate of Absorption: Ka (hr^{-1})	0.768 (13.5)	N/E
Apparent Clearance: CL (L/hr)	66.5 (13.4)	0.201 (42.1)
Covariance between CL and V	---	0.207 (46.8)
Volume of Distribution: V2 (L)	329 (20.2)	0.317 (42.6)
Inter-compartmental Clearance: Q (L/hr)	65.9 (6.59)	N/E
Volume of Distribution: V3 (L)	945 (10.2)	N/E
Receptor Occupancy Baseline: E_0 (%)	1.89 (12.1)	N/E
Maximum Response: Emax (%)	100 (FIXED)	---
Potency: EC_{50} (mg)	3.63 (13.8)	0.210 (43.1)
Residual Error (PK)	19.3% (17.7)	
Residual Error (PD)	12.9% (17.5)	

Framing the Question

Question: What dosing regimens should be studied?

Define explicit criteria for simulation outcomes.

High Dose: Dose at which maximum steady-state concentrations will be below 500 ng/mL in 90% of patients.

Low Dose: Dose at which minimum steady-state receptor occupancy will be above 75% in 90% of patients.

Simulation Considerations

Interested in individual responses in new patient population:

Type 4 Simulation

- Parameter Uncertainty
- Inter-patient Variability
- Residual Error?

Safety criteria concerns *observation* of maximum concentration:
Residual error is necessary for simulation of PK.

RO criteria based upon assumption that biomarker is related to efficacy, actual observation is unimportant:
Residual error not necessary for simulation of RO.

Implementation in S-PLUS

Code PK/PD Model(s)

```
advan4.ss <- function(theta,tfds,dose,tau)  {
   …
   conc <- A*A1*exp(-ka*tfds)+B*B1*exp(-alpha1*tfds)+C*C1*exp(-alpha2*tfds)
   return(conc)
   }
Direct.Response <- function(theta,conc)  {
   …
   resp <- e0 + (emax-e0)*conc/(ec50 + conc)
   return(resp)
   }
```

Create grid to hold simulated responses.

```
Nrep <- 1000
tfds <- seq(0,24,0.1)
doses <- seq(0,200000,5000)
results <- expand.grid(REP=(1:Nrep),TFDS=tfds,DOSE=doses,CONC=0,RO=0)
```

Implementation in S-PLUS

Generate Nrep sets of parameter estimates using NONMEM covariance matrix, screen out non-positive-definite OMEGA BLOCK matrices.

```
parms <- rmvnorm(Nrep,mean=estimates,cov=covariance)
```

Generate ETA values for CL and V2, including covariance.

```
for(ii in 1:nrow(parms))  {
   cov.clv <- rbind(c(parms[ii,8],parms[ii,9]),c(parms[ii,9],parms[ii,10]))
   eta.clv[ii,] <- rmvnorm(1,mean=c(0,0),cov=cov.clv)
   }
```

Incorporate inter-patient variability into parameter values.

```
parms <- cbind.data.frame(REP=(1:Nrep),KA=parms[,1],CL=parms[,2]*exp(eta.clv[,1]),
                          V2=parms[,3]*exp(eta.clv[,2]),Q=parms[,4],
                          V3=parms[,5],E0=parms[,6],EMAX=100,
                          EC50=parms[,7]*exp(rnorm(Nrep,mean=0,sd=sqrt(parms[,11]))),
                          SIGMA.PK=parms[,12],SIGMA.RO=parms[,13])
```

Implementation in S-PLUS

Merge parameters into results matrix by REP number.

```
results <- merge(results,parms,by=c("REP"))
```

Calculate concentration and receptor occupancy.

