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**PK/PD Modeling and Clinical Trial  
Simulations Using Biomarker in  
New Drug Development**


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Contents



- What is PK/PD modeling
- Why and When we need PK/PD modeling
- Where and Who develop PK/PD model
- Critical path
- How to develop PK/PD modeling
- Simulation from developed PK/PD model
- Example of PK/PD model development

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### What is PK/PD model?

Dose  $\Rightarrow$  PK  $\leftrightarrow$  PK/PD relationship  $\leftrightarrow$  PD  $\Rightarrow$  Effect

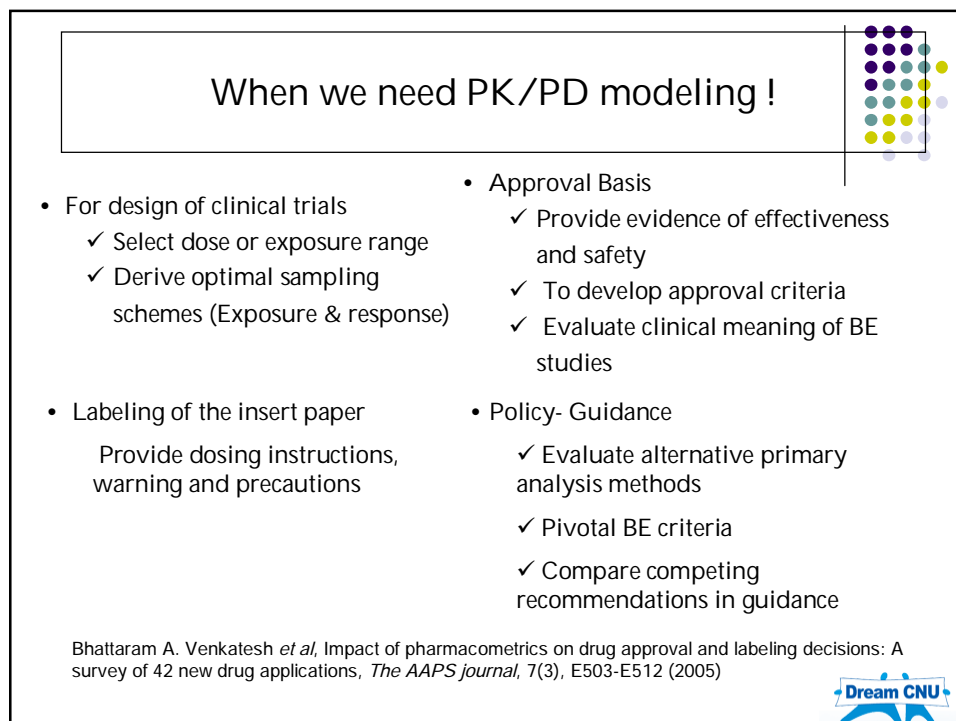
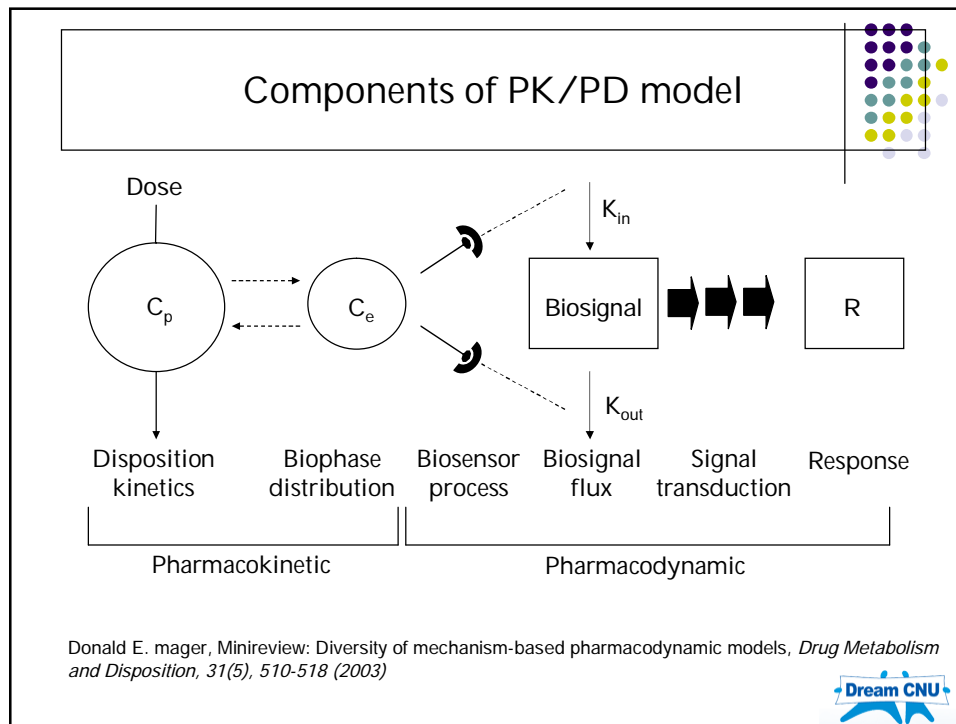
Cp vs Time  $\Rightarrow$  Effect vs Time (Drug concentration at effect site (Ce) vs Time)

