

**DIA 40<sup>th</sup> Annual Meeting**  
Washington, DC

---

**Innovation in Global  
Development and Registration**

**Roy E.S. Bullingham, MD**  
**Daiichi Pharmaceutical Corporation**

**Thaddeus Grasela, PharmD, PhD**  
**Cognigen Corporation**

**Dennis Stalker, PhD**  
**Fujisawa Healthcare, Inc.**

Wednesday, June 16, 2004  
10:30 AM – 12 PM



# **The Role of Exposure-Response Evaluations in Global Drug Development**

Ted Grasela, PharmD, PhD  
Cognigen Corporation

# Exposure-Response Evaluations

## The Accelerating Evolution

---

- Curiosity – 1980's
  - ◆ Evaluation of Population PK in Therapeutic Trials
  - ◆ Grasela et al Clin Pharmacol Ther 1986
- Adolescence - 1999
  - ◆ FDA Guidance for Industry in Population Pharmacokinetics
  - ◆ Value of Real Time Data Assembly and Analysis
- Integral to regulatory decision-making - 2002
  - ◆ FDA Draft Guidance for exposure-response relationships
  - ◆ “Exposure response information is at the heart of any determination of the safety and effectiveness of drugs”
- Maturing as basis for successful commercialization
  - ◆ Capitalizing on exposure response relationships

# Exposure-Response Analyses

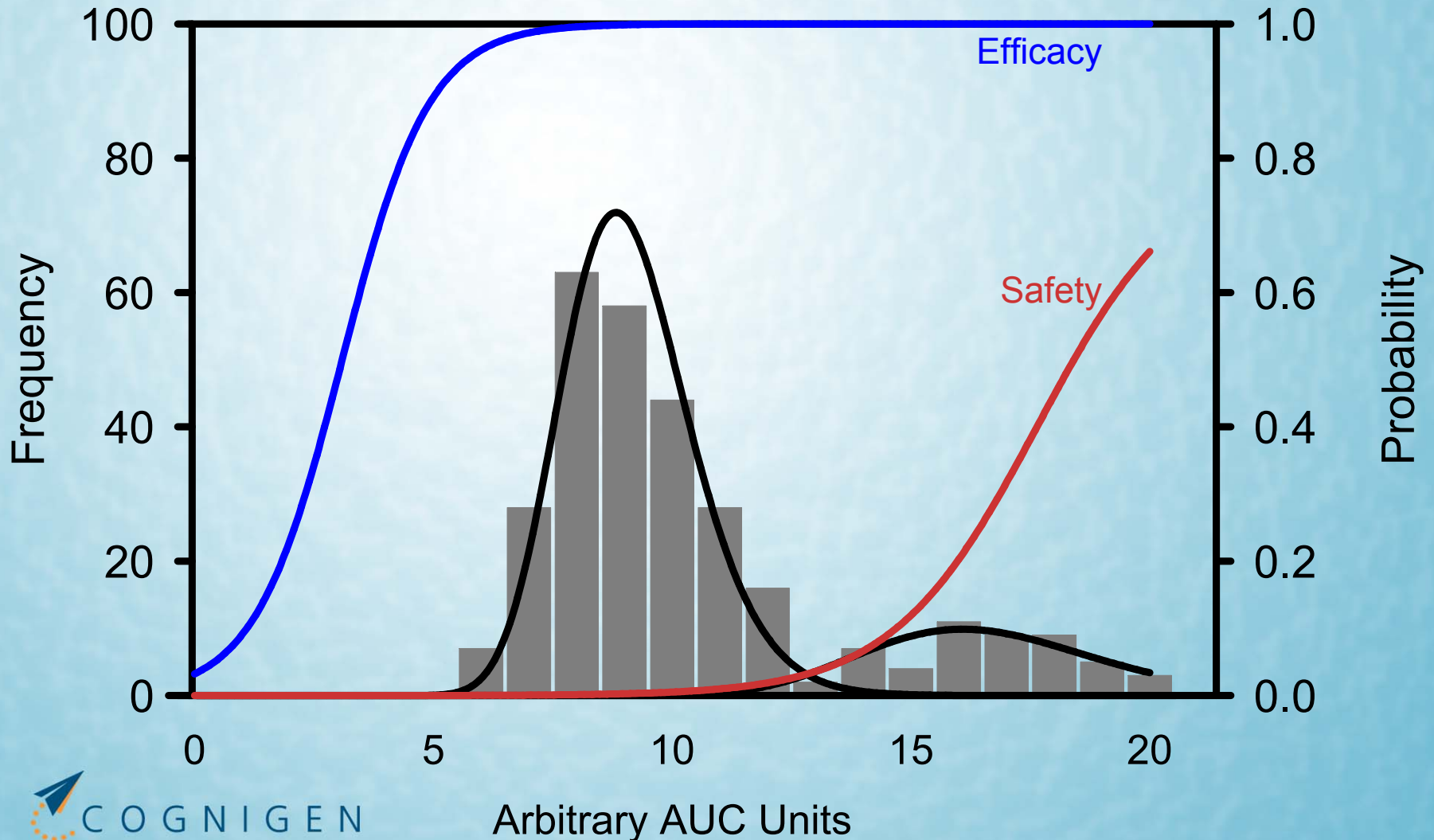
## Potential for a High ROI?

---

- Support discovery and development process
- Contribute to primary evidence of effectiveness and/or safety
- Provide support for primary efficacy studies
- Support new target populations
- Adjustment of dosages in subpopulations defined by intrinsic and extrinsic factors
- New dose regimens, dosage forms and formulations, routes of administration, and minor product changes

# Population Exposure-Response Relationships

## The Impact of Polymorphisms on Therapeutic Index



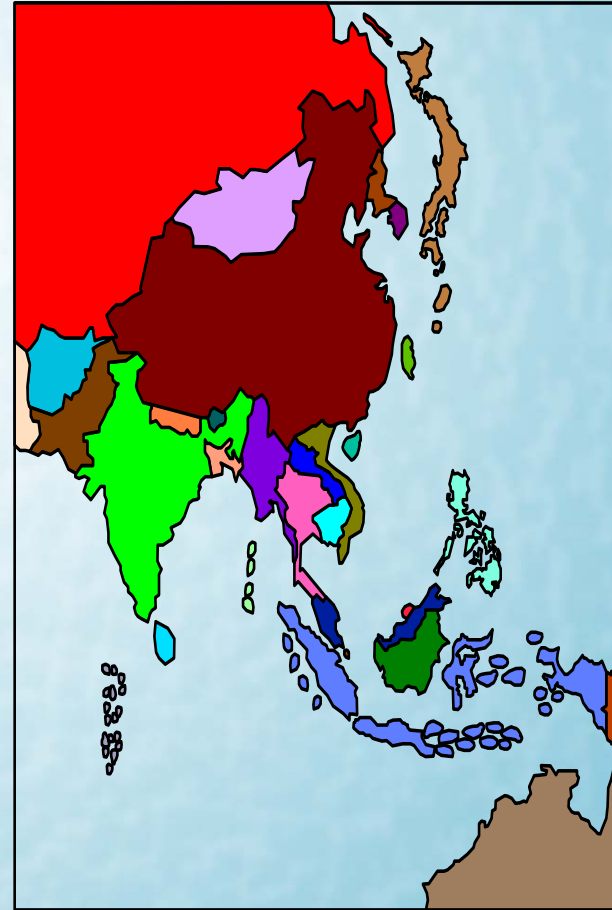


COGNIGEN

**The Role of Population  
Pharmacokinetic and  
Pharmacodynamic (PK/PD)  
Analysis in Bridging Programs  
Supporting Global Registration**

# The Role of Population PK/PD in Global Development

- Clinical trials generate representative patient populations in countries where approval is sought
- “Representative” defined by drug and disease characteristics; not citizenship
- Sparse PK sampling and PK/PD analysis is a foundation for population comparisons