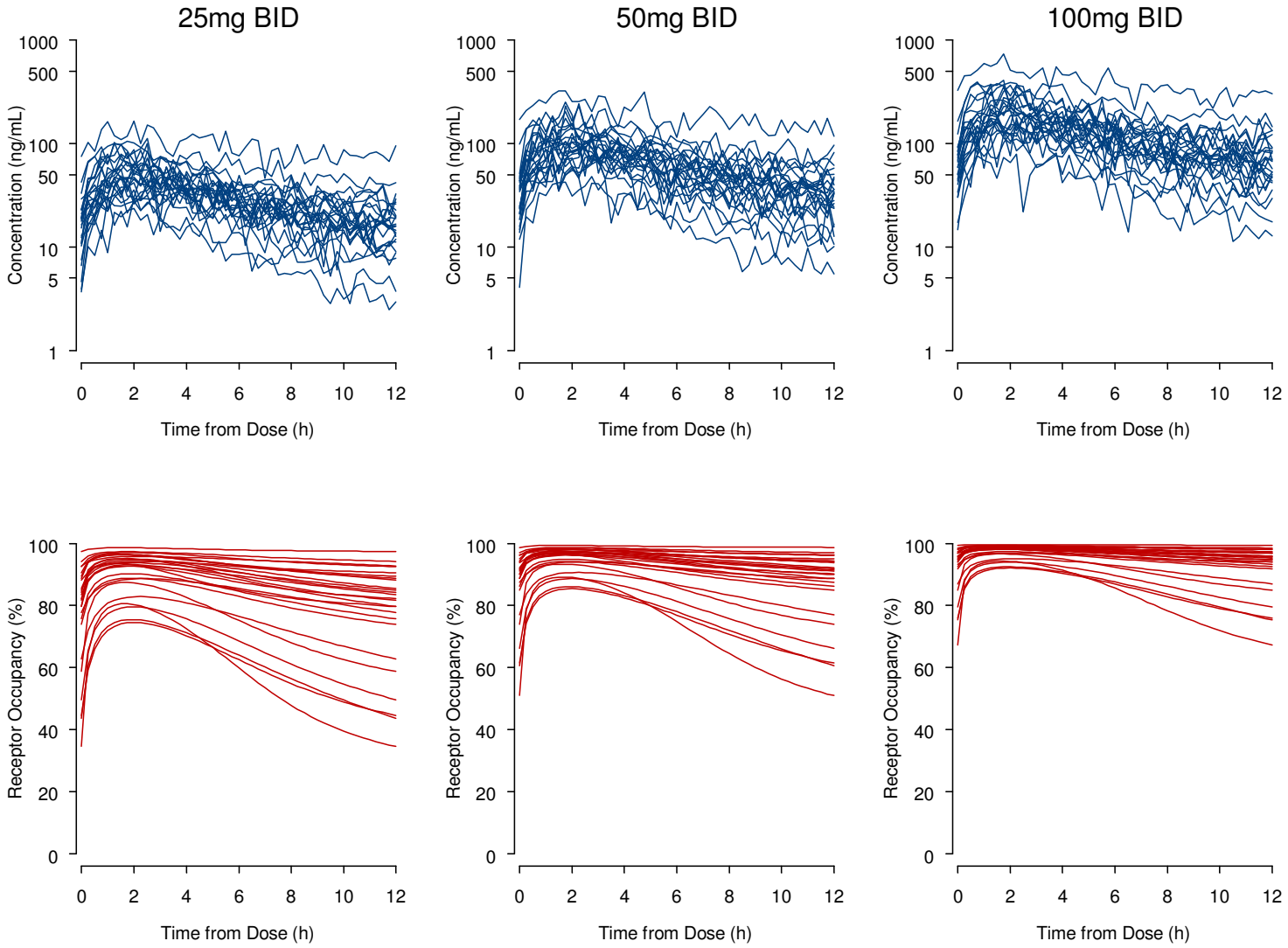
```
results[,"CONC"] <-
            advan4.ss(results[,(6:10)],results[,"TFDS"],results[,"DOSE"],tau=12)

results[,"RO"] <- Direct.Response(results[,(11:13)],results[,"CONC"])
```

