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Modeling & Simulation Learn to Speak the Language:
Modeling

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Population PK Methodologies

- **Naïve Pooled Data:**
  - Estimate population mean parameters by treating all data as if it arose from the same individual
- **Standard Two-Stage:**
  - Estimate each individual's PK and then use individual parameters to estimate the population parameters
- **Nonlinear Mixed Effects Modeling (NONMEM®):**
  - Mixed effect modeling allows for the fixed effects (mean values) effects and random quantities (variability) and to be simultaneously quantified.
- **Bayesian Estimation:**
  - Use prior distribution of parameters in a population of subjects and data from an individual to estimate the individual's parameters

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Case Study
Study Design

- 100 subjects
- Drug X once daily, orally, for 4 weeks
- Clinic Visits:
  - Screen, Baseline, Day 1 of dosing, and Weeks 2, 3, and 4 of dosing.
    - Week 2, 3, and 4 visits were required to occur within a ±2 day interval of the scheduled day.
- PK Samples:
  - One sample during the clinic visits on Weeks 2, 3, and 4
    - 3 samples per subject
    - Sample Time: anytime during the 24-hour dosing interval

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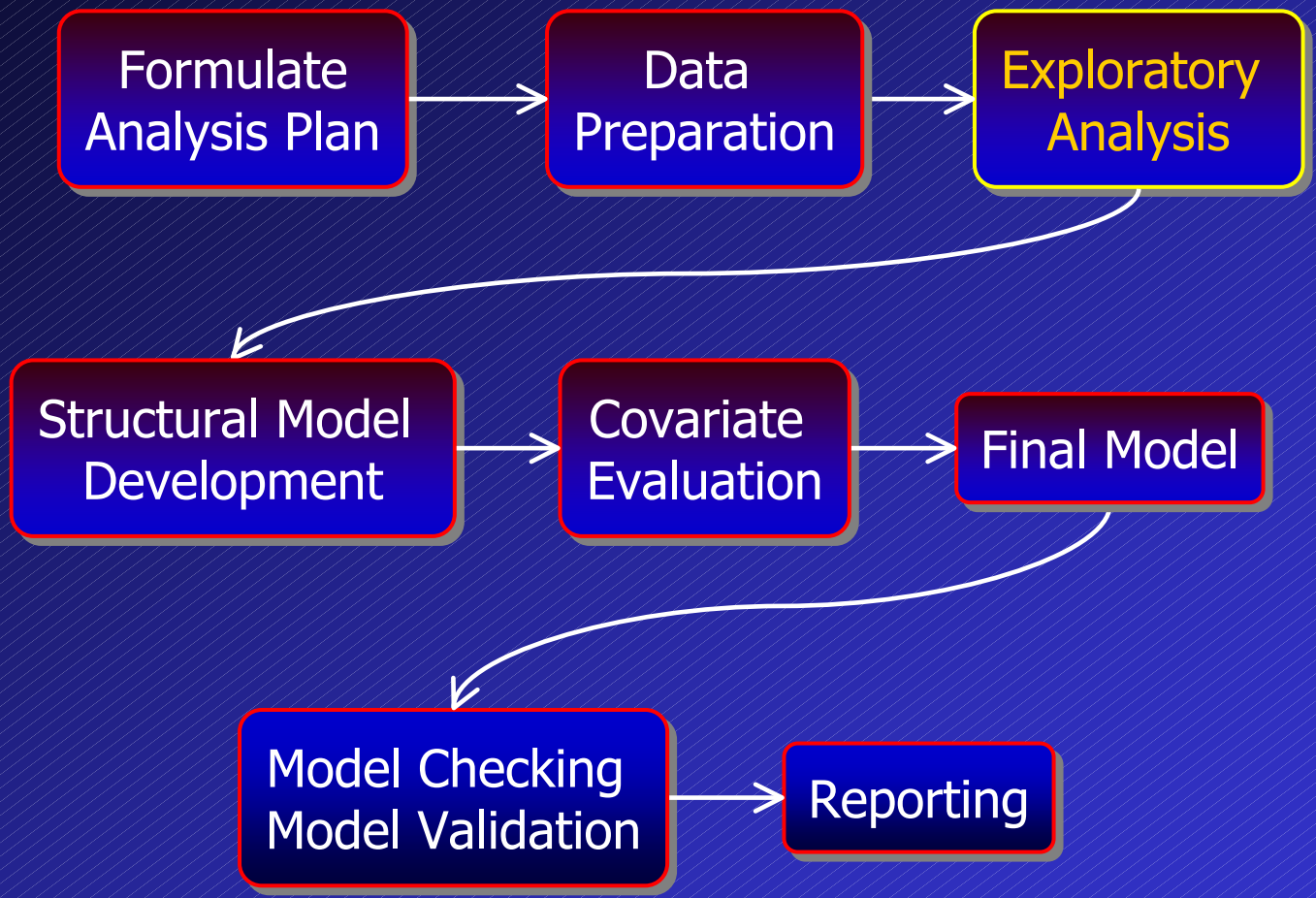
Phases of a Population Analysis



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Exploratory Data Analysis (EDA) What is it?

- The stage of analysis where you gain an understanding of your data
  - Examples of displays to be created during EDA
    - Scatterplot of Cp (concentration) vs TSLD
    - Histograms of continuous subject characteristics
    - Histograms of the number of subjects, the number of samples per subject, the distribution of time since last dose, etc.
    - Summary statistics of subject characteristics, race, gender, age, weight, race by gender, gender by dose, etc.

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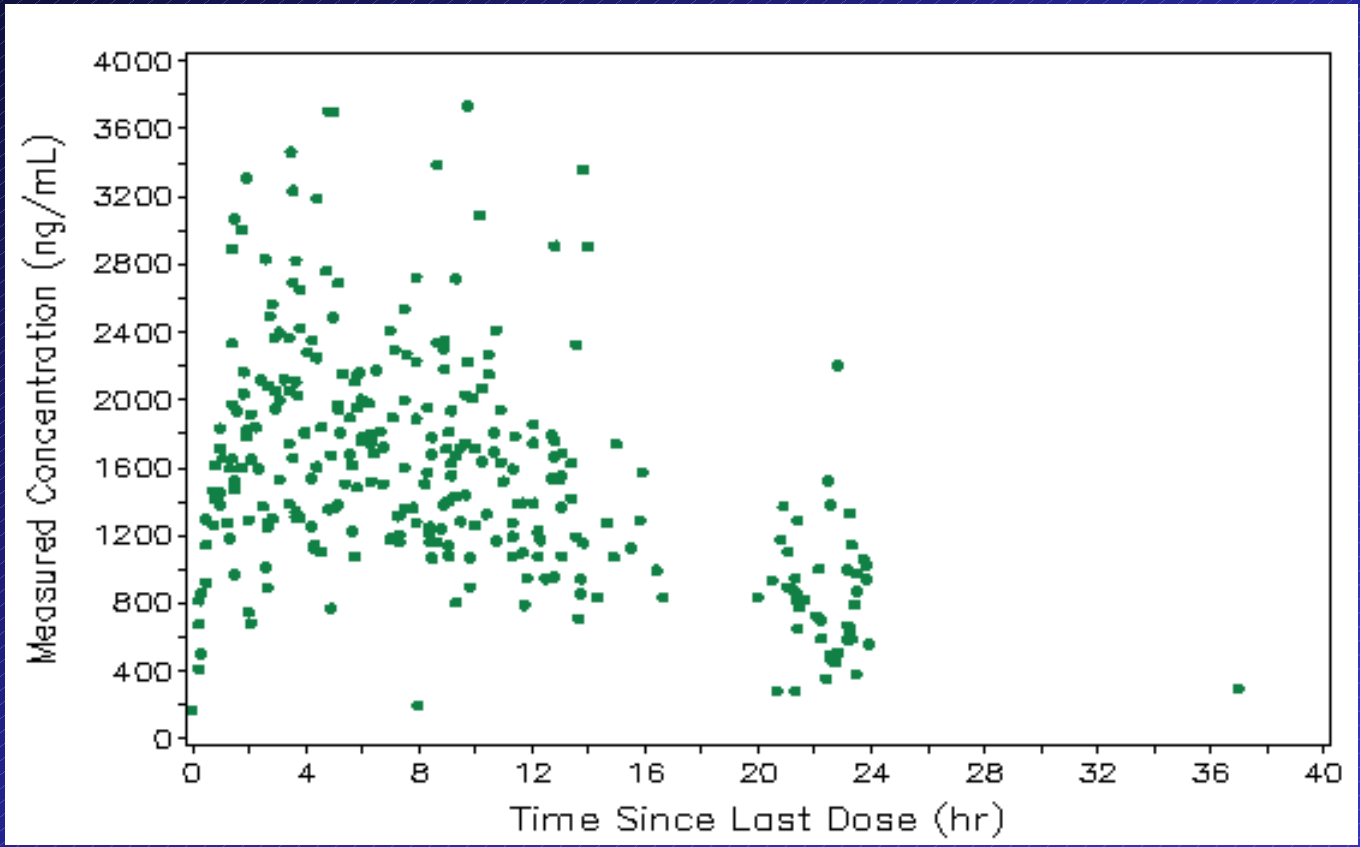
Exploratory Analysis
Cp vs TSLD