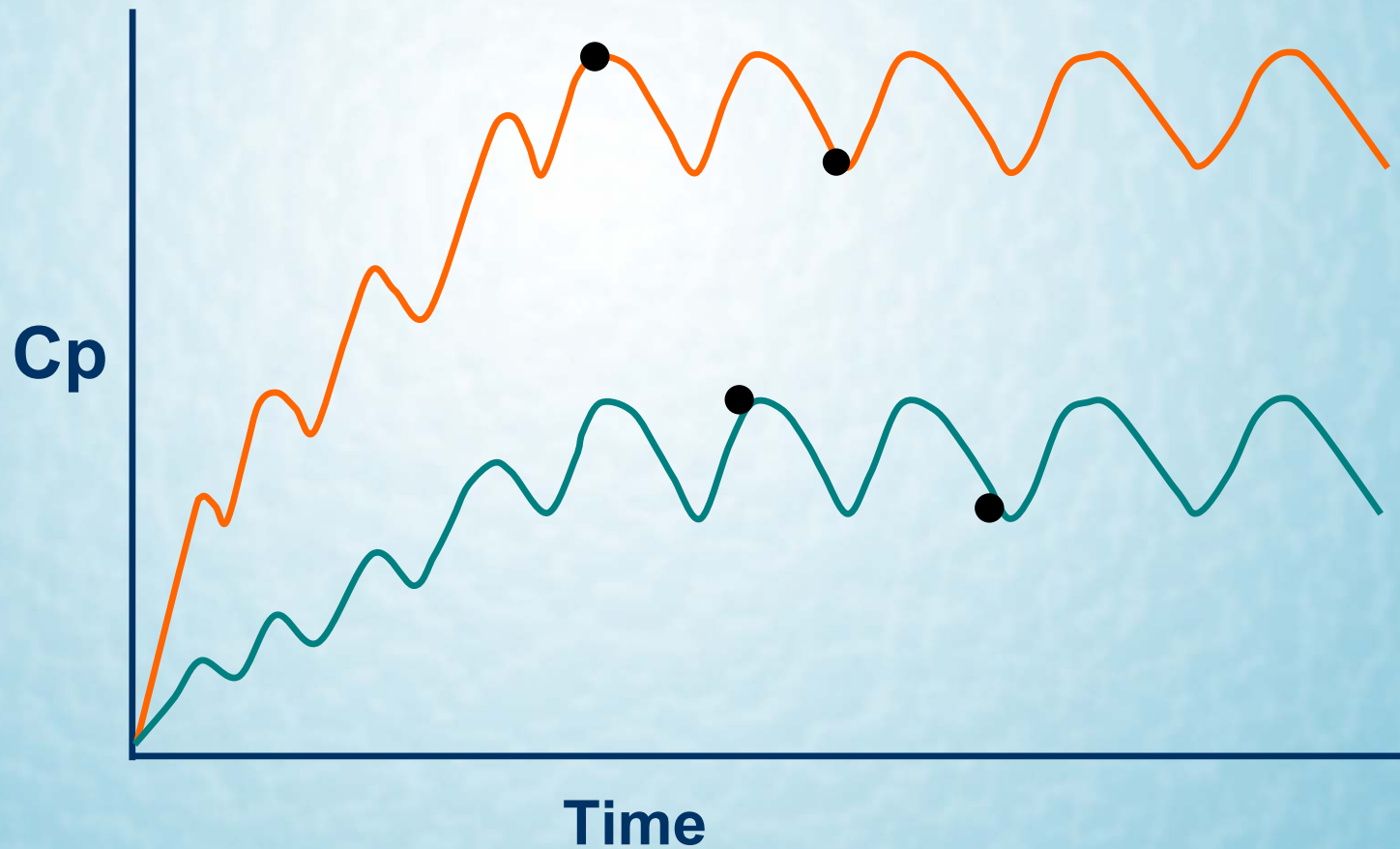
# Rationale for Measuring Concentrations During Trials

---

- Mechanism for comparing representative and relevant patient populations
- Variability in PK can make dose a poor measure of systemic exposure.
- Information on individual systemic exposure is important in the evaluation of:
  - ◆ adverse events,
  - ◆ exaggerated drug effect, and
  - ◆ lack of response.
- PK/PD evaluations are one of the scientific foundations for bridging programs

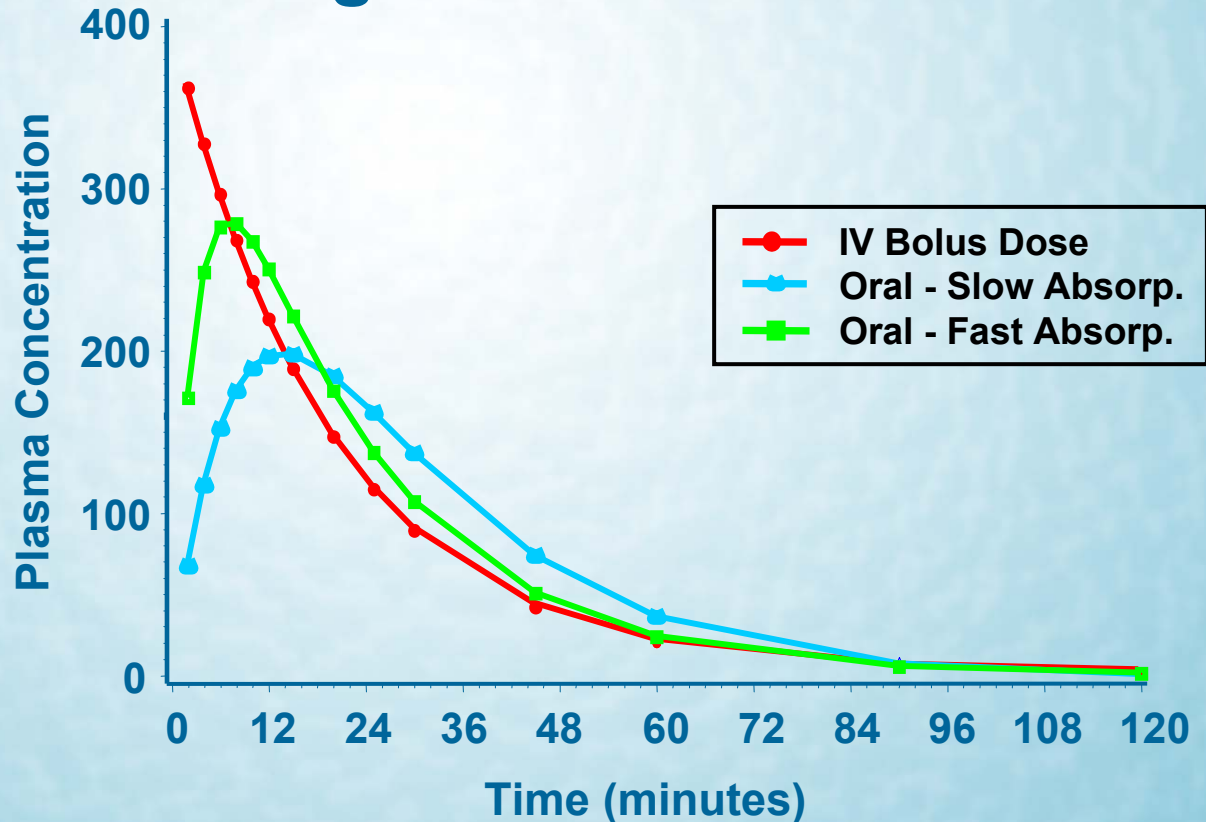
# Quantifying Drug Exposure in Clinical Trials Using Sparse Sampling

