Using Exposure-Response Relationships to Define Therapeutic Index: A Proposed Approach Based on Utility Functions

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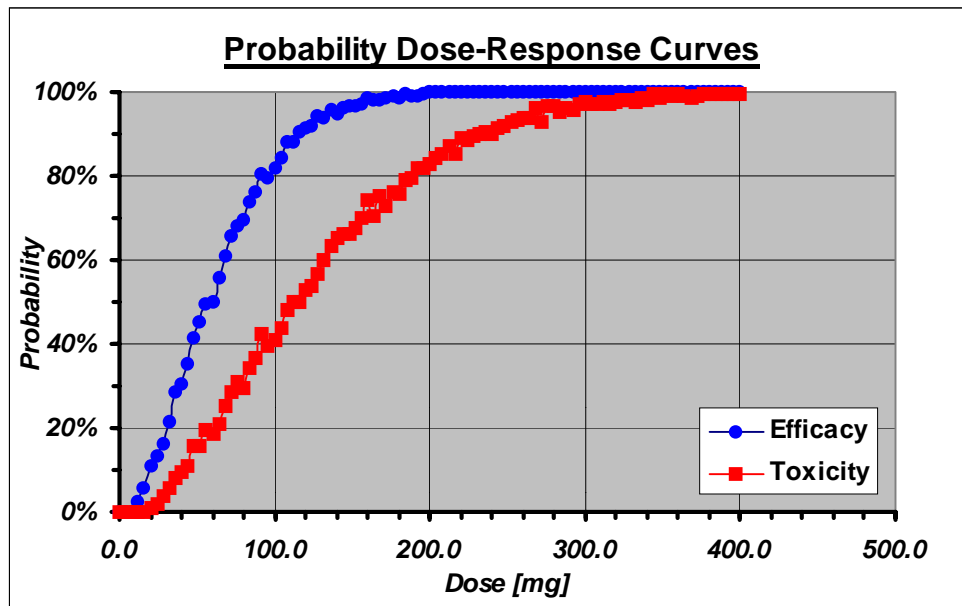*Richmond, VA*
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Presentation at
ACPS Clinical Pharmacology Subcommittee Meeting
October 23, 2002, Rockville, MD

<u>Sources of Variability</u>

Dosing Regimen

↓

Exposure

↓

Response (Marker)

↓

Clinical Outcomes

Efficacy/Benefit
Toxicity/Harm
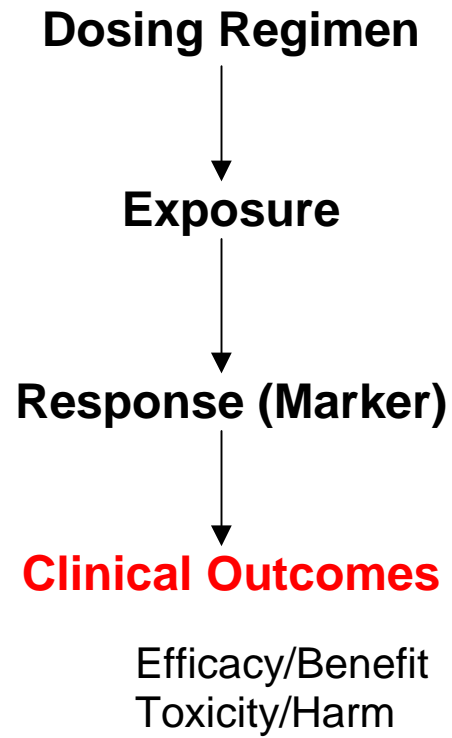
Exposure-Response Relationship (ER)

<u>Narrow Therapeutic Index (NTI) Drugs</u>

<u>Definition:</u>

Concerns about the **severity of clinical toxicity** ("overdosing")

> and/or

Concerns about the **severity of clinical lack of efficacy** ("underdosing")

On a **standard dosing regimen** (fixed dosing, individualized dosing or dose titration).