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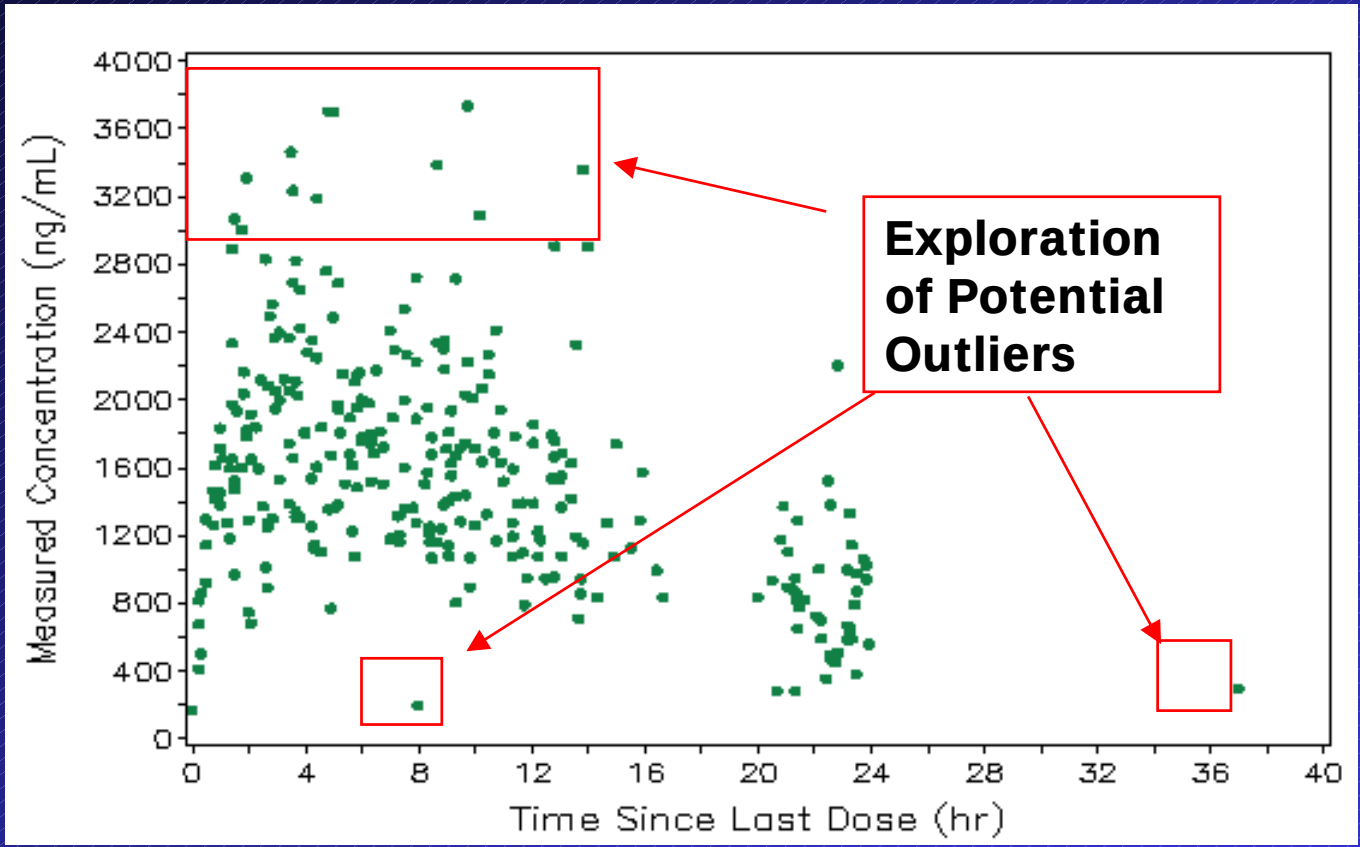

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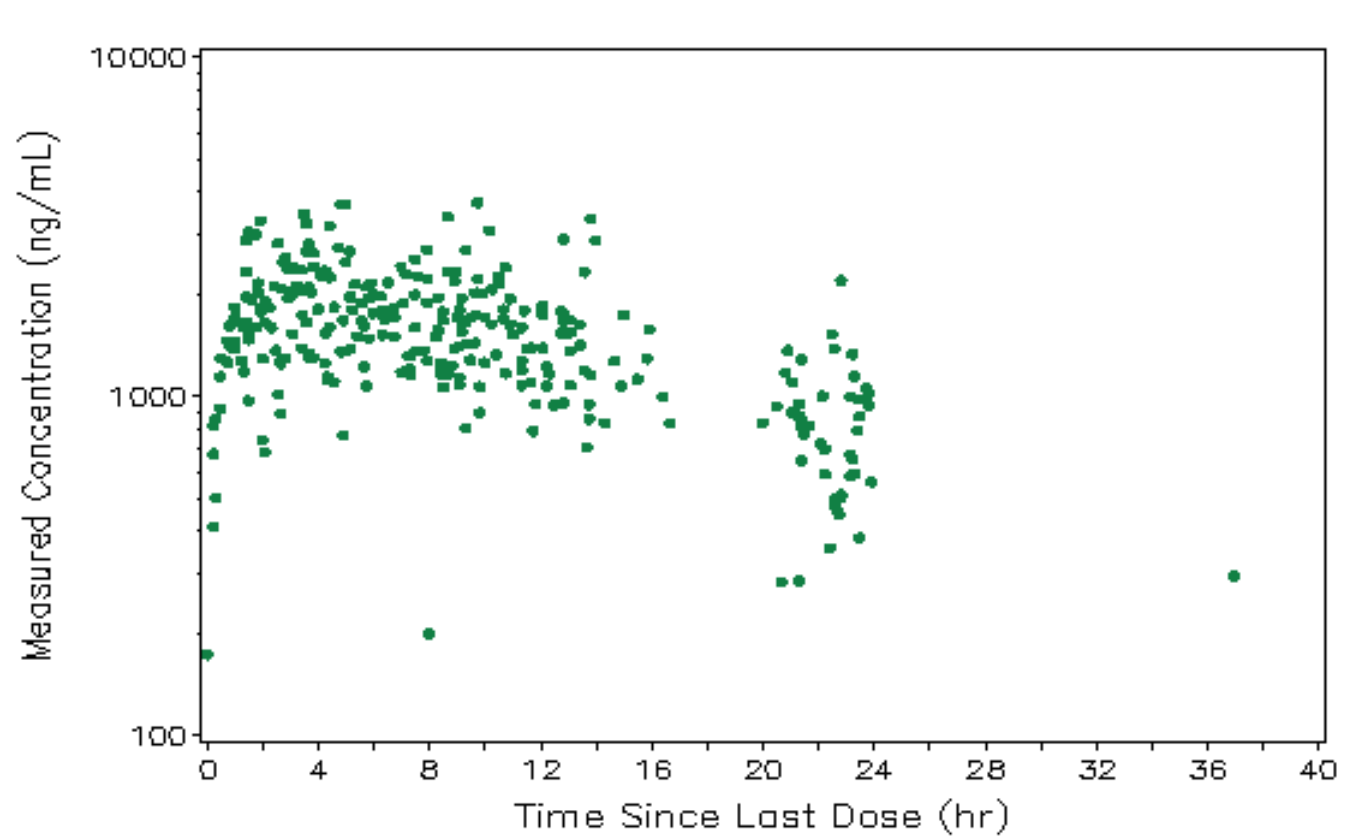
Exploratory Analysis
Cp vs TSLD (log Scale)