---



# Rich Sampling Traditional Approach

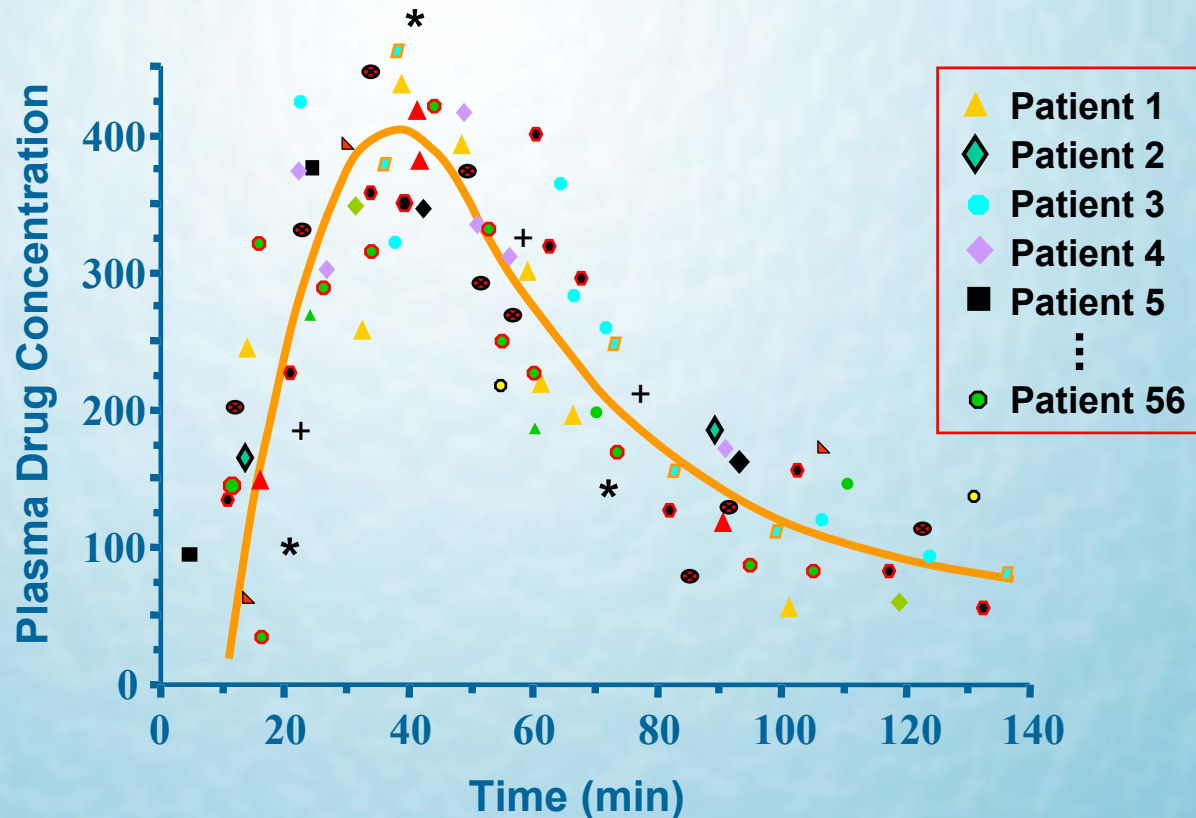
## Single Dose - Full Profile



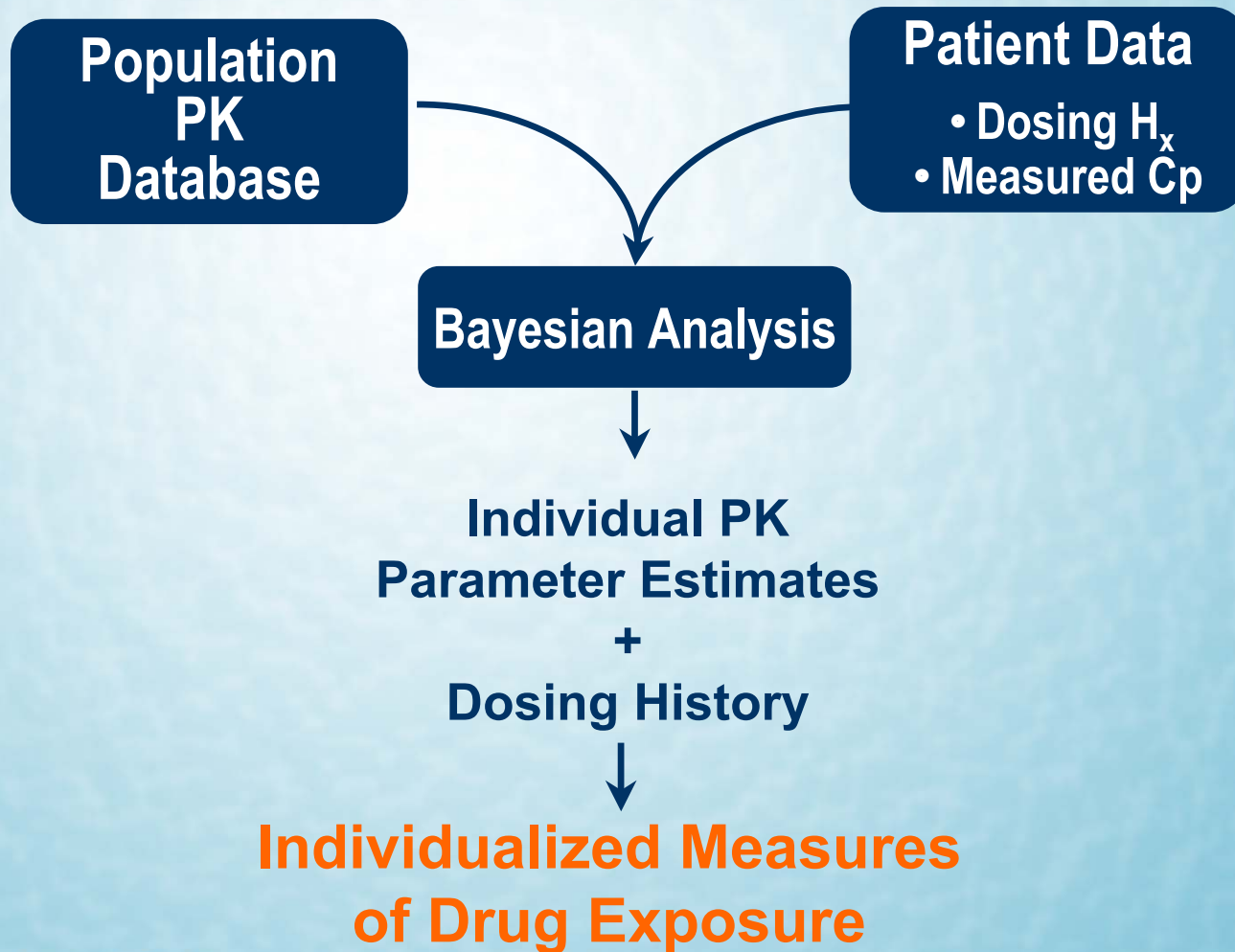
# Sparse Sampling Population PK Modeling

Few data points per patient, but

- ◆ Large study population
- ◆ Sparse sampling at variable times post-dose (specified time intervals)