Usually defined by the Difference/Ratio in Dose-Response Curves (e.g., TD_{50}-ED_{50}, TD_{10}/ED_{90}) or Effect-Plasma Concentration Relationships (TC_{50}-EC_{50})

<u>Utility Function</u>

Utility Value = Probability * Utility Factor

<u>Clinical Efficacy:</u>   Probability of occurrence, given a certain dosing regimen (ER) **and** Clinical (negative) consequences = utility factor
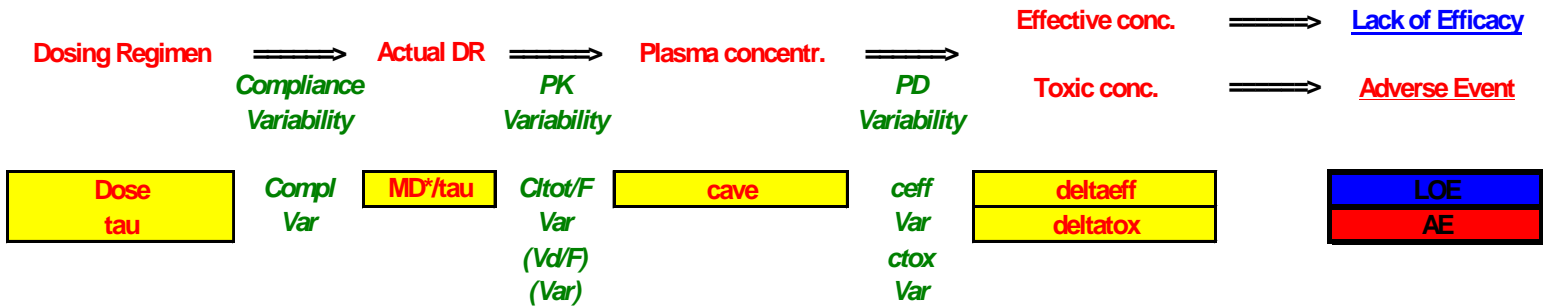
<u>Clinical Toxicity:</u>   Probability of occurrence, given a certain dosing regimen (ER) **and** Clinical (negative) consequences = utility factor

<u>"Therapeutic Index":</u>   Composite (e.g., difference of the above)

                follows ER (estimated probability) **and**
is affected by assigned utility factor for efficacy and toxicity (**judgment**)

Simple PK/PD Model

Basic PK/PD Model:

Dosing Regimen	$\Longrightarrow$	Actual DR	$\Longrightarrow$	Plasma concentr.	$\Longrightarrow$		Effective conc.	$\Longrightarrow$	Lack of Efficacy
	Compliance Variability		PK Variability		PD Variability		Toxic conc.	$\Longrightarrow$	Adverse Event

| Dose tau | Compl Var | MD*/tau | Cltot/F Var (Vd/F) (Var) | cave | ceff Var ctox Var | deltaeff deltatox | LOE AE |

Sample Scenario:

		Population Mean			Population Variability	
Dosing	Dose	90	mg			
	Compl	100		Var	20	
	tau	24	hrs			
PK	CLtot/F	10	l/hr	Var	40	
	Vd/F	100	l	Var		
PD	ceff	0.250	mg/l	Var	20	
	ctox	0.500	mg/l	Var	20	