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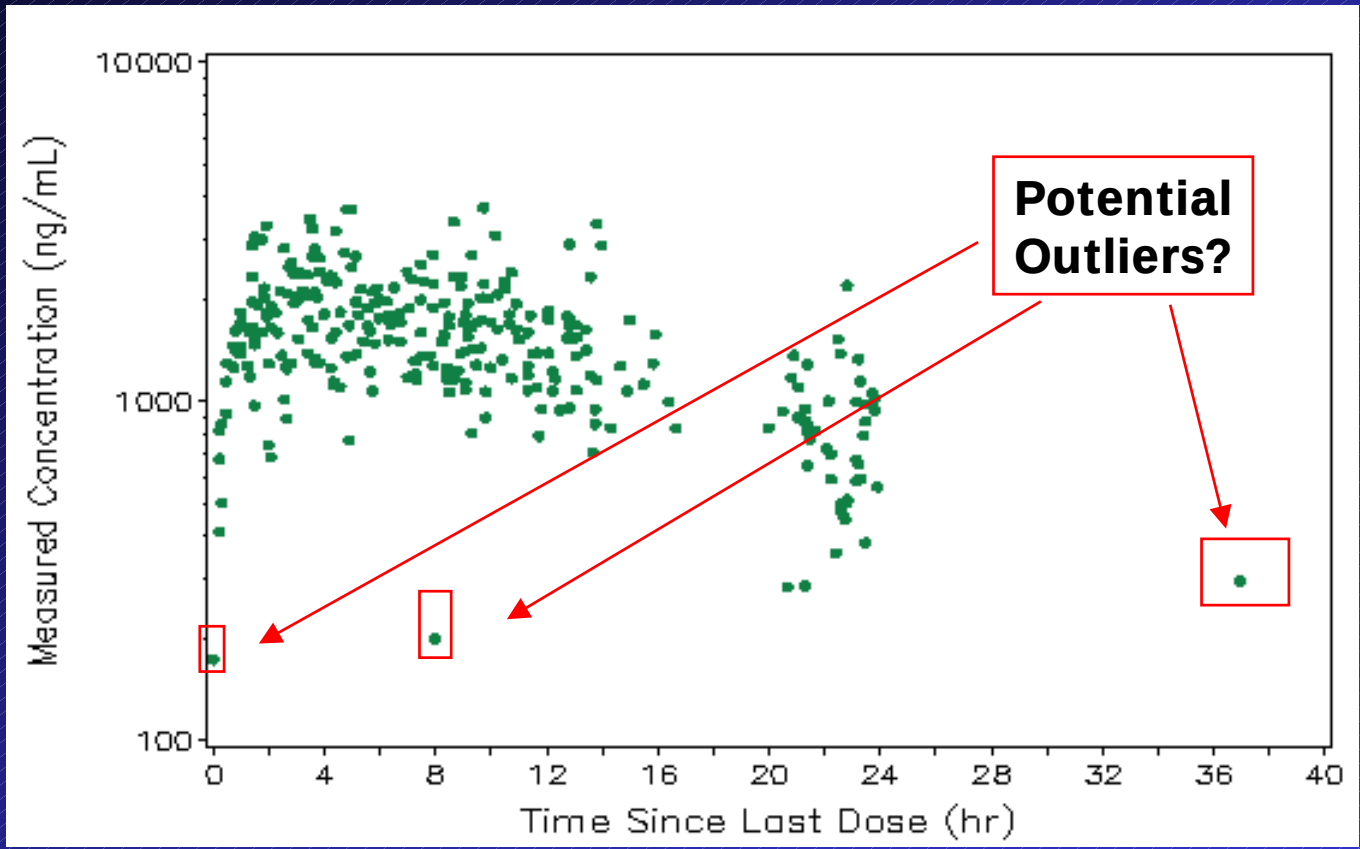

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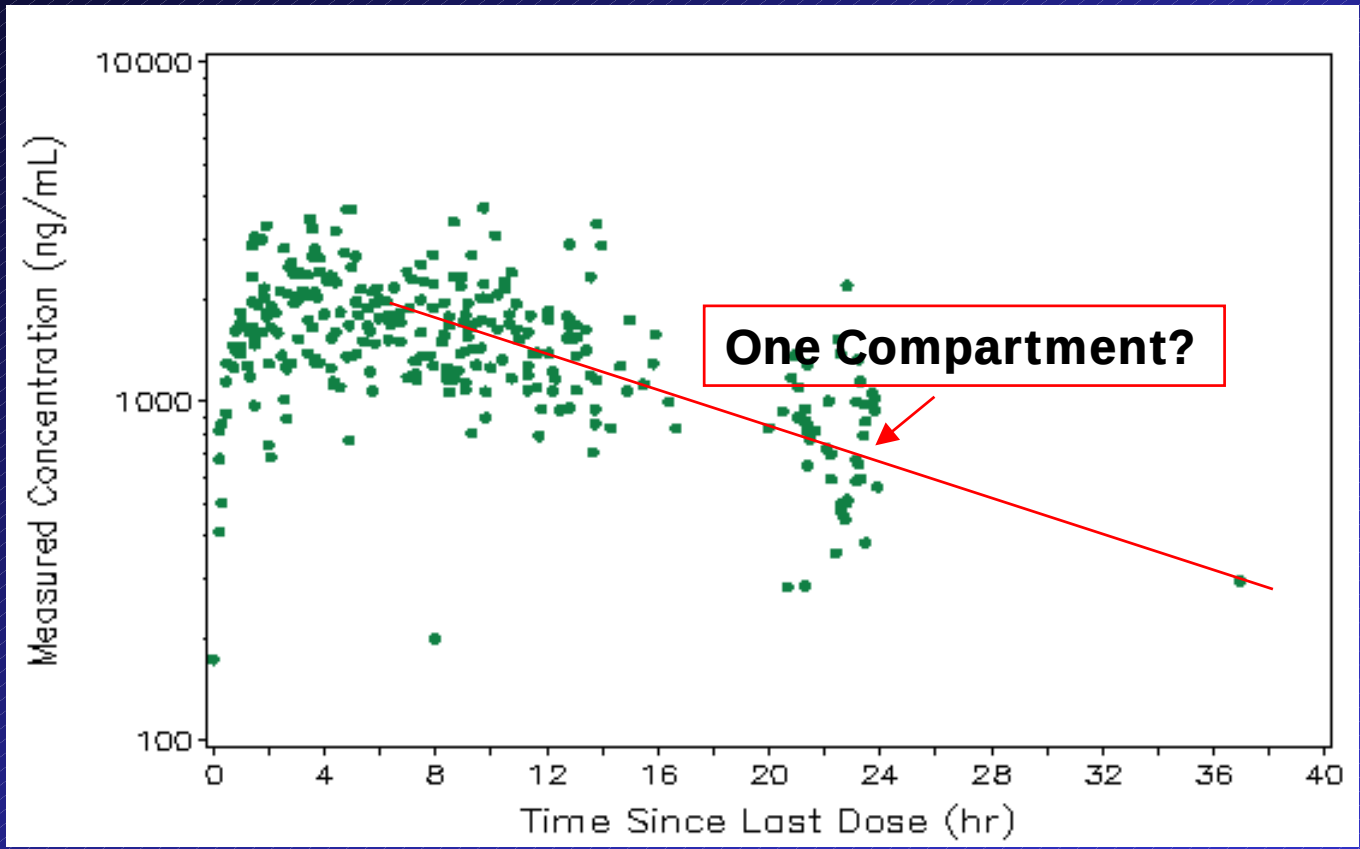

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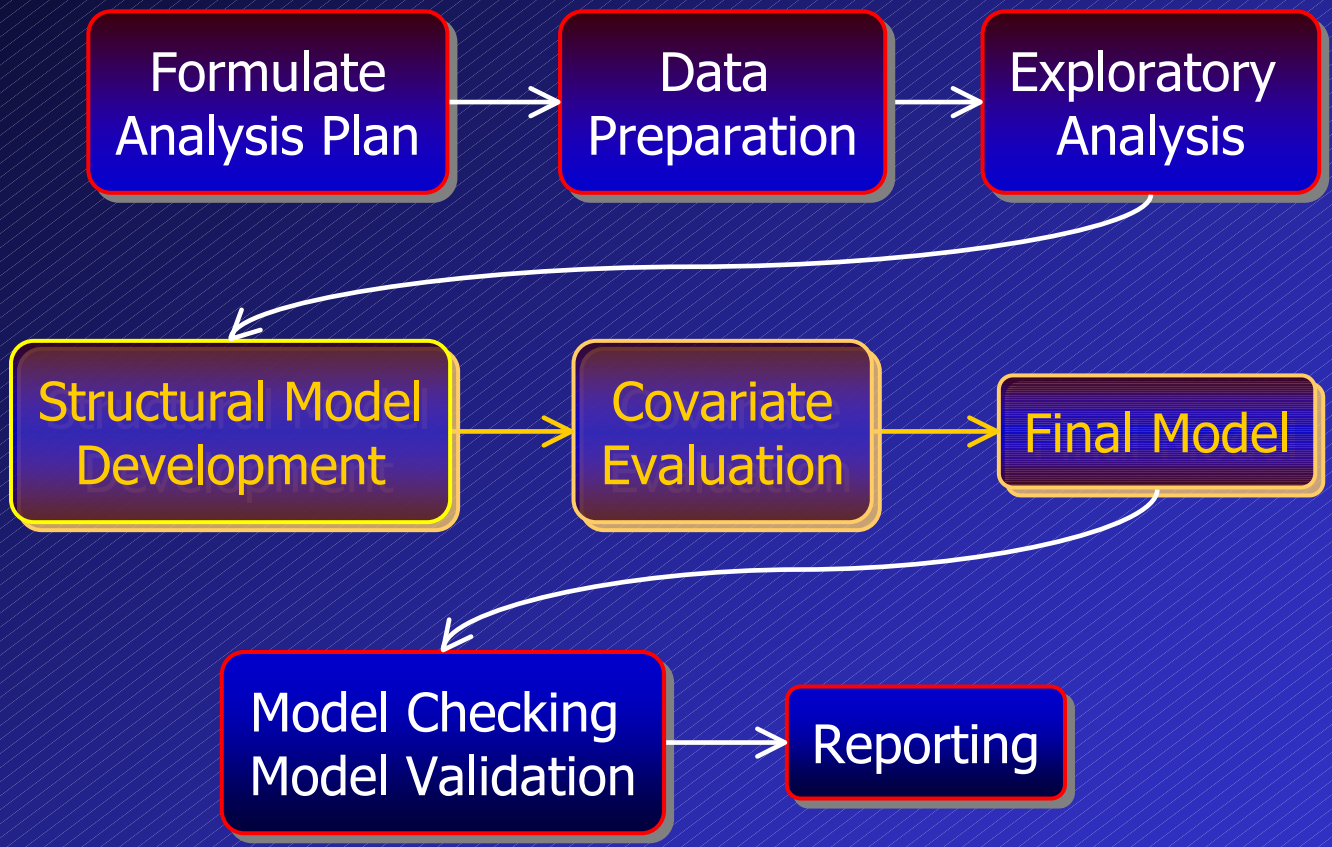
Phases of a Population Analysis