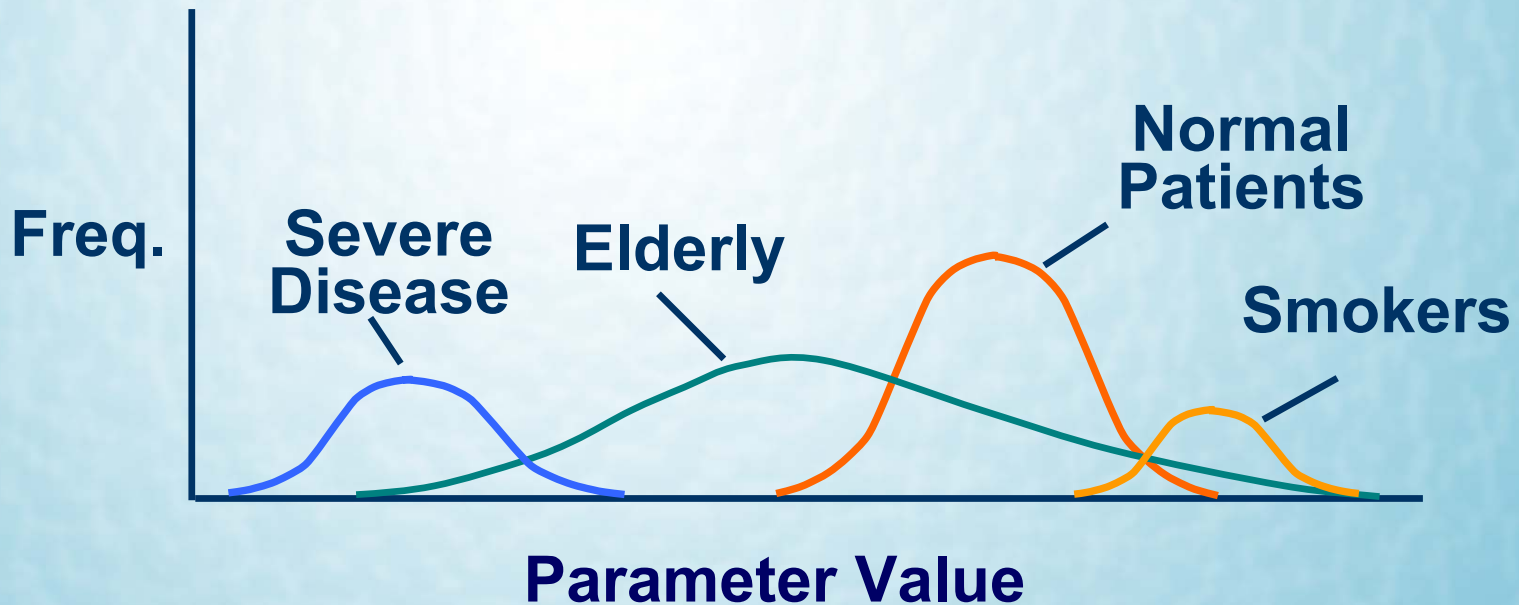
# Quantifying Drug Exposure in Clinical Trials