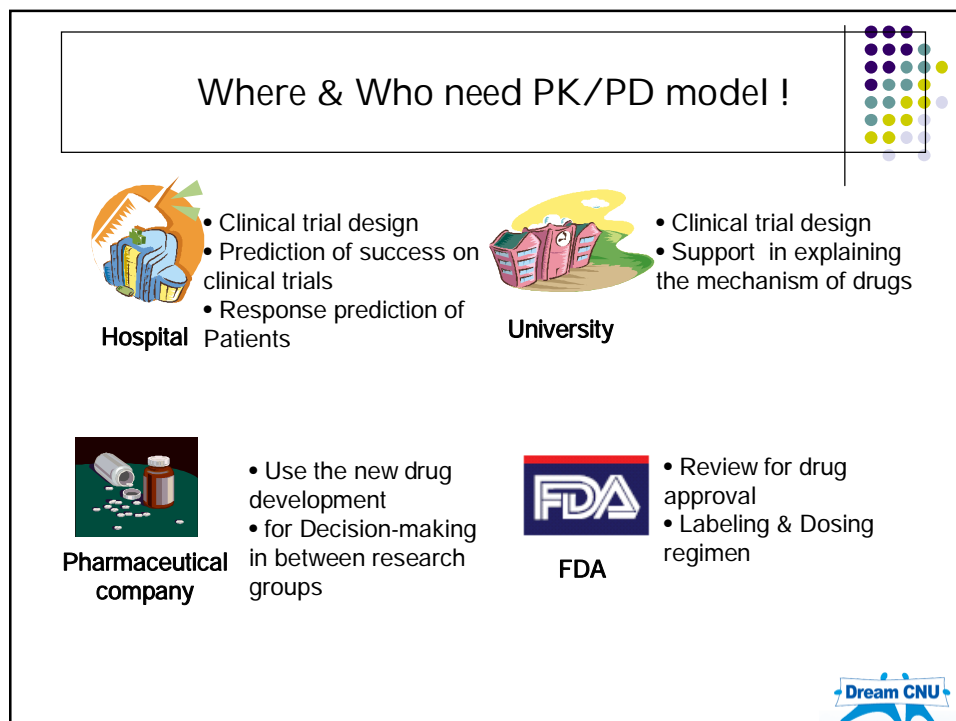
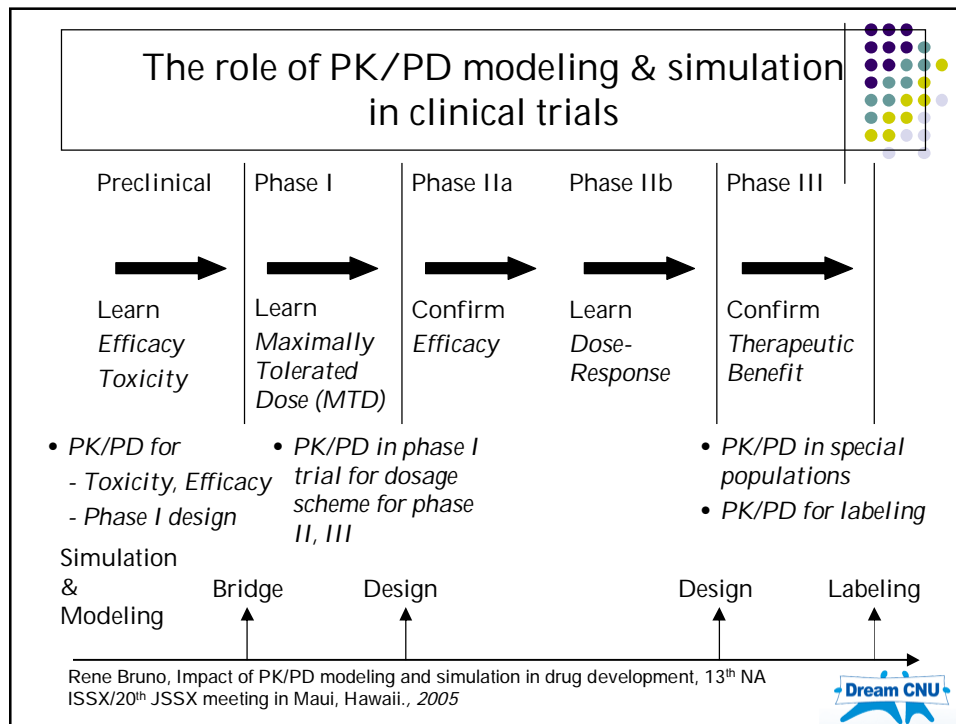
- **Definition:** PK/PD mathematical modeling to express the relationship between drug concentrations in plasma and at the effect site by examining the plasma drug concentration vs. effect relationship, thus revealing the true PD profiles of a drug, i.e., the relationship between  $C_e$  and pharmacological effects.