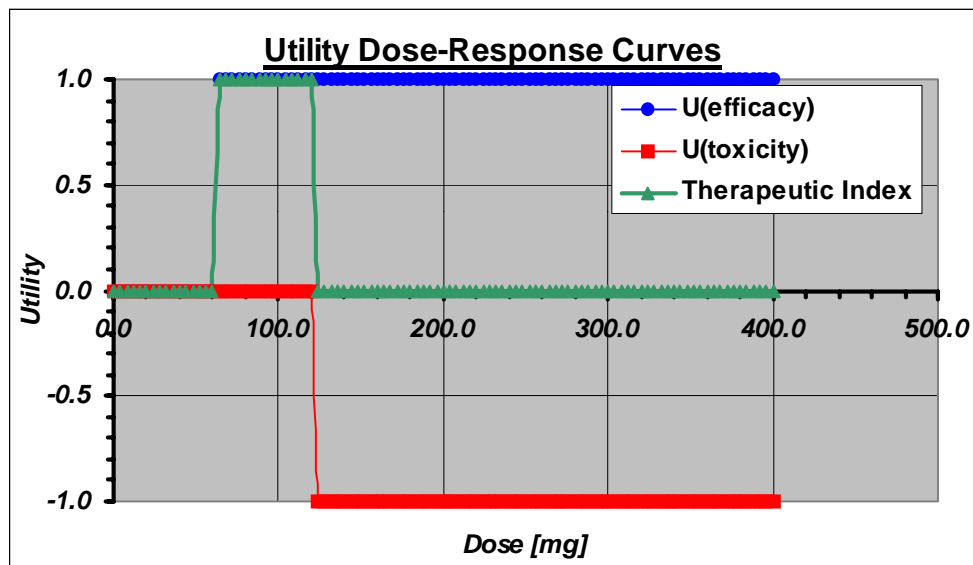# Model Results
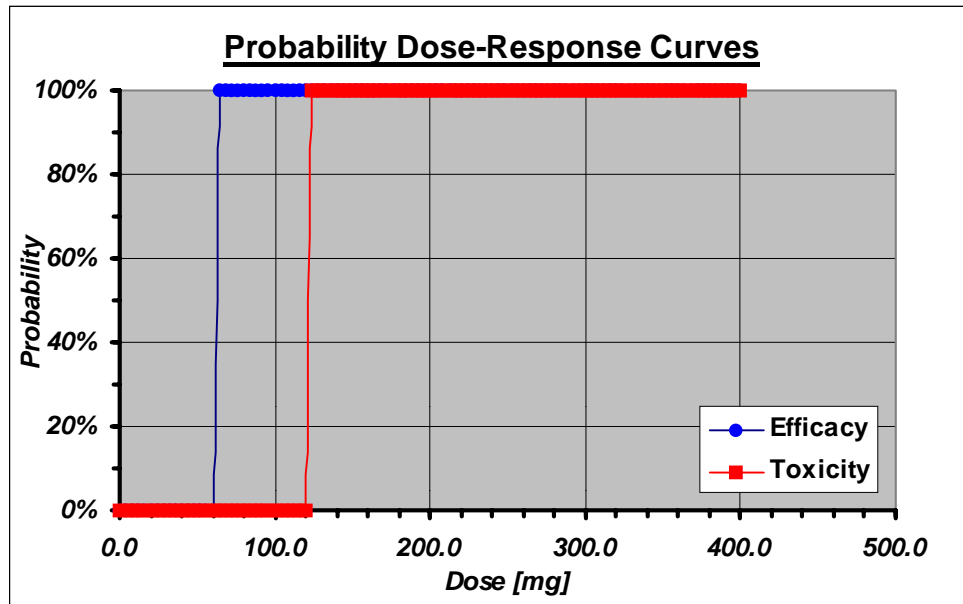
Dose-Response Curve for Efficacy and Toxicity :
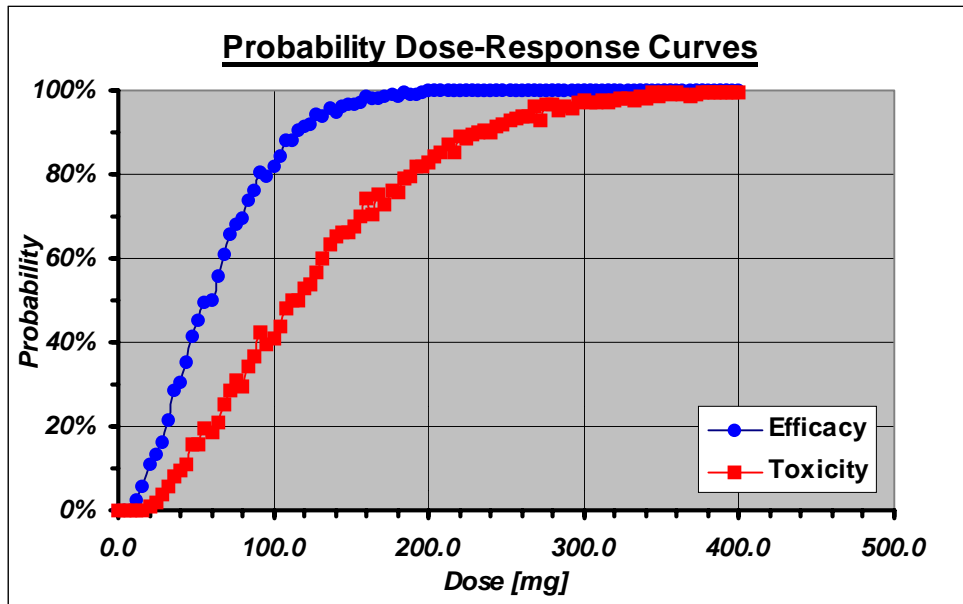