# Application of PK/PD

## Determinants of Clearance Distribution

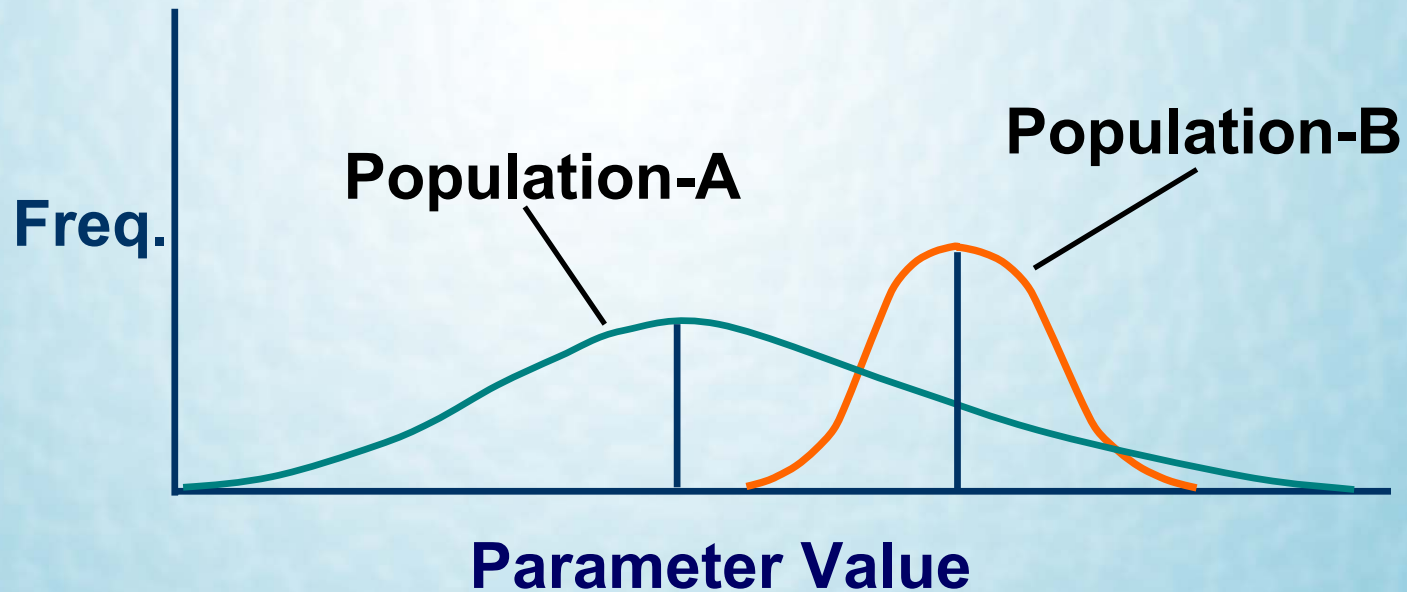
---



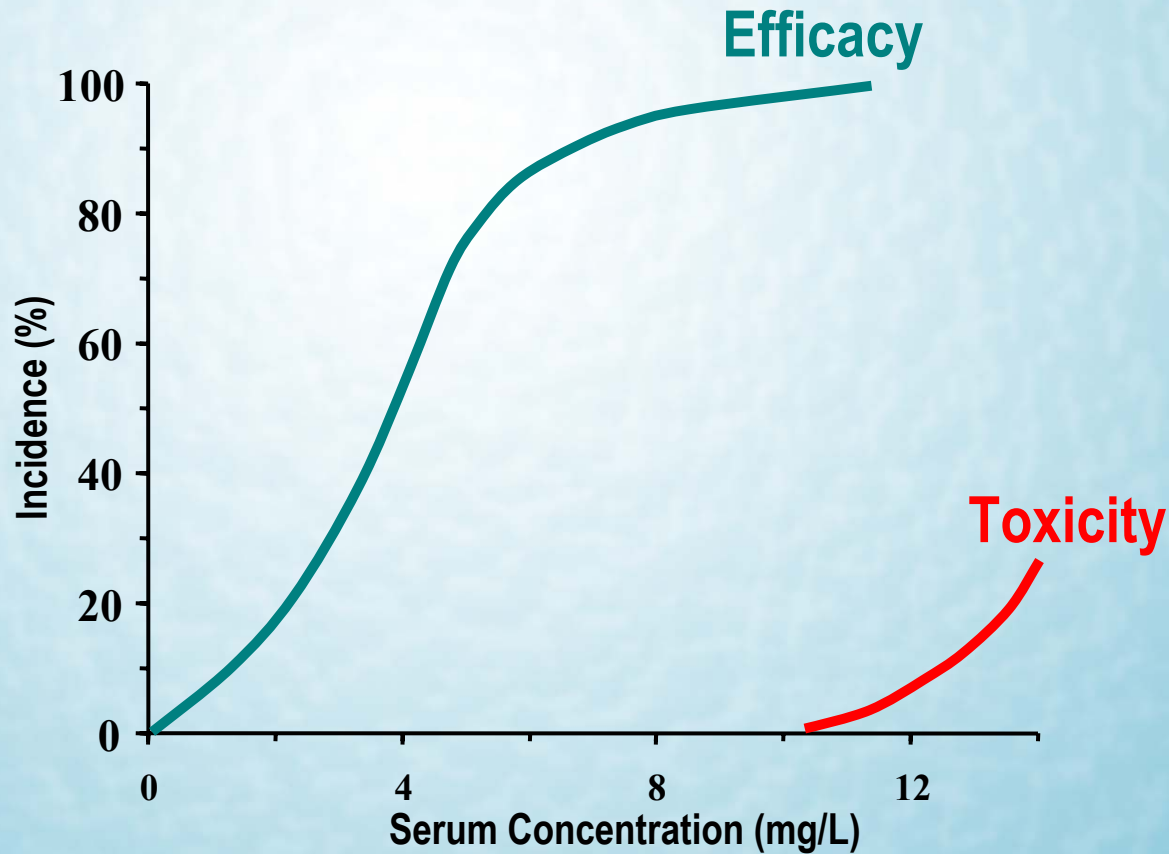
# Application of PK/PD

## Population Distributions of PK/PD Parameters

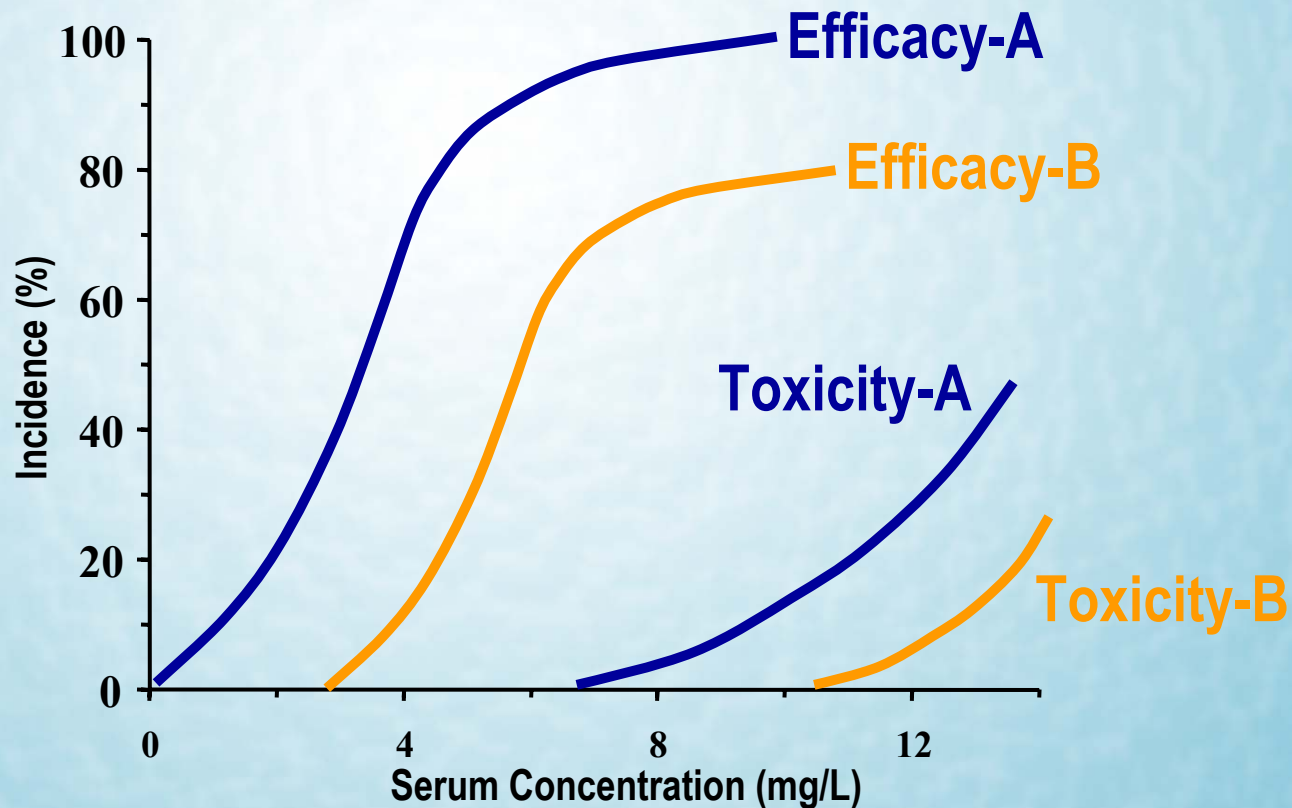
---



# Therapeutic Response and Toxicity



# PK/PD in Global Bridging Programs: Population Response Comparison



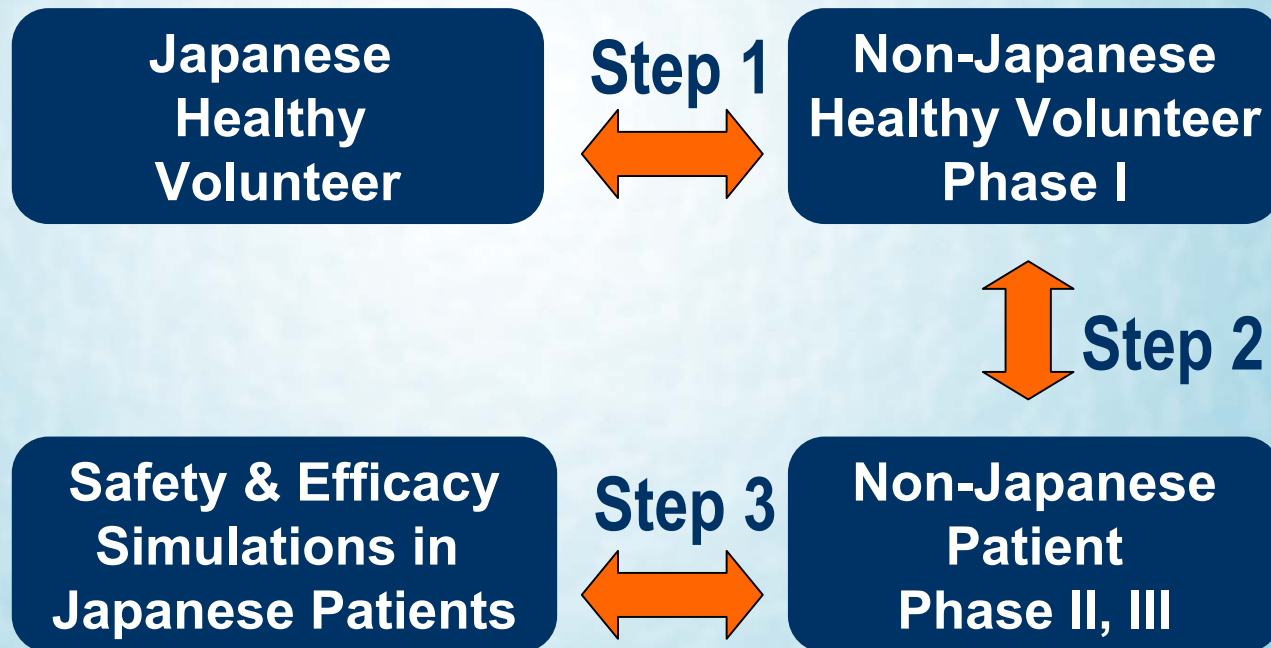


C O G N I G E N

**Role of Population  
PK/PD Analysis in  
Linezolid Bridging Program**

# Bridging Strategy For Linezolid

---