PD and PK/PD relationships, In: Handbook of essential pharmacokinetics, pharmacodynamics and drug metabolism for industrial scientists, Kwon Younggil intext Kluwer Academic/Plenum Publishers, NY, 2001

### Hysteresis and Delay of Drug Effects

- No delay in PK and PD process
- Delay of drug distribution
- Indirect response
- Slow receptor binding
- Sensitization
- Active metabolite
- Homeostasis
- Tolerance





## -Critical Path – FDA report to improve the system of new drug development.





- Critical path: The scientific process through which a potential human drug can be developed efficiently.
  - ✓ Predict whether a product candidate will be safe and effective, so can decide which candidates to move to each successively more rigorous phase of testing
  - ✓ Assess whether a product candidate is safe and effective, once the potential product is moved into human testing
  - ✓ Manufacturing large amount of the product, and assess the quality of the finished product
- Critical path tools: Animal models of human disease, Biomarker, PK/PD Modeling & clinical trial design, quality assessment technology

Critical path opportunities reports, FDA, March (2006)  
 Critical path opportunities lists, FDA, March (2006)  
 Critical path opportunities for generic drugs, May (2007)  
[www.fda.gov/oc/initiatives/criticalpath/faq.html](http://www.fda.gov/oc/initiatives/criticalpath/faq.html)




## Critical Path -FDA Report-





- Topic 1: Better evaluation tools-developing new biomarker and disease models
- Topic 2: Streamlining clinical trials
- Topic 3: Harnessing bioinformatics **PK/PD Modeling & Simulation Topics**
- Topic 4: Moving manufacturing into the 21<sup>st</sup> century
- Topic 5: Developing products to address urgent public health needs
- Topic 6: At-risk populations-pediatrics

Critical path opportunities reports, FDA, March (2006)  
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## How to Develop PK/PD modeling - Steps of the PK/PD modeling -