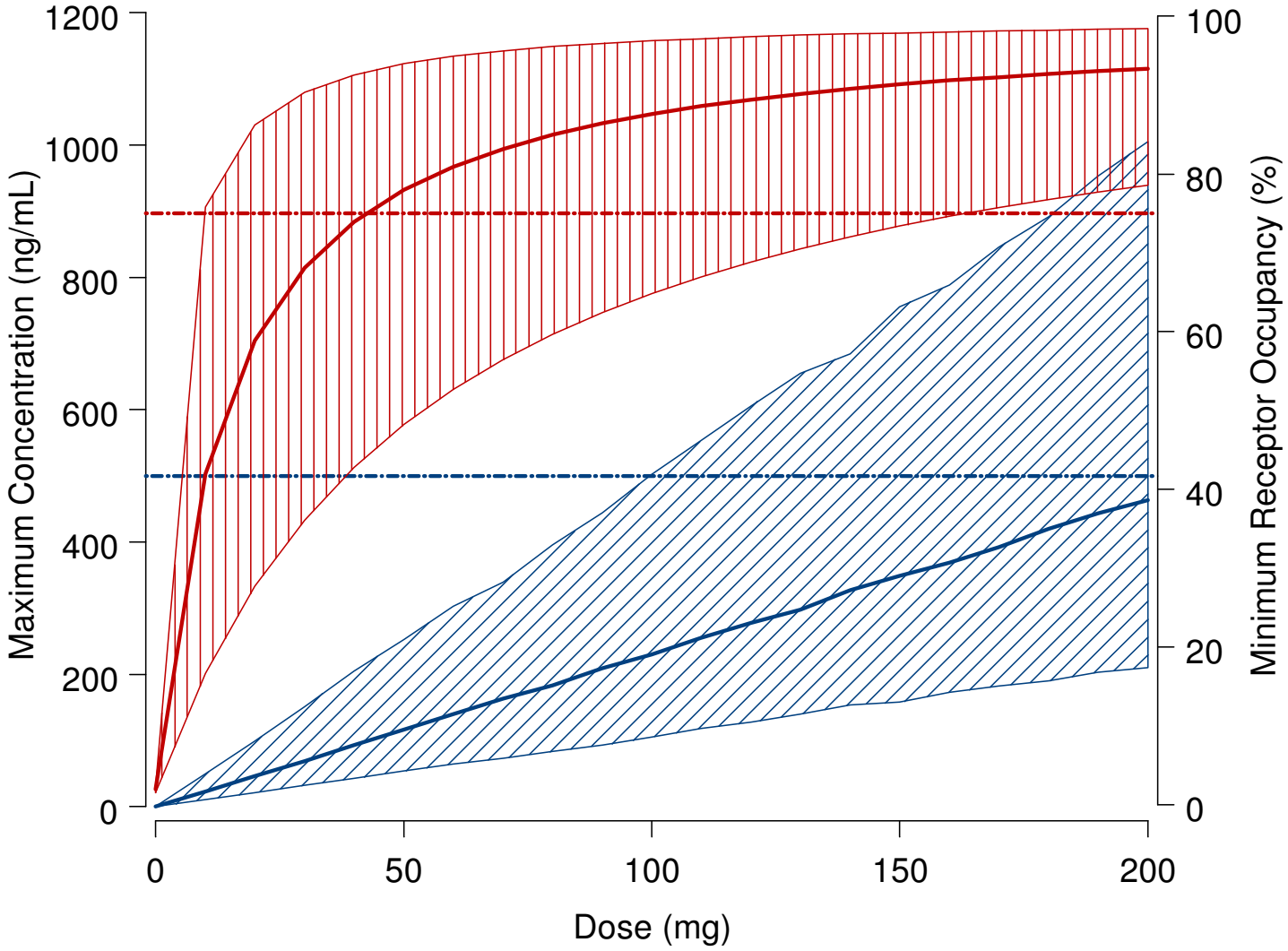
Add residual error to PK observations.

```
results[,"CONC"] <- results[,"CONC"]*
              (1 + rnorm(nrow(results),mean=0,sd=sqrt(results[,"SIGMA.PK"])))
```