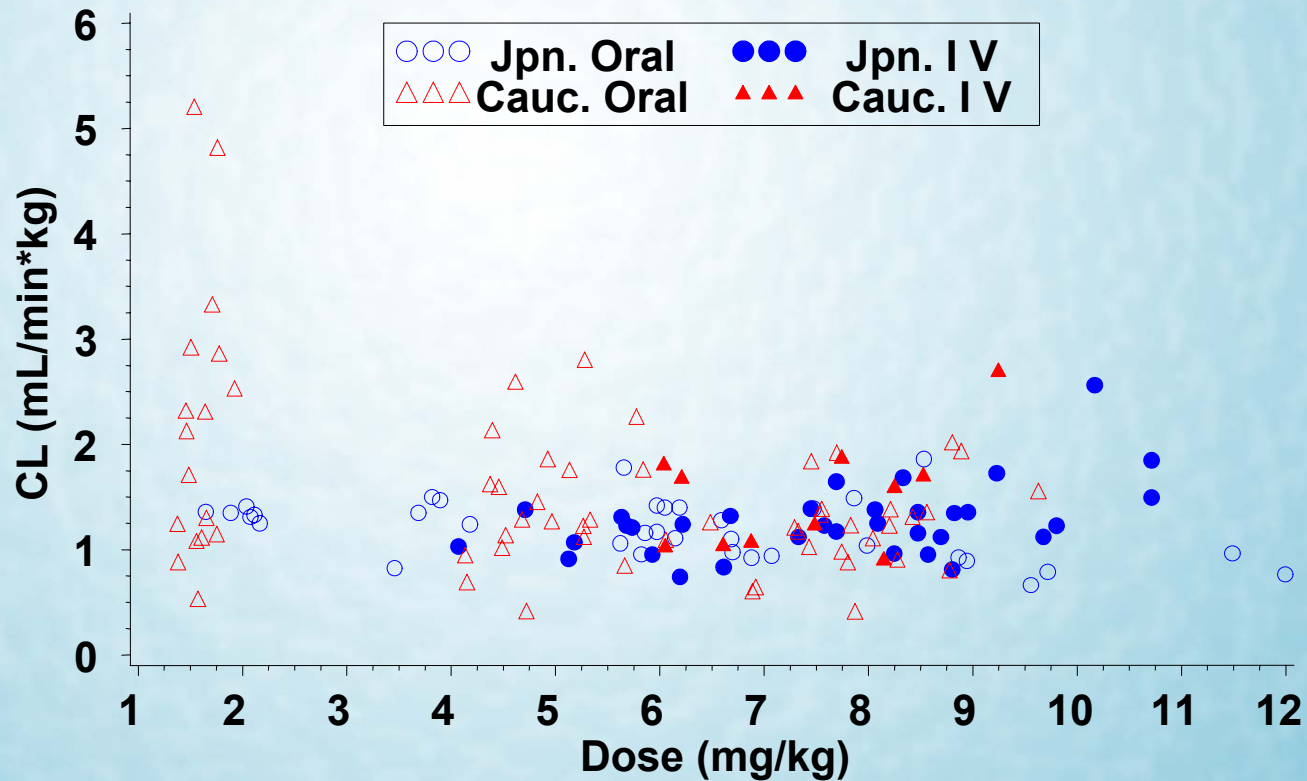


# Role of Population PK/PD Analysis in Linezolid Bridging Program

---

- Model development using Phase I data
- Model validation and extension using Phase II data
- Bayesian analysis of Phase II/III sparse sampling data to estimate exposure
- Exposure response relationships for safety and efficacy
- Simulations to demonstrate clinical implications of the PK/PD model

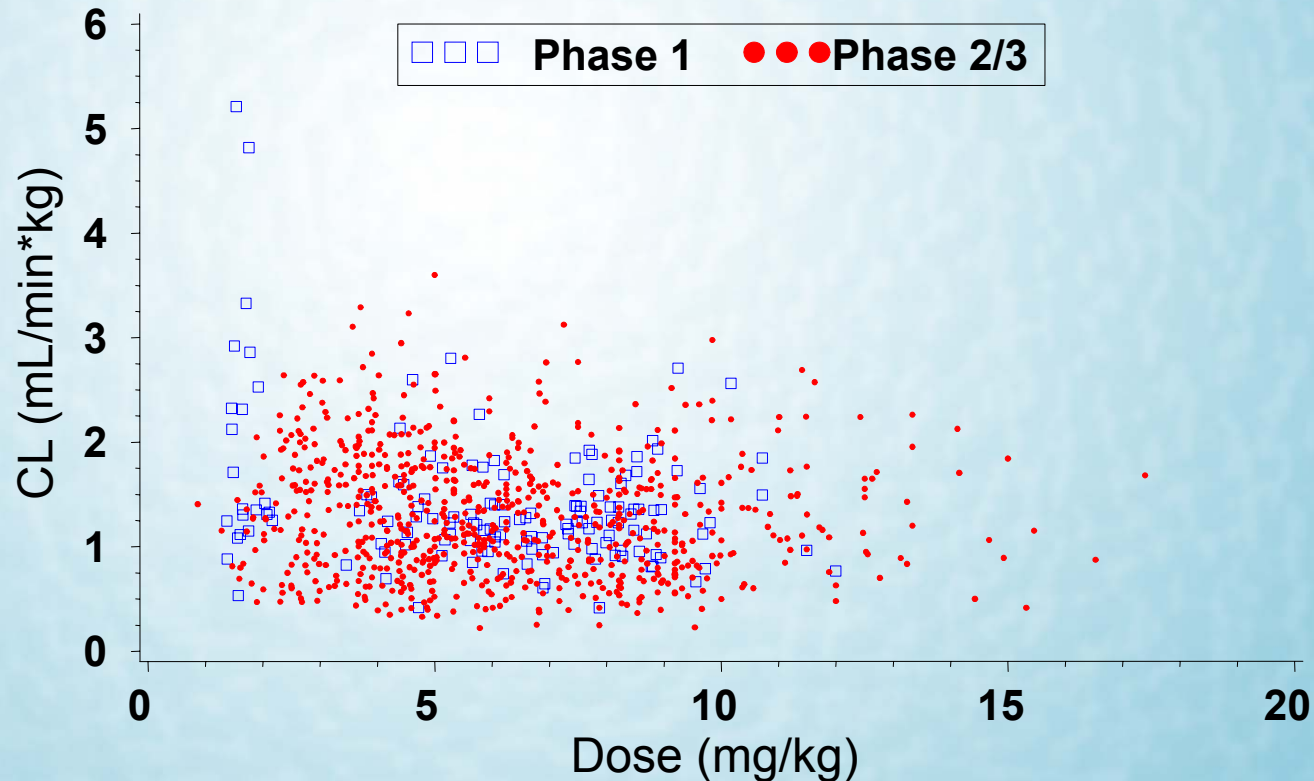
# Phase I Studies: Clearance Values for Japanese and Caucasian Subjects by Dose