- Understand the study design and Characteristics of drugs
  - ✓ Liphophilic or hydrophilic, transporter substrate, metabolic enzyme induction, active metabolite etc.
- Understand the PK data and the PD data
  - ✓ Relationship between PK and PD : Direct, indirect, receptor binding etc.
- Model development with selection criteria
- Model evaluation
  - ✓ Internal validation: On population underlying the sample. (Bootstrapping)
  - ✓ External validation: On related but different population data.
- Simulation and Prediction



### Step 1 : Collection of PK and PD data



- PK and PD of a new drug X following a single IV administration of two dose level (0.1 mg, 0.5mg)
- The mechanism of action of the drug is uncertain

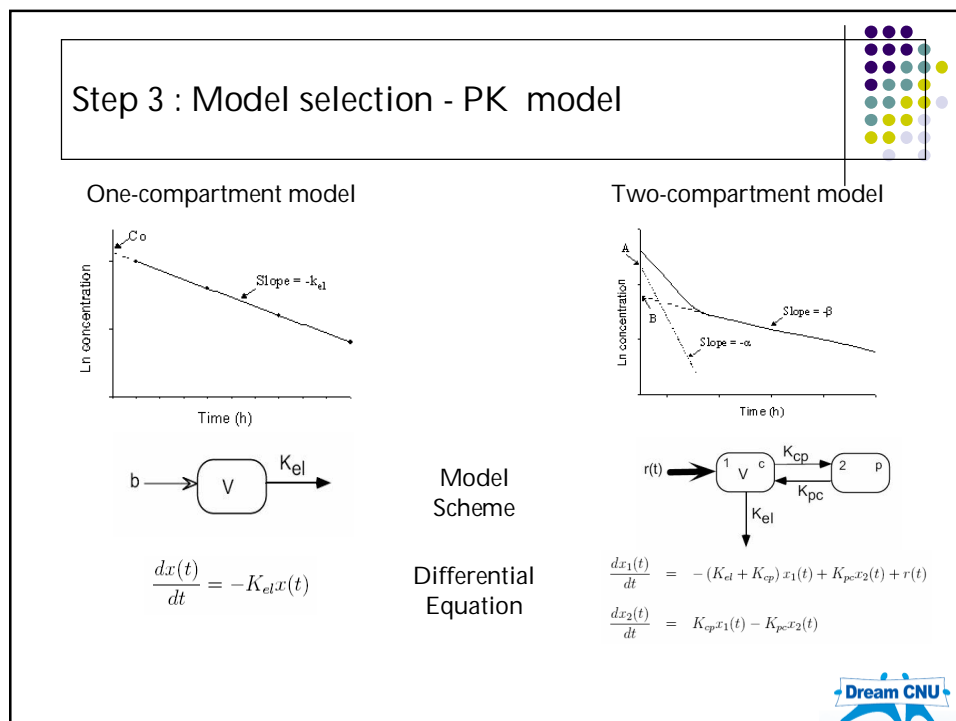
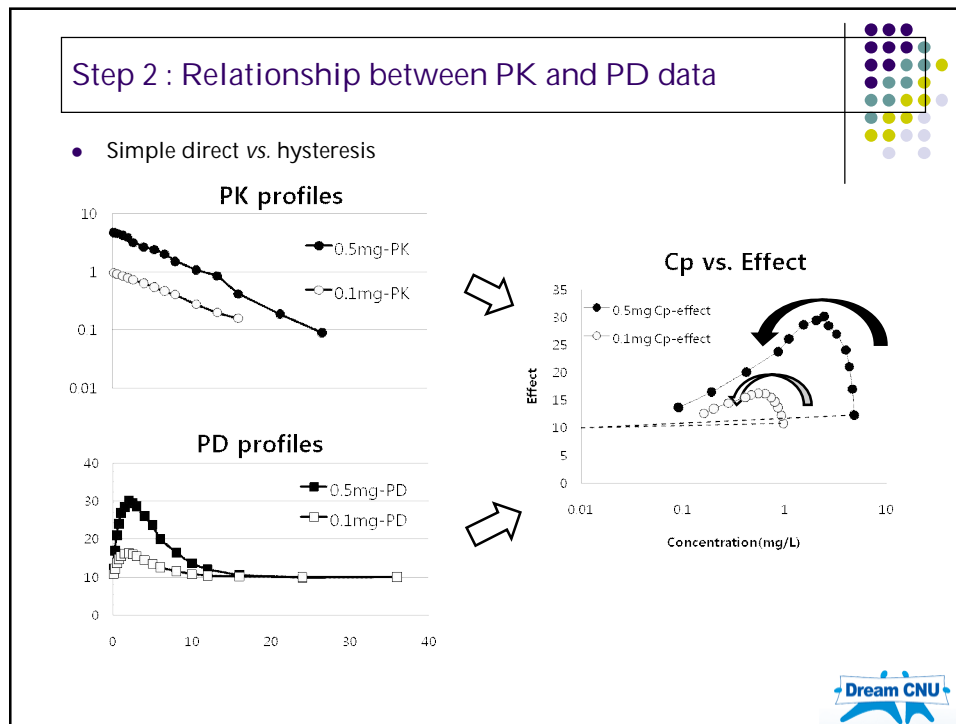
<Dose 0.1mg>