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Population PK/PD Parameters

- Θ Theta: Fixed Effects
  - Vector of typical values or central tendencies of parameters
    - θ (theta)
- Random Effects (minimum two levels)
  - Ω - Omega: Matrix of interindividual (between subject) variance estimates (IIV)
    - η (eta)
  - Σ - Sigma: Residual Variability
  - Matrix of intraindividual (within subjects) variance estimates
    - ε (epsilon)

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Control Stream Terminology

```
$PROBLEM ex1
$INPUT ID DATE TIME AMT DV TRT WTKG HTIN AGE SEX EVID MDV PROT
$DATA /doc/phor/pkpd/nonmem-testsuite/data/ex1.dat
$SUBROUTINES ADVAN2 TRANS2
$PK
CALLFL = -2
TVCL = THETA(1)
CL = TVCL * DEXP(ETA(1))
TVV = THETA(2)
V = TVV * DEXP(ETA(2))
TVKA = THETA(3)
KA = TVKA * DEXP(ETA(3))
ALAG1 = THETA(4)
S2 = V/1000

$ERROR

Y = F + EPS(1) + F*EPS(2)

$THETA (0, 28) (0, 90) (0, 3) (0, 0.1)
$OMEGA 0.25 0.25 0.25
$SIGMA 0.02 0.1
$ESTIMATION POSTHOC MAXEVAL=1000 PRINT=5 MSFO=ex1.msf
$COVARIANCE
$TABLE ID DATE TIME AMT TRT CL V KA NOPRINT FILE=ex1.tbl NOHEADER NOPRINT
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$SUBROUTINES:

- Tells which PRED-PP subroutines to use:
- ADVANx for compartment definitions
- TRANSx for parameterization options

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$THETA:

- Vector of typical values or central tendencies of parameters