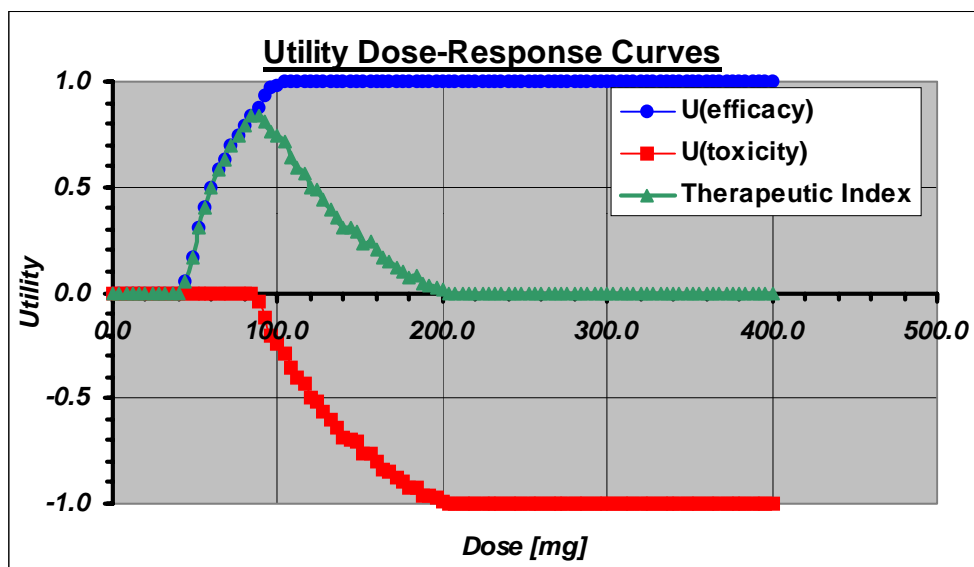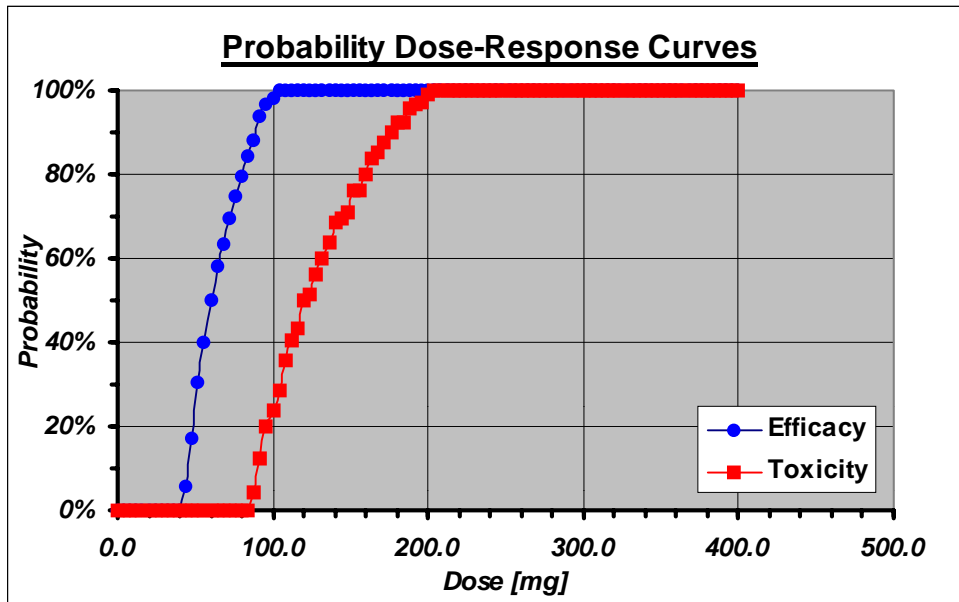## Therapeutic Utility Curve ($U_{eff}=1$, $U_{tox}=-1$):
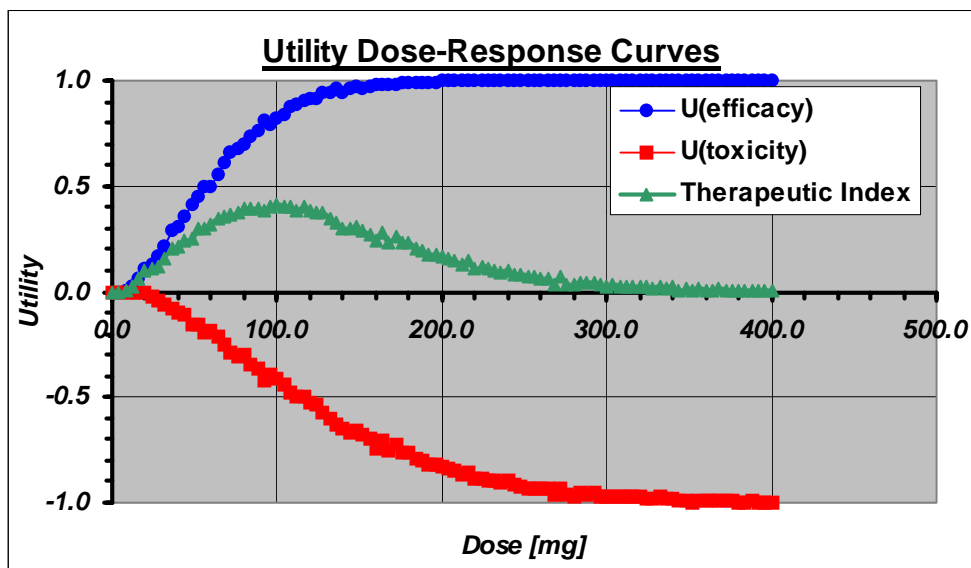
Simulation of Various Scenarios (I)