Time(hr)	Conc.(ng/ml)	Effect
0.083	0.97	10.8
0.25	0.93	12.2
0.5	0.86	13.7
0.75	0.8	14.8
1	0.74	15.5
1.5	0.64	16.2
2	0.55	16.3
2.5	0.47	16
3	0.41	15.5
4	0.28	14.5
5	0.2	13.5
6	0.16	12.6
8	ND	11.5
10	ND	10.8
12	ND	10.4
16	ND	10.1
24	ND	10
36	ND	10

<Dose 0.5mg>

Time(hr)	Conc.(ng/ml)	Effect
0.083	4.82	10.3
0.25	4.61	17
0.5	4.32	21.1
0.75	3.98	24.1
1	3.22	27
1.5	2.69	28.5
2	2.43	30.2
2.5	2.05	29.5
3	1.53	28.7
4	1.09	26.1
5	0.86	23.8
6	0.42	20.1
8	0.19	16.5
10	0.09	13.7
12	ND	12.1
16	ND	10.6
24	ND	9.9
36	ND	10.1

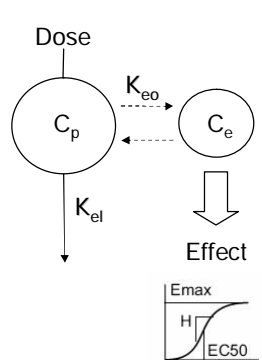




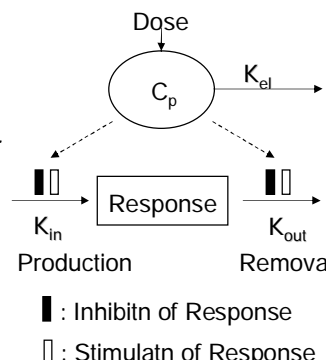


Step 4 : Model selection - PD model  
-Biophase distribution model vs. Indirect response model-


- Biophase model: Explain the delay of pharmacological effect using delay parameter( $K_{eo}$ )
- Indirect response model(IDR): Described the time pattern of the response variable(R) that is affected by a drug, which inhibit or stimulate the  $K_{in}$  and  $K_{out}$ . The response is produced at the zero-order rate and lost at the first-order rate.




VS.