- Specifies initial estimates for fixed effect parameters

$OMEGA and $SIGMA: Specifies initial estimates of the variance of IIV (omega) and RV (sigma)

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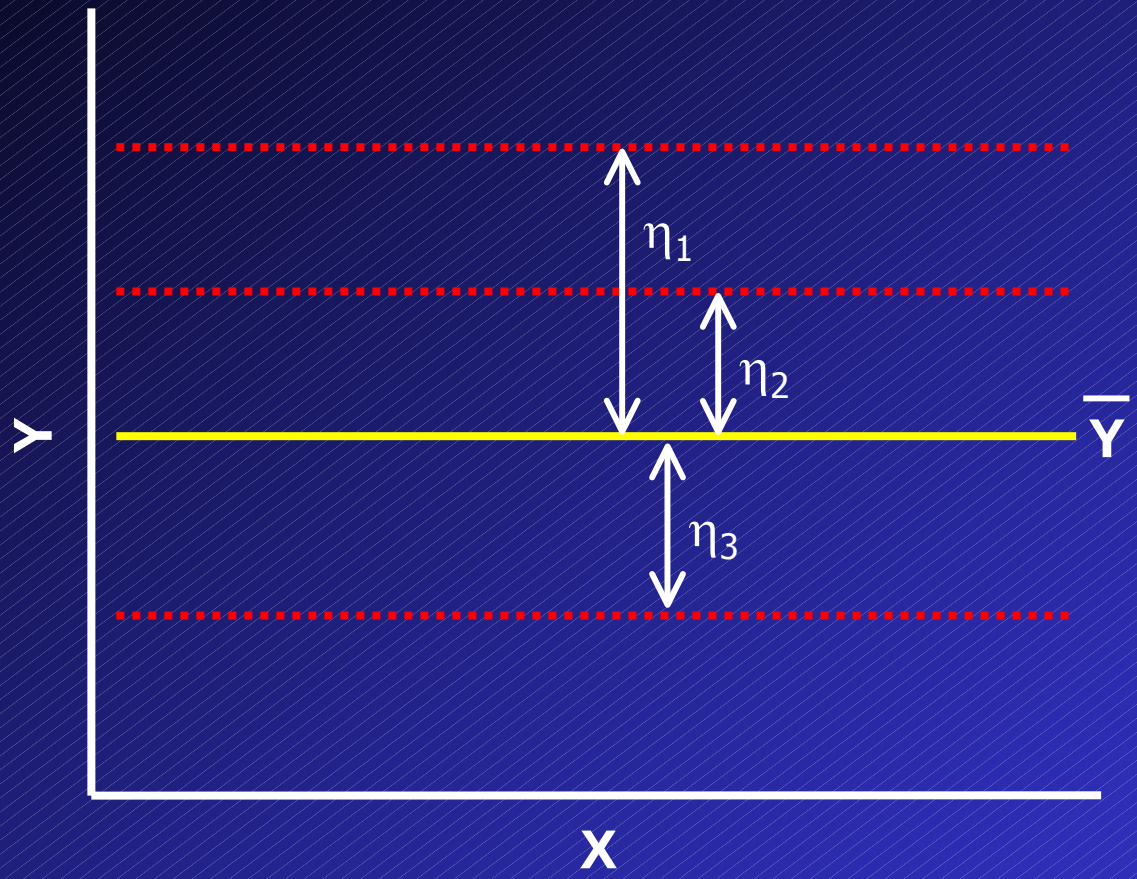
Modeling Population PK

Interindividual Variability (IIV), Between Subject



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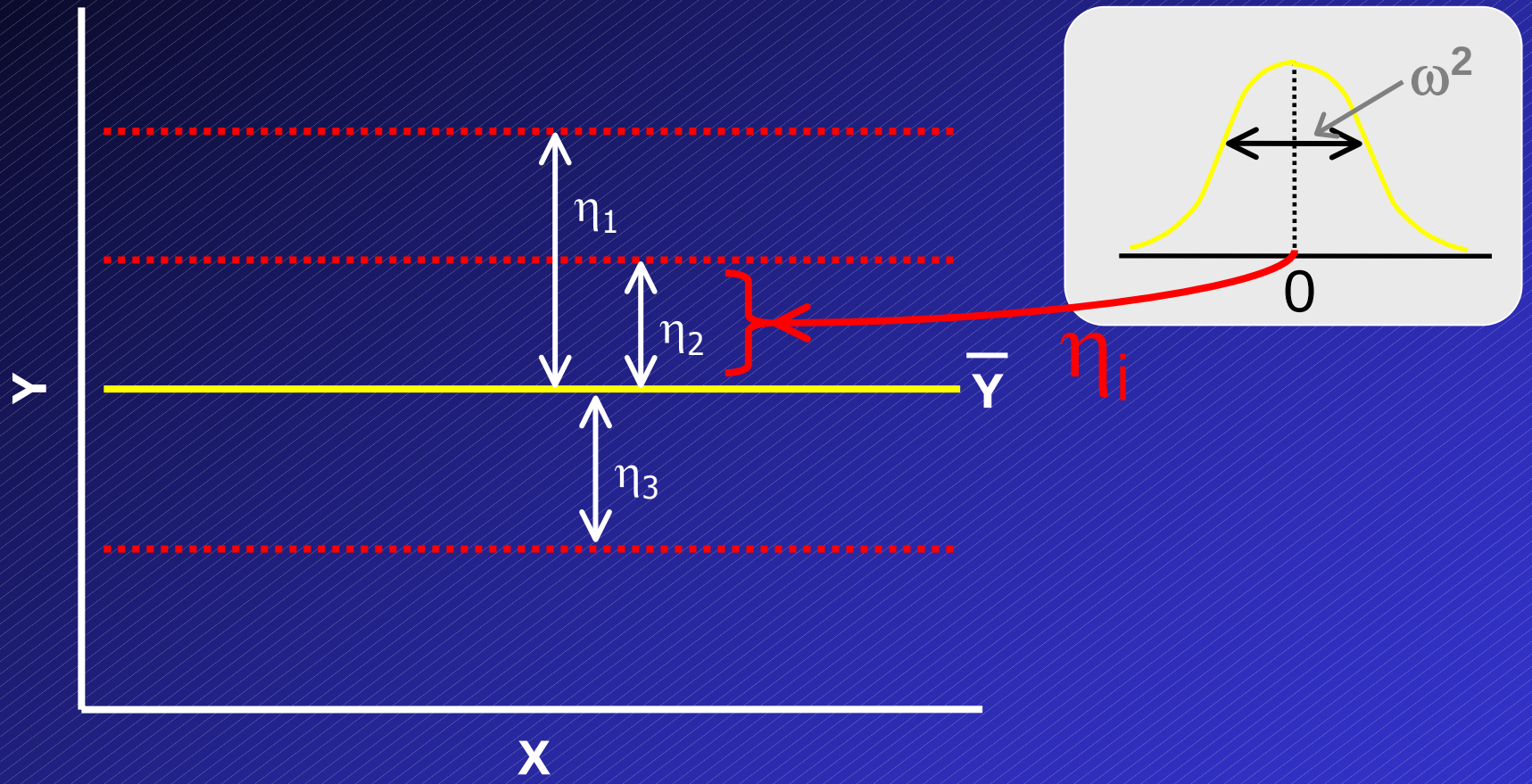

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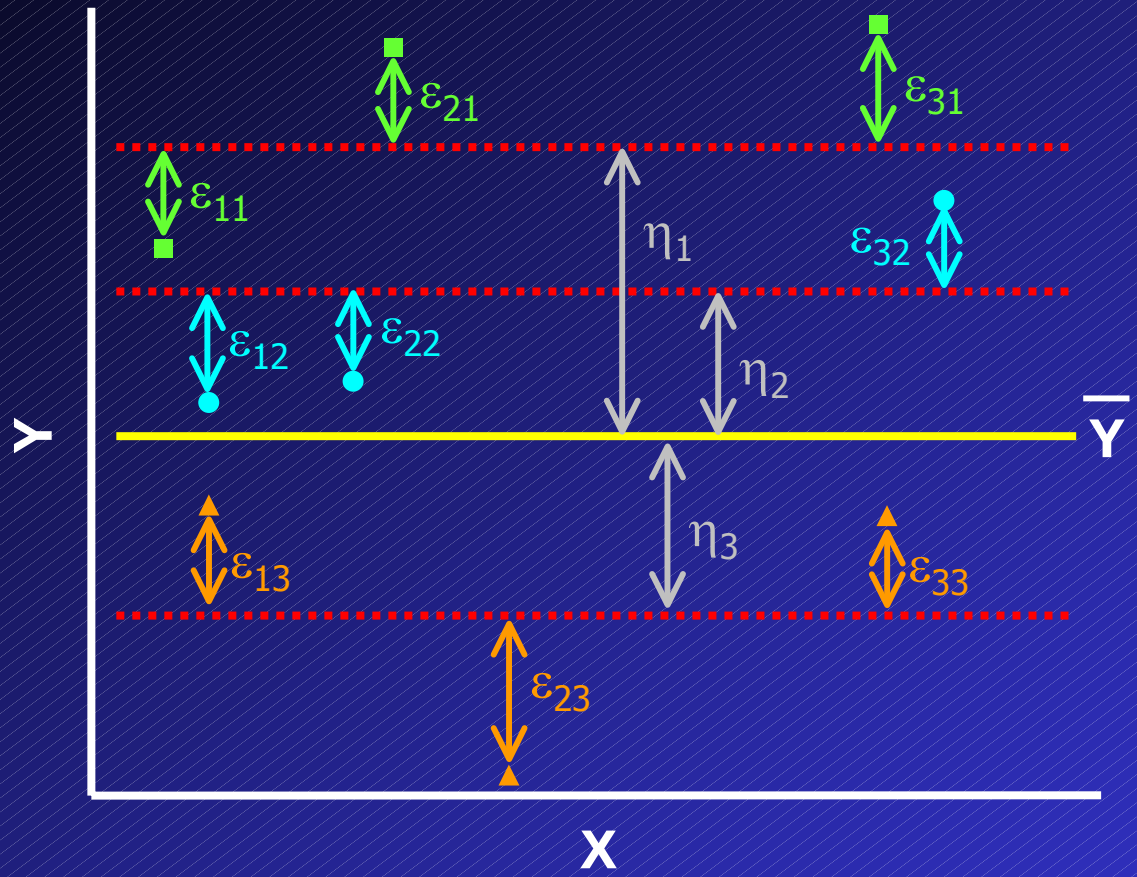
Modeling Population PK

Intraindividual Variability, RV, Within Subject



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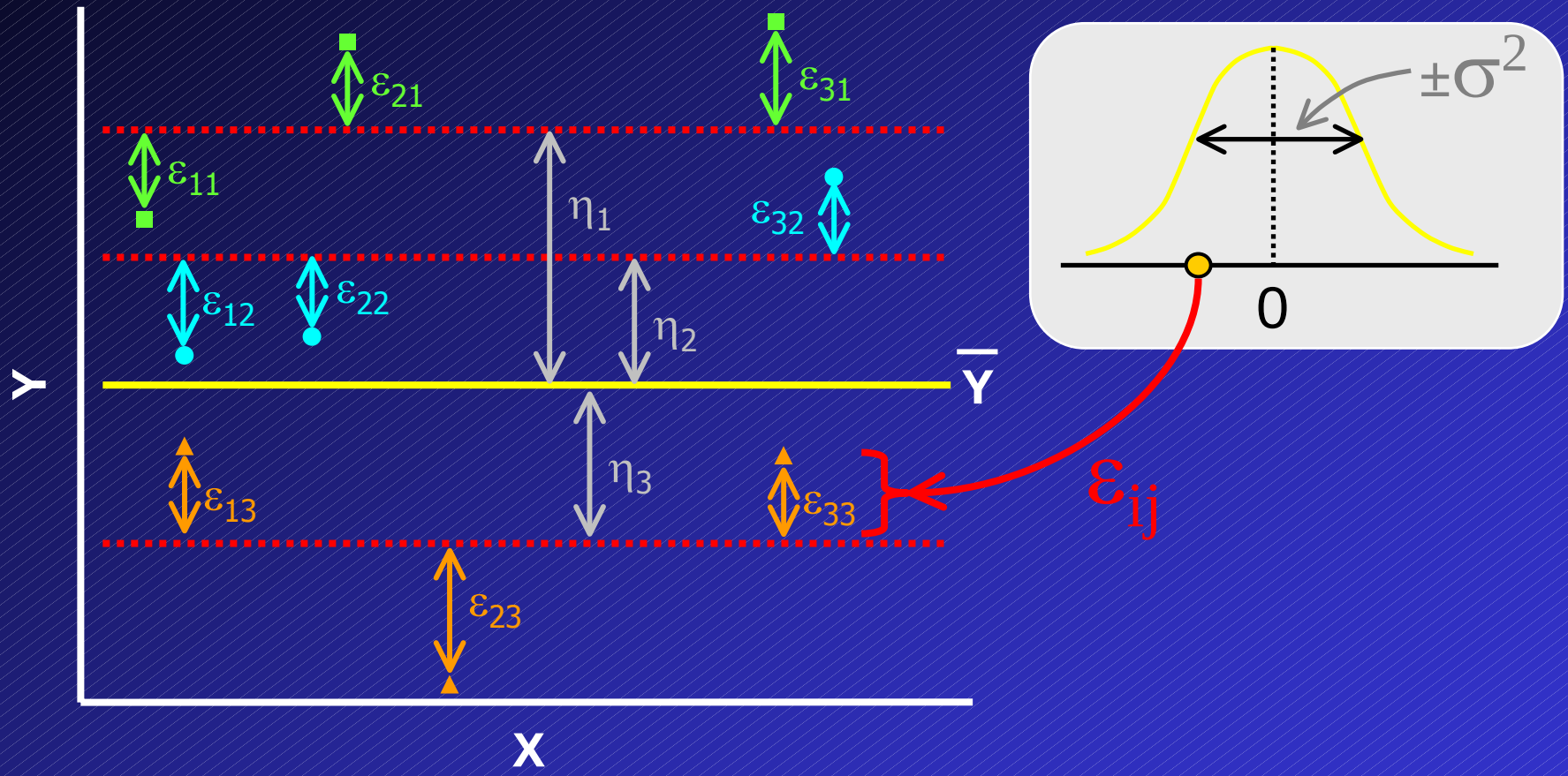

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```

$ESTIMATION: Specifies the estimation method to be used

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NONMEM®'s FO (First Order) Estimation Method

- Default (and quickest) estimation method
- Named for the linearization method which uses a first-order Taylor series expansion
- **POSTHOC:** option to calculate individual-specific empiric Bayesian estimates of η's and provides individual-specific estimates of parameters

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NONMEM®'s FOCE

- First-order conditional estimation (FOCE) method estimates individual η's during the minimization (no need for POSTHOC)
- much more time-consuming