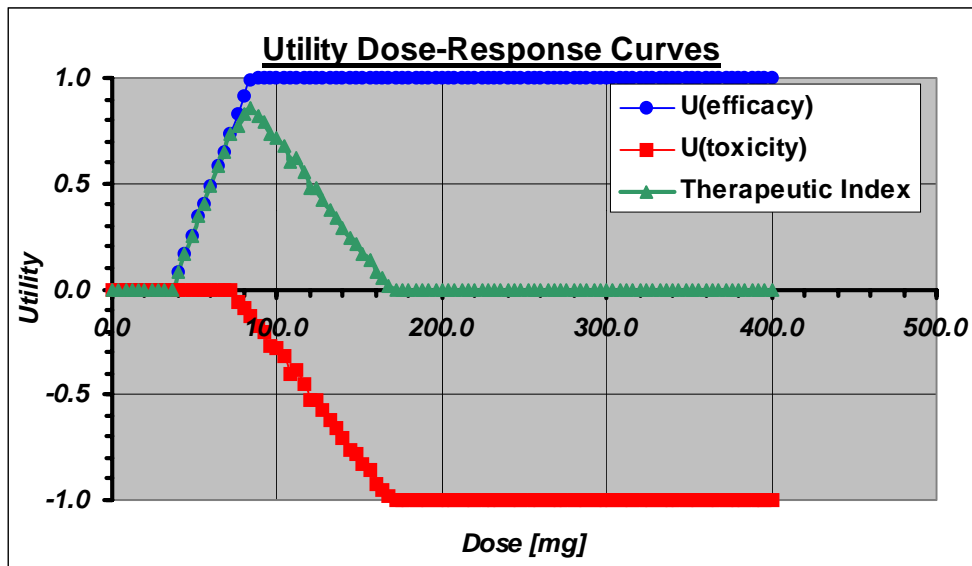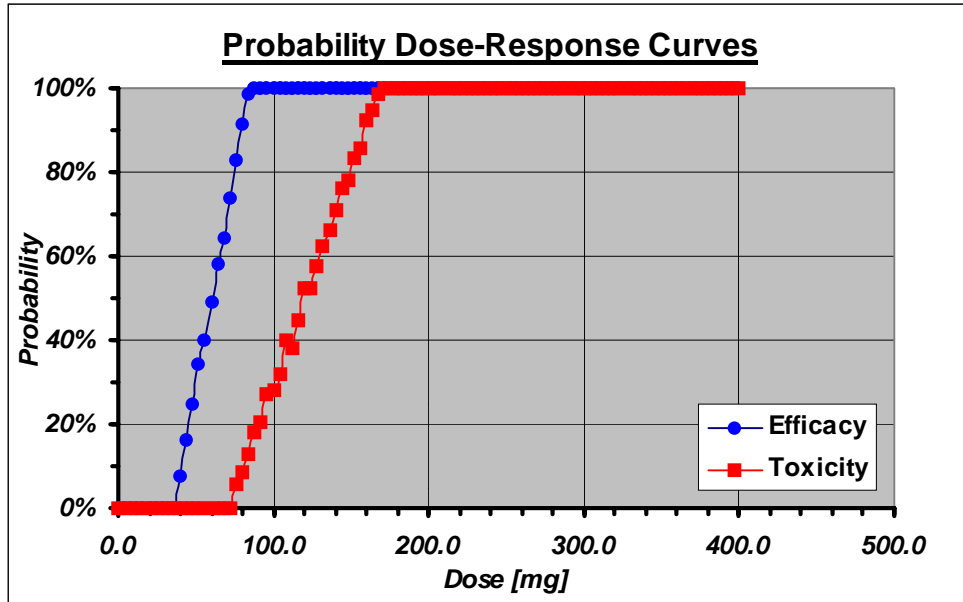## 1. No Variability in Any Source:

Simulation of Various Scenarios (II)
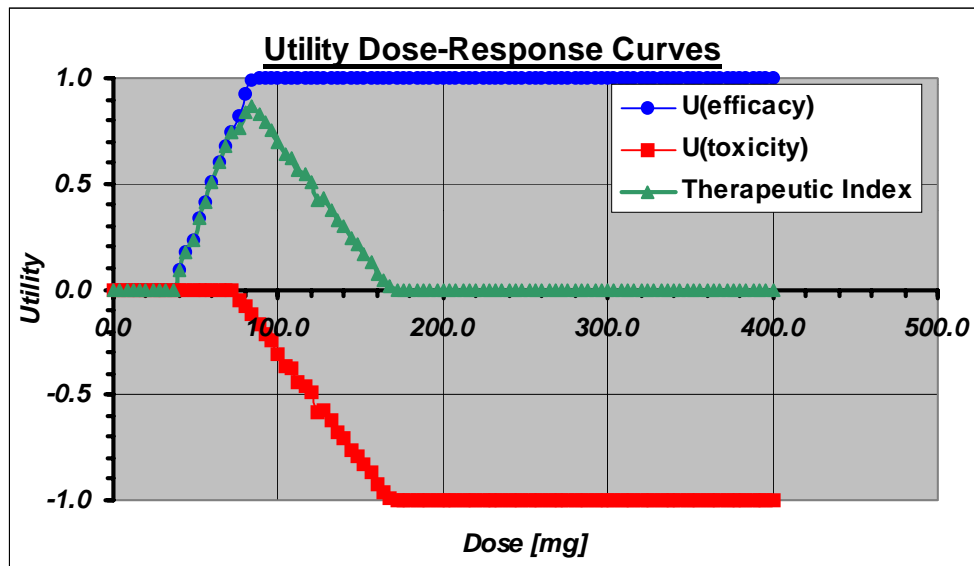
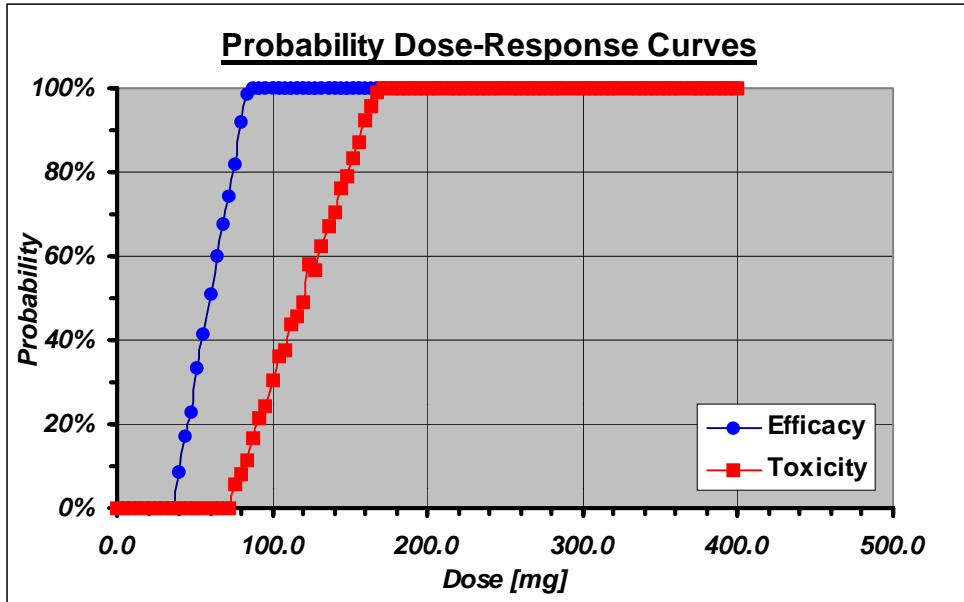## 2. Variability in Compliance/Dosage Form (20% COV):