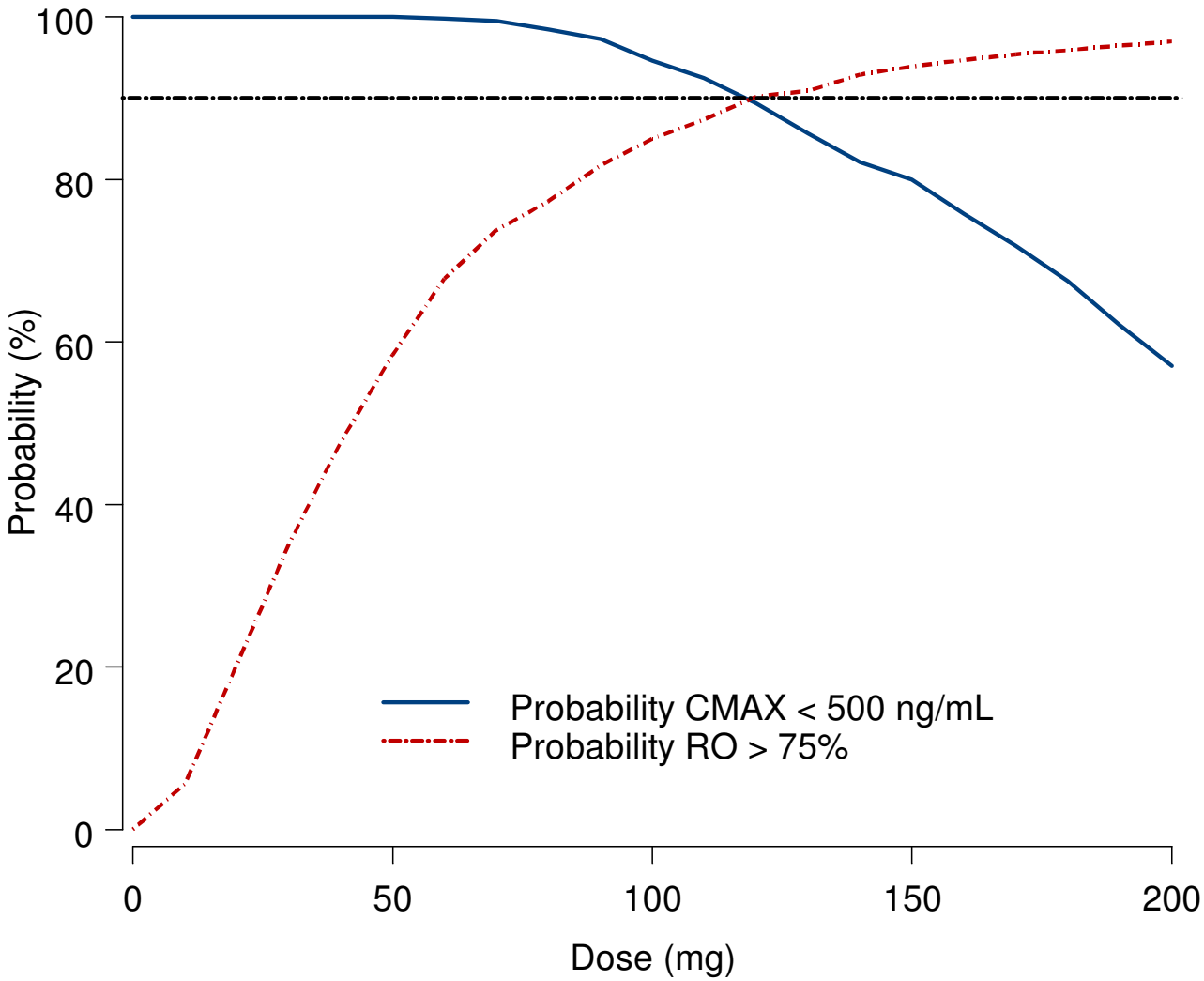
Representative Profiles