- **INTERACTION** option allows for interaction between η's and ε's
  - FOCE with INTERACTION can correct bias sometimes observed with FO and rich, full-profile data

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Base Population PK Model (Prior to Covariate Evaluation)

Parameter	Final Parameter Estimate	
	Population Mean	%SEM
Ka (1/hr)	0.565	13.7
CL (L/hr)	2.93	3.4
V (L)	58.2	7.5
IIV CL (%CV)	30.59	21.9
IIV V(%CV)	17.35	107.0
RV (%CV)	19.29	13.1

Min. Value of the Objective Function (MVOF) = 3863.901

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Objective Function Value (OBJF)

- Minimum value of the objective function (MVOF) is a global measure of goodness of fit and is proportional to –2LL of the data
- ΔOBJF used in an approximate test for adding/deleting parameters
- Akaike Information Criterion (AIC): useful in non-hierarchical model comparisons = ΔOBJF+2(Δp)

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Typical Goodness of Fit Plots (GOF-Plots)

- DV vs PRED (Measured versus Predicted)
  - DV=Dependent Variable
  - PRED=Population mean Predicted Value
- RES vs PRED
    - Residuals
- WRES or CWRES vs PRED
  - WRES=Weighted Residual
  - CWRES=Conditional Weighted Residuals
- WRES or CWRES vs TSLD
  - TSLD=Time Since Last Dose
- IPRED vs DV
  - IPRED=Individual Predicted
    - (Takes into account η)