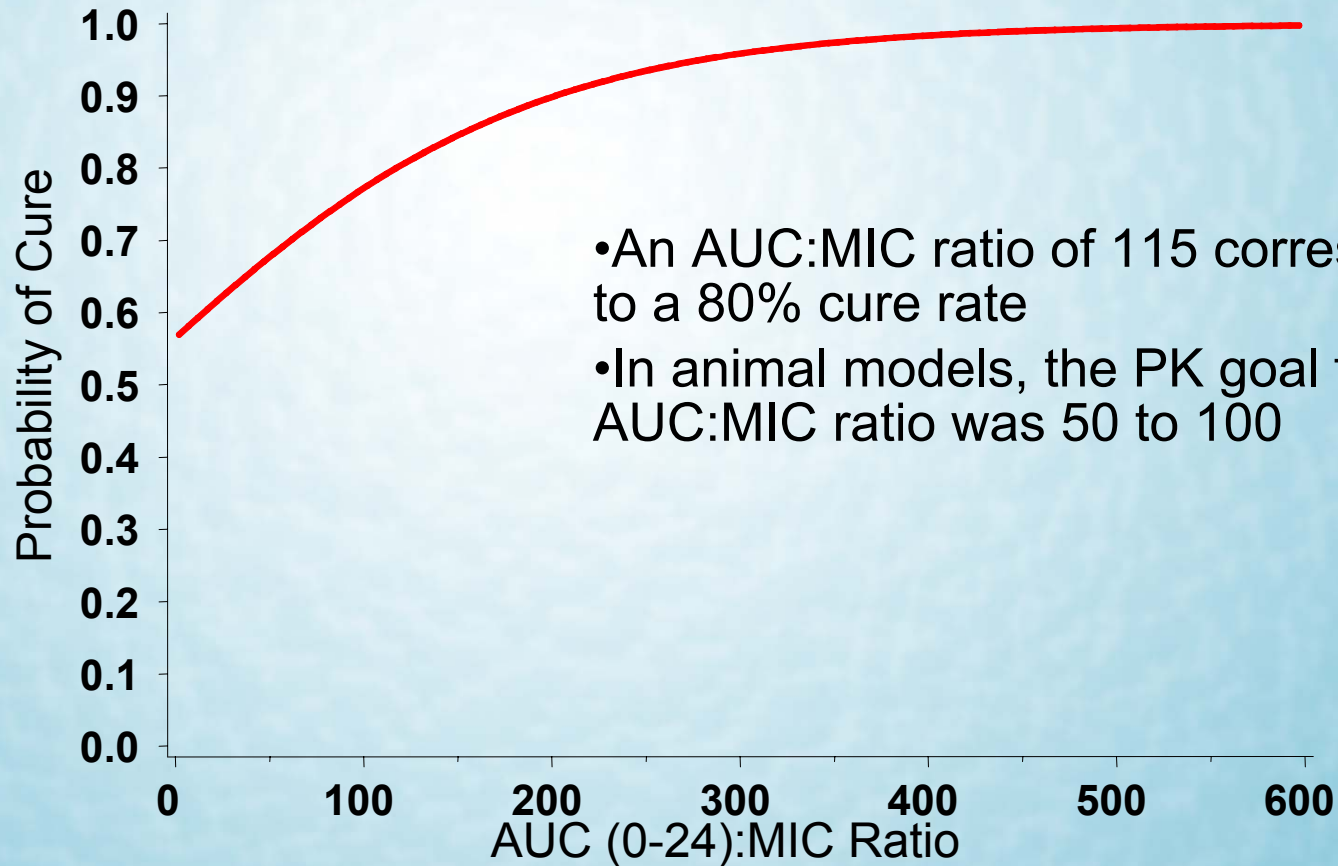
# Clearance values for Phase I, II, III Studies

## Bayesian Estimation Used for Sparse Sampling in Phase II and III Trials

---



# Phase II Bacteremia Study: Probability of Clinical Cure

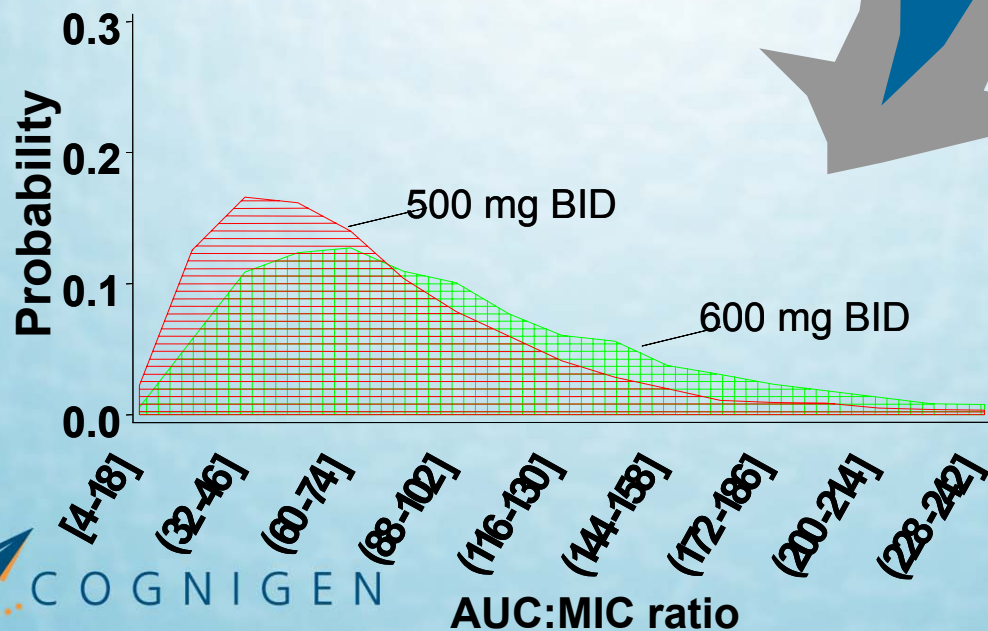
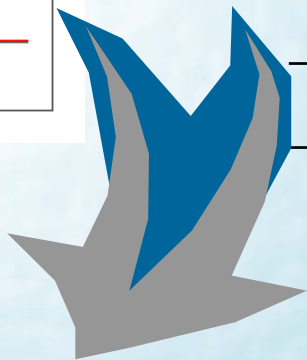
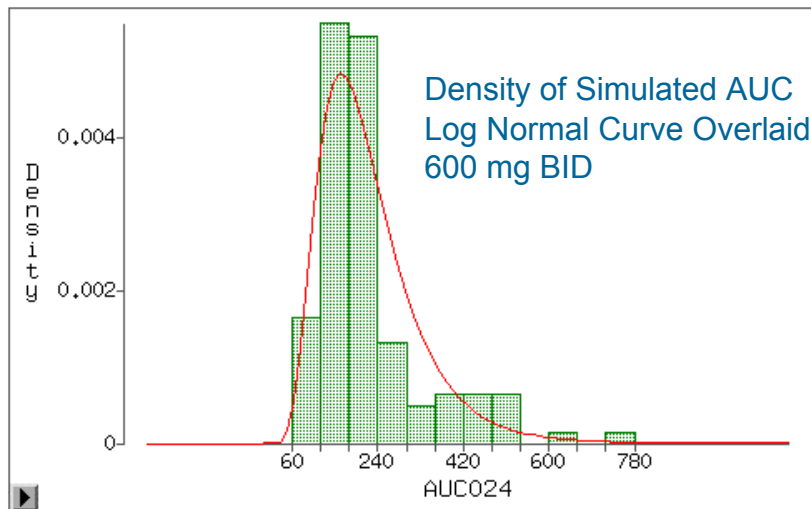


- An AUC:MIC ratio of 115 corresponds to a 80% cure rate
- In animal models, the PK goal for AUC:MIC ratio was 50 to 100

# Monte Carlo Simulation of AUC:MIC Ratio

Distribution of MRSA MICs

MIC	n(%)
<b>0.25</b>	<b>4(0.08)</b>
<b>1.0</b>	<b>263(5.27)</b>
<b>2.0</b>	<b>3033(60.66)</b>
<b>4.0</b>	<b>1692(33.83)</b>
<b>8.0</b>	<b>8(0.16)</b>
<b>Total</b>	<b>5000(100.0)</b>



**Probability Density of AUC:MIC Ratio**  
82 kg Patients

# Linezolid Phase II PK/PD Efficacy Analyses and Bridging Simulations

Weight (kg)	BID Dose (mg)	Expected Cure Rate (%)	95% Confidence Intervals about The Cure Rate
82.2 kg	500	70.0	(69.8, 70.2)
	600	74.1	(73.8, 74.3)
60 kg	500	72.1	(71.9, 72.4)
	600	76.7	(76.4, 77.0)

# What Does It Take To Make This Happen?

# Exposure-Response Analyses

## Generating Knowledge in Real Time

---

- Critical Challenges:
  - ◆ Decide what knowledge is needed
  - ◆ Generate knowledge efficiently so that results are available when they are needed for decision-making
  - ◆ Incorporate knowledge into the decision-making process