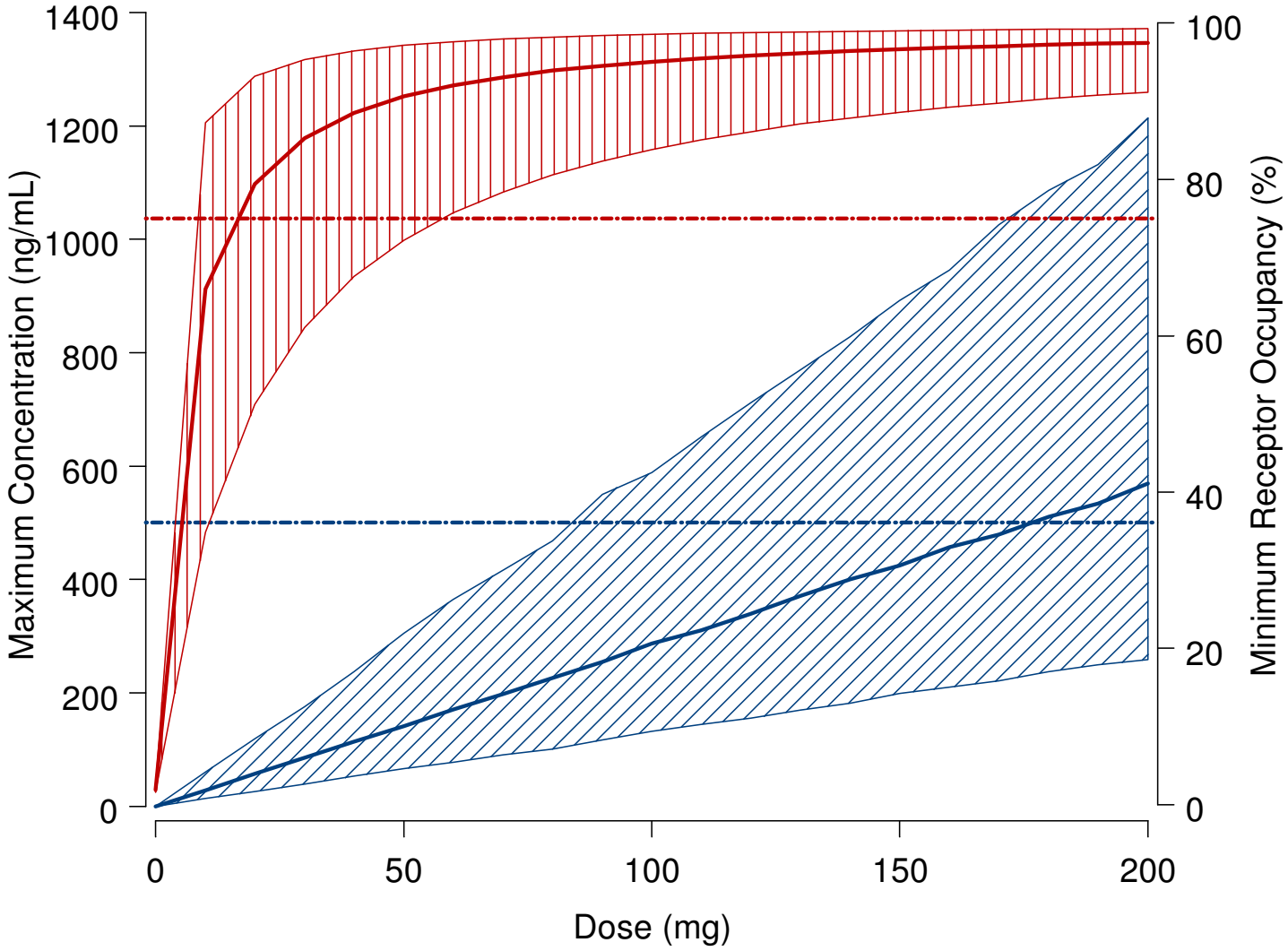
90th Prediction Intervals of Response: QD Dosing