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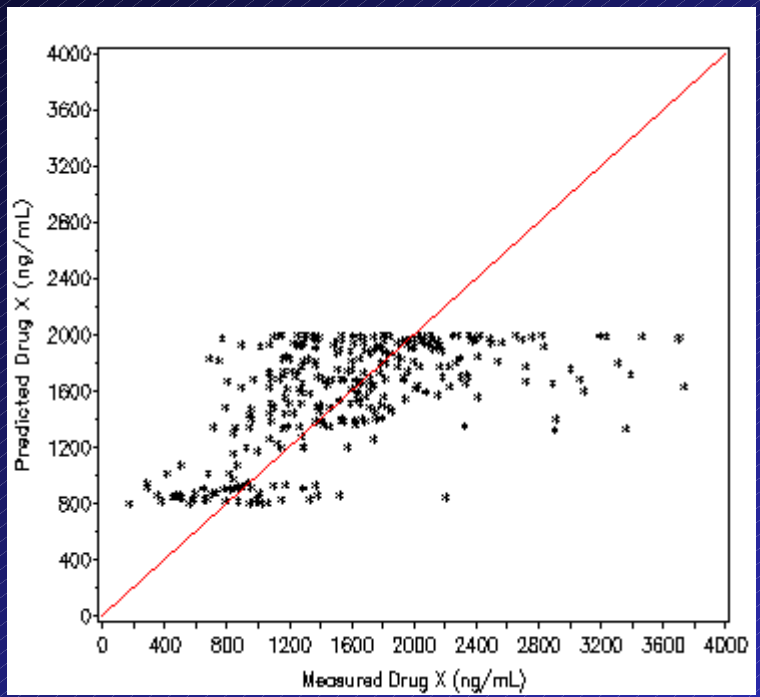
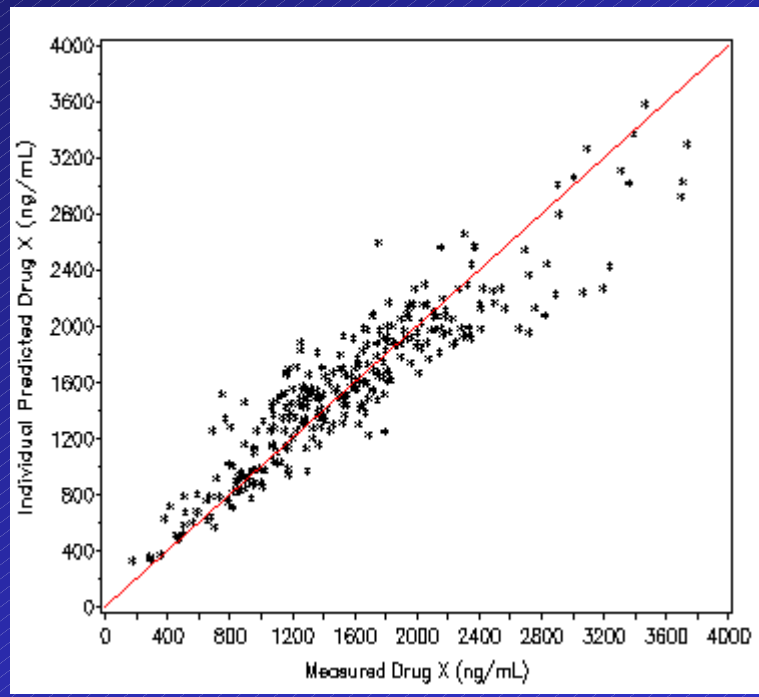
Base Population PK Model Goodness of Fit Plots (GOF-Plots)





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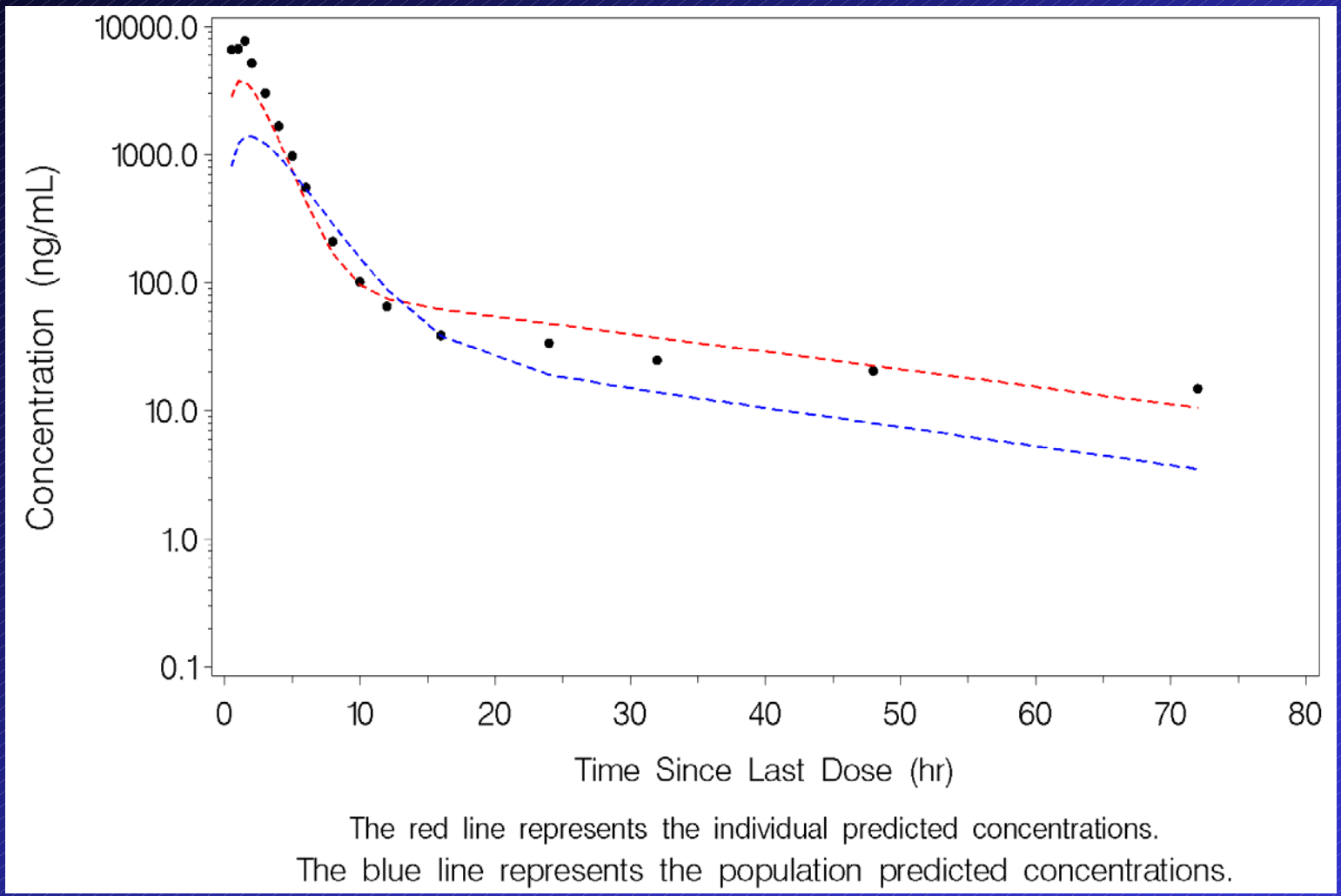
Base Population PK Model Goodness of Fit Plots (GOF-Plots)



The red line represents the individual predicted concentrations.
The blue line represents the population predicted concentrations.

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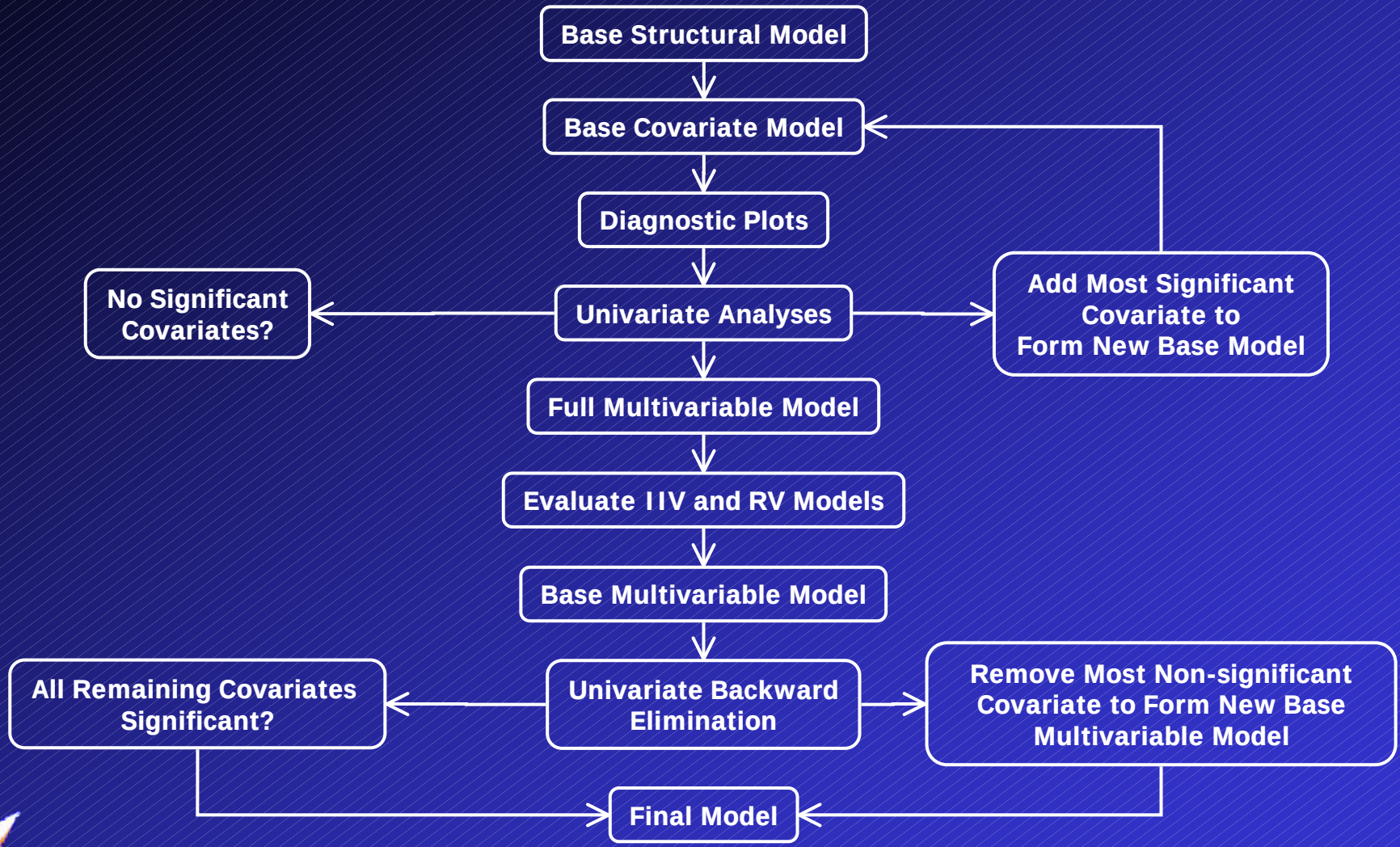
Model Development Process



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Exploring Covariate Effects

- Many methods/procedures available, some automated
  - GAM, WAM
  - Stepwise in SAS®
- Choice of method may depend on objectives, goals, timeframe
- Depending on # of predictors, can be the most time-consuming phase of an analysis

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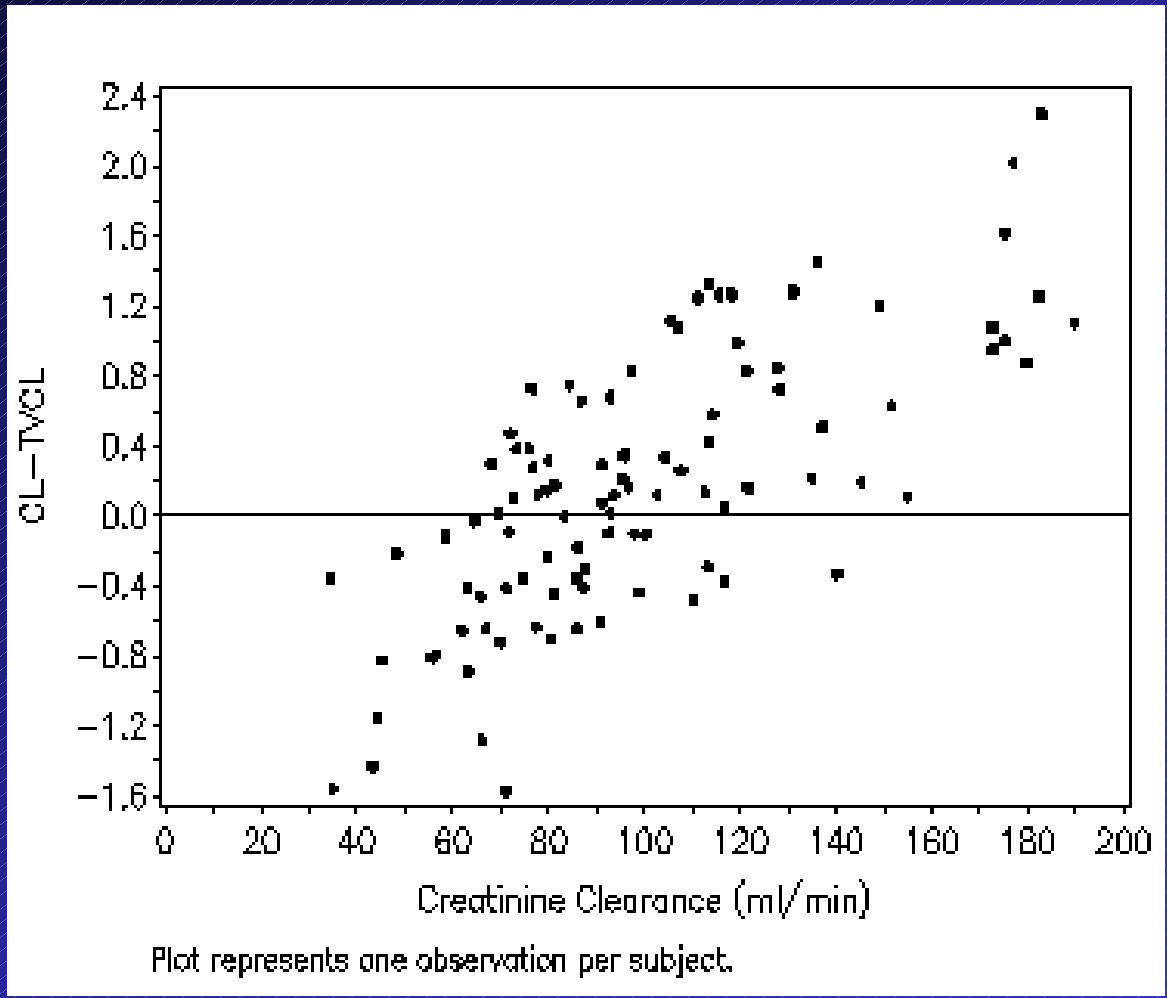
Delta Plots



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Final Population PK Model

Parameter	Final Parameter Estimate	
	Population Mean	%SEM
Ka (1/hr)	0.491	11.8
CL(L/hr)	3.13	2.1
V(L)	53.4	7.2
CL (CrCL effect)	0.627	9.5
V (WTKG effect)	0.781	14.2
IIV CL (%CV)	17.55	22.2
IIV V (%CV)	18.87	77.0
RV (log SD)	0.19	11.6

MVOF = 3763.901

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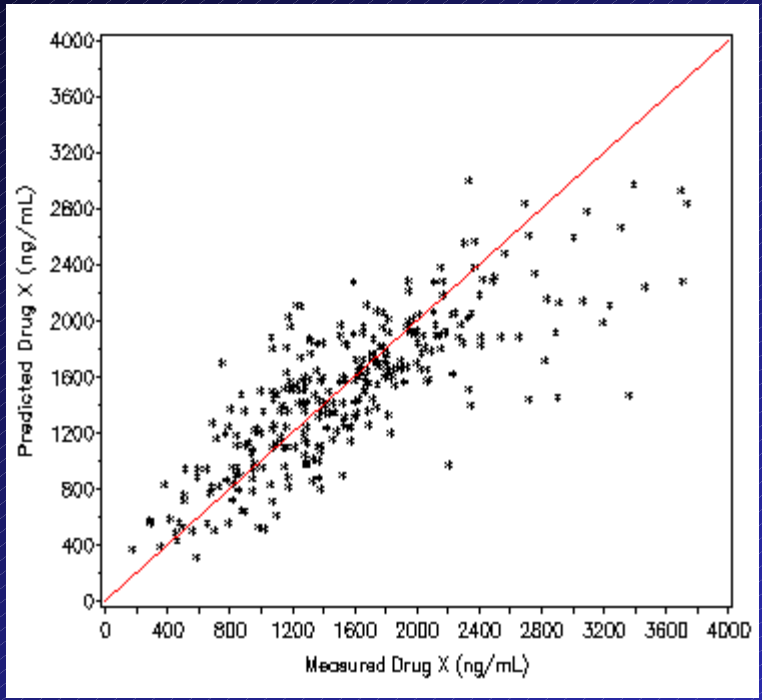