# Exposure-Response Analyses

## The OODA Loop

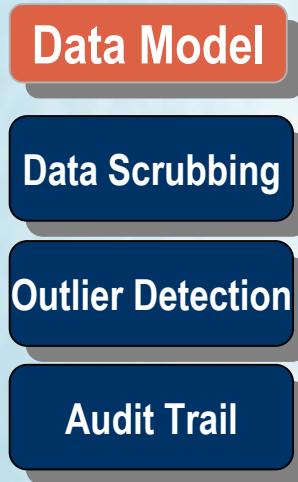
---

Real Time Data Assembly

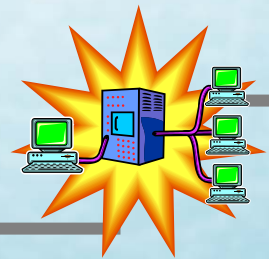


# Exposure-Response Analyses Information Architecture

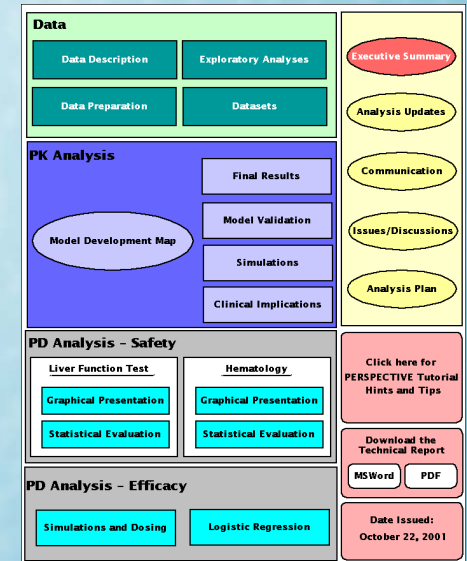
## Operational Data Store



## Data Marts



## Analysis Engine



## PERSPPECTIVE Hypertext Data Analysis Mapping

# Data Assembly for Population Analysis

## Problems for ER Analyses

---

- Timetable for development is always aggressive
- Considerable pressure on data management personnel to expedite data clean-up
- Information required for population PK/PD analysis is generally not available until primary safety and efficacy data prepared
- Results in high discard rates and delays in completing analyses and simulations
- Lost opportunities to impact on development and regulatory decision making

# Data Assembly for Population Analysis

## Real Time Data Assembly

---

### A Strategy for Monitoring Delavirdine PK During the Phase III Clinical Development Program

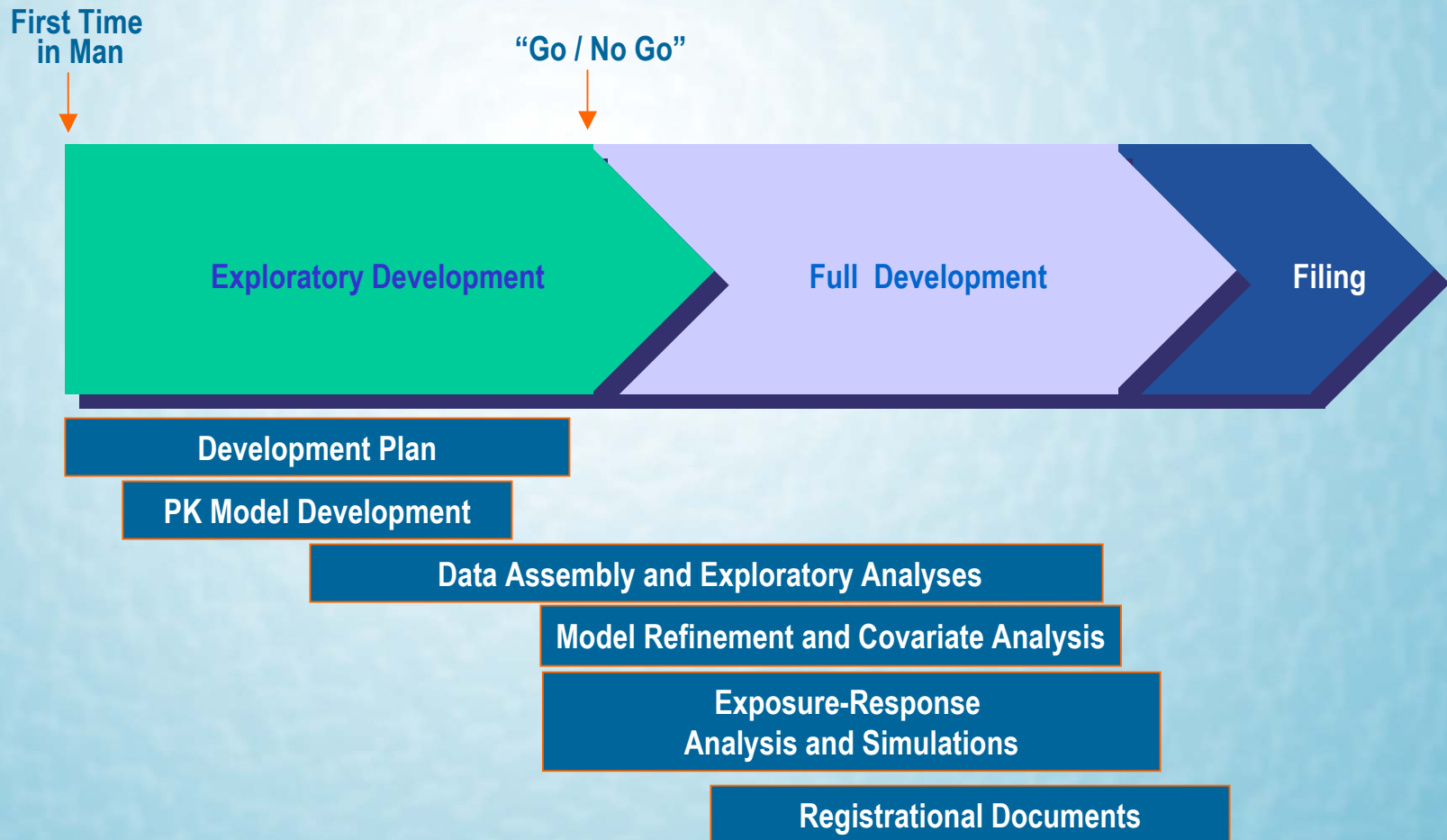
DIA Journal vol 33, pp. 273-279, 1999

*“...Real-time data assembly would permit population PK data analysis to be performed before the end of a clinical trial and would make it possible to include the results in the filing of the new drug application (NDA).”*

1999 Guidance for Industry  
in Population Pharmacokinetics

# Exposure-Response Analyses and Simulations

## Scope and Span of Effort



# Benefits of Population PK/PD in a Global Bridging Strategy

---

- Linezolid was approved at the 600 mg BID dose in Japan, Taiwan, Singapore, and South Korea based on modeling and simulation results.
- Focal point for regulatory submissions addressing ICH E5 guidelines and demonstrating similarity of populations
- Provides a strategy for pooling all Phase I, II, and III data to explore exposure-response relationships on a variety of outcomes
- Reduce study burden during global development
- Foundation for writing appropriate global labeling and demonstrating potential marketing advantages

# The Next Level of Performance

---

- Prospective study design, CRF design, sampling strategies, training and logistics to improved data quality and value of analyses
- Deploy data management and analysis environment to enable real time knowledge generation
- Influence decision-making via collaboration between Modelers and Customers
  - ◆ Project Management, Clinical Pharm, Medical, Regulatory Affairs, Data Management, and Statistics
  - ◆ Regulatory Agencies



# Thank You

For more information contact:  
Thaddeus Grasela, PharmD, PhD  
President and CEO  
[ted.grasela@cognigencorp.com](mailto:ted.grasela@cognigencorp.com)  
Phone: 716.633.3463 ext. 227