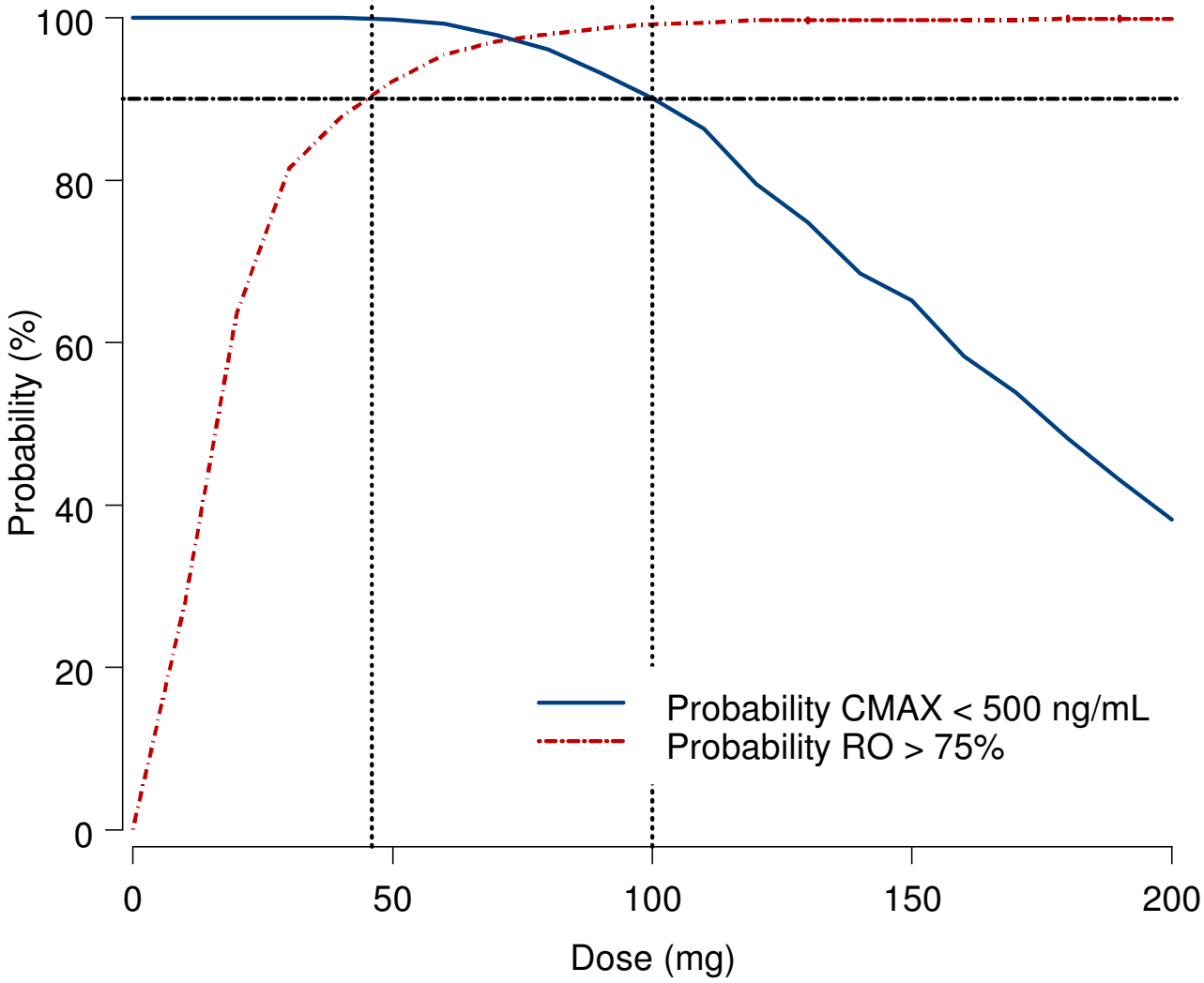
Probability of Response: QD Dosing



90th Prediction Intervals of Response: BID Dosing



Probability of Response: BID Dosing



Conclusions

Simulation provides information on probability of patient responses to aid study design and drug development.

- QD dosing regimen not viable with current compound.
  - Receptor occupancy cannot be maintained without exceeding target concentration limit.
- Maximum dose for POC study is 100 mg BID.
  - Cmax below threshold in 90% of patients.
- Minimum dose for POC study is 50 mg BID.
  - Receptor occupancy maintained in 90% of patients.

Making Inferences About Study Level Responses

Phase 2/3 Example

Compound Y is a second-in-class investigational drug entering late-phase clinical development. Must demonstrate non-inferiority to comparator in order to be commercially viable.

Design Phase 2/3 study:

1. Marketed dose of comparator achieved mean response of 60 units during registration trials.
2. Doses of 50 and 100 mg are targeted for clinical development.

Question: What dose is required to demonstrate non-inferiority to comparator?

Framing the Question

Question: What dose is required to demonstrate non-inferiority to comparator?

Define statistical criteria for non-inferiority:
Mean response within 5% of comparator (> 57)

Define criteria for successful dose:
Dose which has 90% chance of demonstrating non-inferiority in Phase 2/3 study.

Define study design:
Parallel, 25 patients / arm, receiving placebo, 50mg and 100mg of Compound Y.

Simulation Considerations

Interested in study level responses in new patient populations:

Type 5 Simulation

- Parameter Uncertainty
- Inter-patient Variability
- Residual Error
- Nested Simulation

Generate N simulated studies, summarizing individual level responses as the mean.