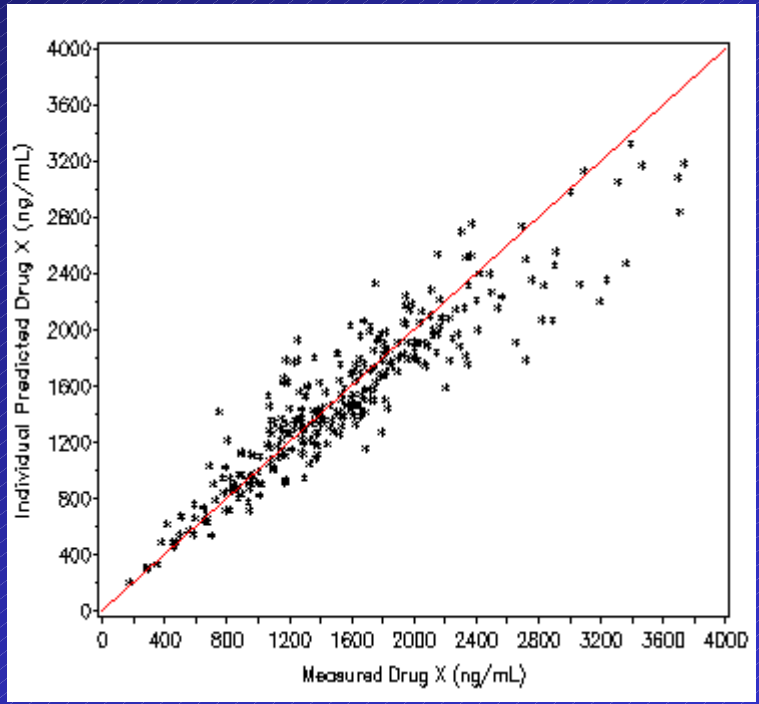
Final Model Diagnostics





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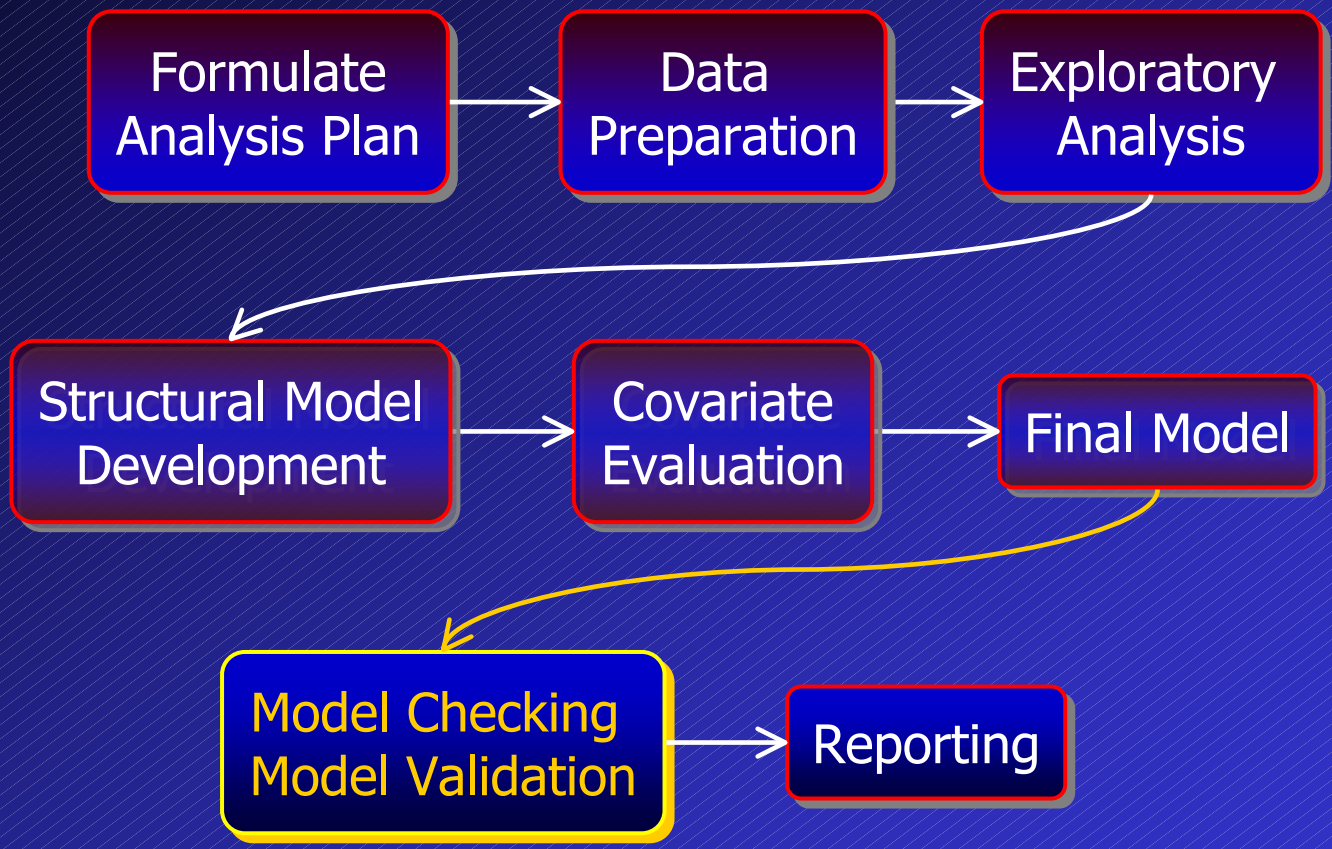
Phases of a Population Analysis



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Model Checking and Evaluation

- Model evaluation (previously known as model validation, see guidance) – many options
  - Internal vs. External
  - Bootstrap or cross-validation procedures
  - Posterior predictive check: simulate data from final model & check against raw data
  - Objective Function Mapping: determine if model is at a local or global minimum

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References

- American College of Clinical Pharmacology. A Pharmacometrics Resource: Theory. May 23, 2005. Available at: http://accp1.org/pharmacometrics/theory.htm. Accessed October 18 2006.
- FDA. Guidance for Industry: Population Pharmacokinetics. February 1999. Available at: http://www.fda.gov/cder/guidance/1852fnl.pdf. Accessed October 18 2006.
- J. Fiedler-Kelly. A 3-day Introductory Workshop in Population PK Data Analysis: A Hands-on Course Using NONMEM®. Buffalo, NY. June 2006.
- LB Sheiner and SL Beal. A Short Course in Population Pharmacokinetics Data Analysis Using the NONMEM System. University of California, San Francisco, CA. May 1997.

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