Simulation of Various Scenarios (III)

3. Variability in PK (20% COV in CL_{tot}/F):
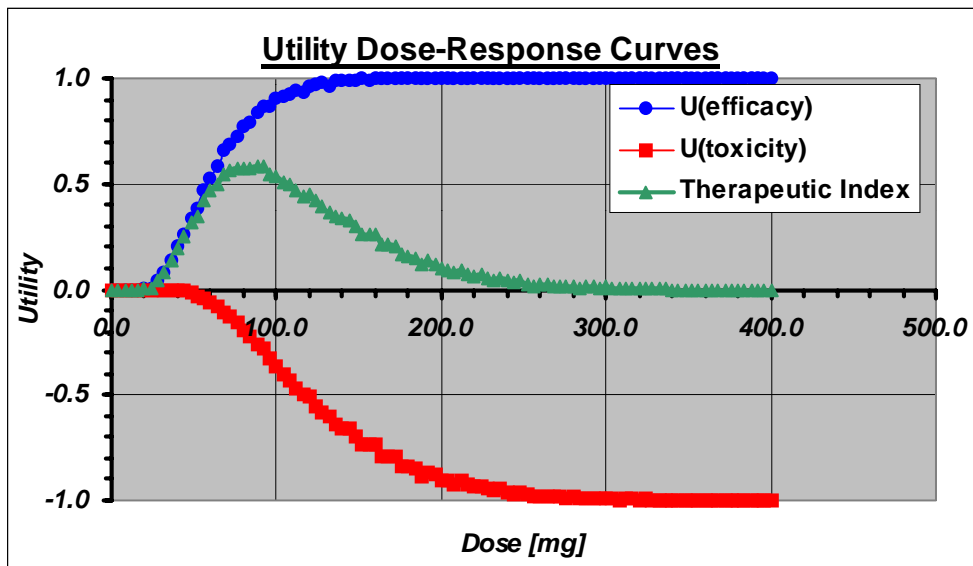
Simulation of Various Scenarios (IV)

4. Variability in PD (20% COV in effective/toxic c_p):

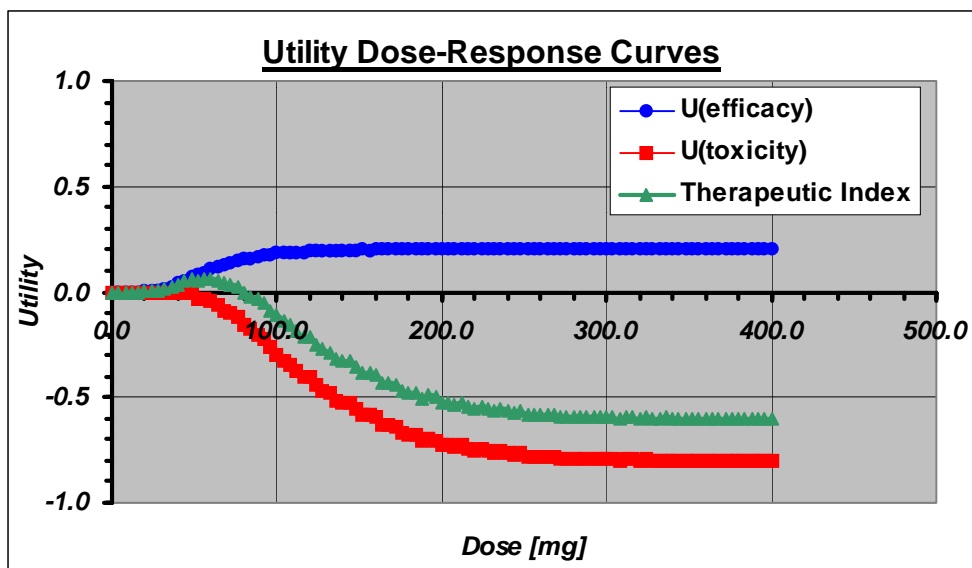Probability Dose-Response Curves

Utility Dose-Response Curves

Simulation of Various Scenarios (V)