PD Model

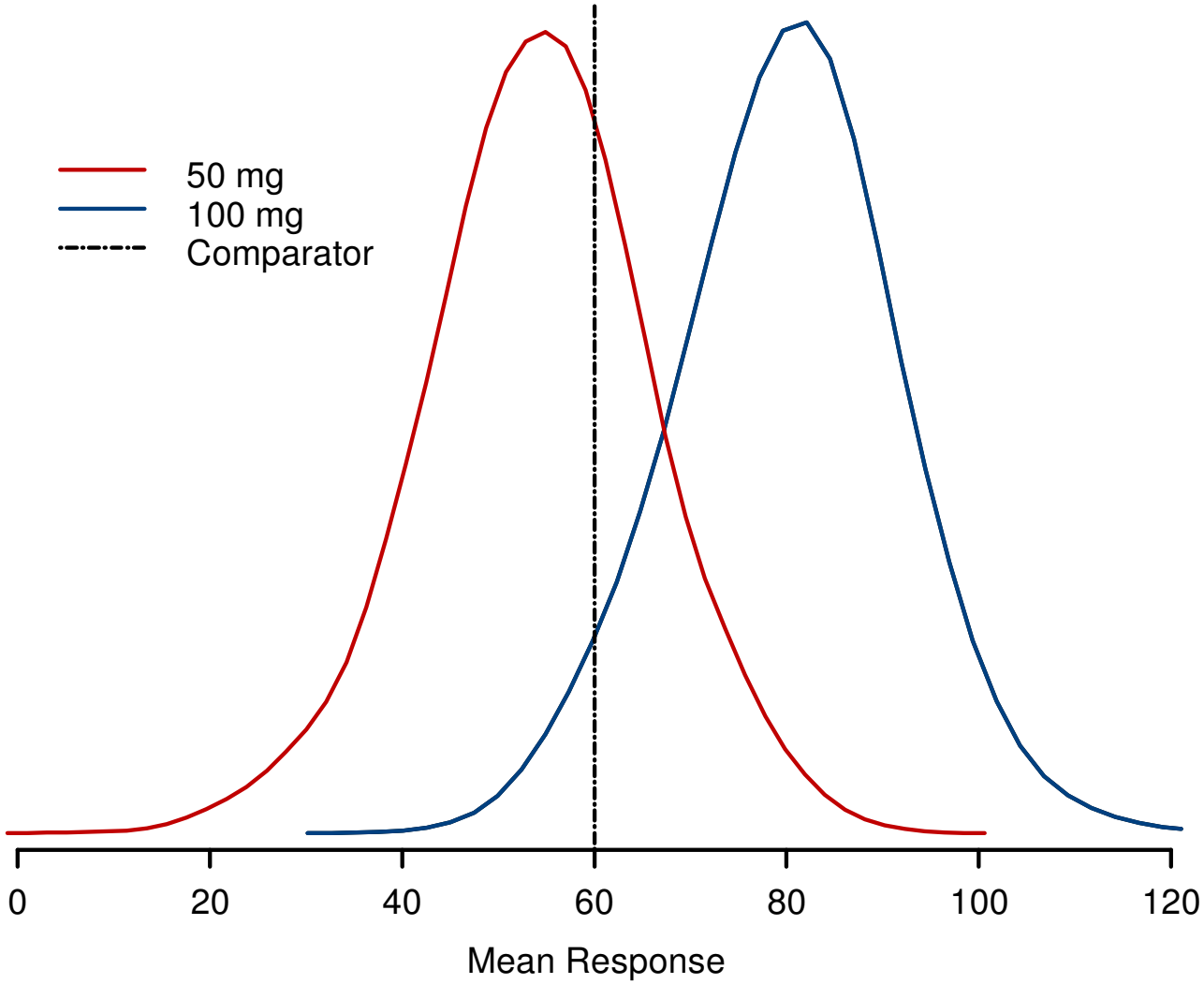
$$Y = E_0 + \frac{E_{\max} \bullet Dose^{\gamma}}{ED_{50}{}^{\gamma} + Dose^{\gamma}}$$

Parameter	Estimate (%SEE)	Inter-Patient Variability (%SEE)
E_0	10 (20%)	0.09 (30%)
E_{max}	90 (10%)	0.09 (40%)
ED_{50}	50 (30%)	0.25 (50%)
Gamma	3 (50%)	---
Residual Error	0.04 (30%)	

Implementation

1. Generate N patient populations, sampling from parameter uncertainty to generate N sets of parameter values.
2. Sample from inter-patient variability to generate individual parameter values for 25 patients within each population.
3. Calculate individual responses from 25 x N sets of individual parameter values.
4. Sample from residual error to add “noise” to individual responses.
5. Calculate the mean of the 25 patient responses for each of the N study arms.
6. Repeat for each dose level.

Distribution of Mean Response



Probability of Non-Inferiority

Non-inferiority:
Mean response within 5% of comparator (> 57)

Successful dose:
90% chance of demonstrating non-inferiority

Probability of mean response > 57

- 50 mg: 40.5%
- 100 mg: 97.7%

Conclusion: 100 mg dose has ~98% chance of demonstrating non-inferiority to comparator.

Summary

- Understand the question which is being asked.
- Have a focused objective for the simulation exercise.
- Define explicit criteria for simulation outcomes.
- The question being asked determines the type of simulation to be performed.
  - Incorporate parameter uncertainty to extrapolate beyond the current analysis population.
  - Incorporate inter-patient and inter-occasion variability to simulate individual-level responses.
  - Incorporate residual error if the observation is of interest, rather than the expectation of response.
  - Use nested simulations to explore summary statistics of study level responses.

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