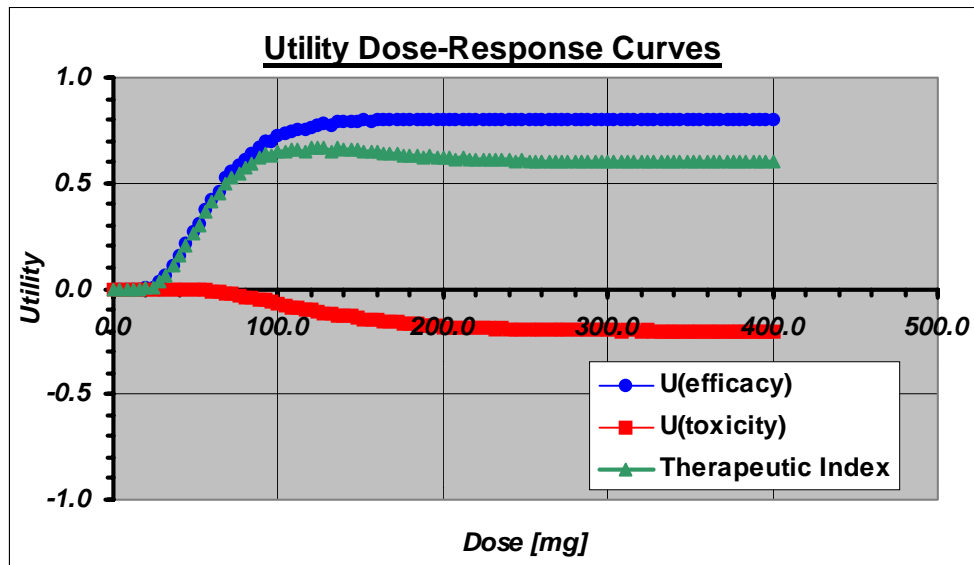## 5. Changes in Utility Factors:

$U_{eff}=1$, $U_{tox}=-1$ (NTI?)

$U_{eff}=0.2$, $U_{tox}=-0.8$ (marginal efficacy, significant toxicity)

Simulation of Various Scenarios (VI)

5. Changes in Utility Factors, continued:

U_{eff}=0.8, U_{tox}=-0.2 (significant efficacy, marginal toxicity)

Future Work

1. Monte Carlo Simulations using various variability distributions (e.g., subpopulations).

2. Investigation/modeling of other, more realistic dosing strategies:
    individualized dosing - based on known PK/PD covariates,
    dose-titration - based on PK or PD (surrogate) marker(s)

3. More complex PK/PD models (e.g., saturable PK, time-dependent PK/PD, non-steady-state)

4. Identification of currently approved (presumed NTI) products with available PK/PD information and possible utility information to allow modeling/proof-of-concept

Criteria for Assigning Utility Factors

General: Monitoring of clinical events (patient-diagnosed, physician-diagnosed, special testing)

Treatment setting (patient-self-treatment, outpatient, inpatient)

Efficacy (Benefit): Treatment impact on disease or condition (prevention, symptom relief, cure)

Severity of disease or condition

Alternative treatments

Toxicity (Harm): Reversibility

Impact on Activities of Daily Living (ADL)

Conclusions

The proposed approach combines

Clinical pharmacology information (ER), namely probability of efficacy and toxicity

With

Therapeutic Judgment (Utility values)

To

Assess quantitatively the "**Therapeutic Index**"

Therefore, this framework may be useful in developing a consensus on how to evaluate and identify **NTI Drugs**

Questions to the Committee:

1. Does this **general** approach appear reasonable to pursue further?

2. What **specific** modifications and additions should be considered?

3. What would be an effective and efficient process to assign generally acceptable **utility factors** for presumed NTIs?

4. What drugs/classes of drugs may have sufficient information (proprietary or published) to collect **real data**?