■ : Inhibitn of Response  
□ : Stimulatn of Response





✓Step 5 : Running Computer programs

- **ADAPT II: BMSR, USC, Prof. David Z. D'argenio, 1990**
  - Step 1: PK and PD data input
  - Step 2: Model selection from the model library or user defined model
  - Step 3: Input differential equation.
  - Step 4: System and variance parameter definition
  - Step 5: Initial estimation of the parameters
  - Step 6: Running program : iteration
  - Step 7: Evaluation of the results
- **NONMEM: UCSF, Prof. Lewis B. Shiner, 1980**  
Nonlinear Mixed Effect Modeling for population PK/PD model

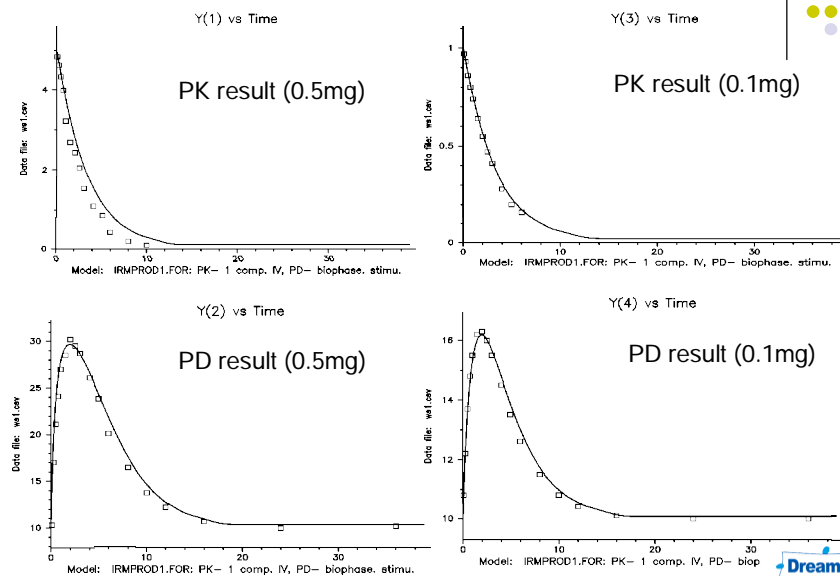
## Step 6 : Model decision - Model selection criteria

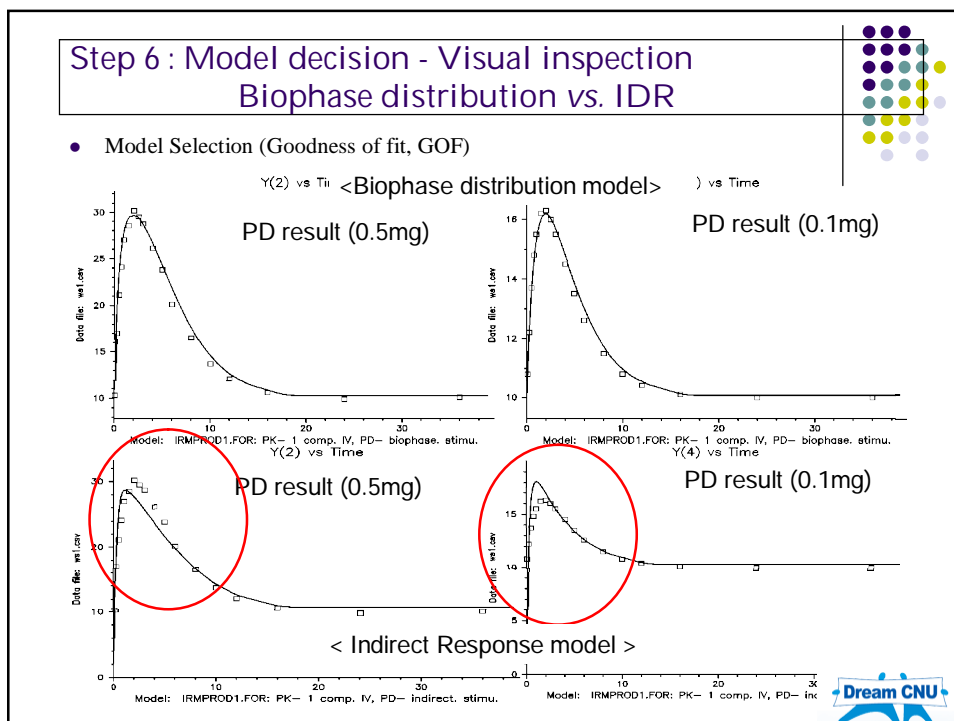
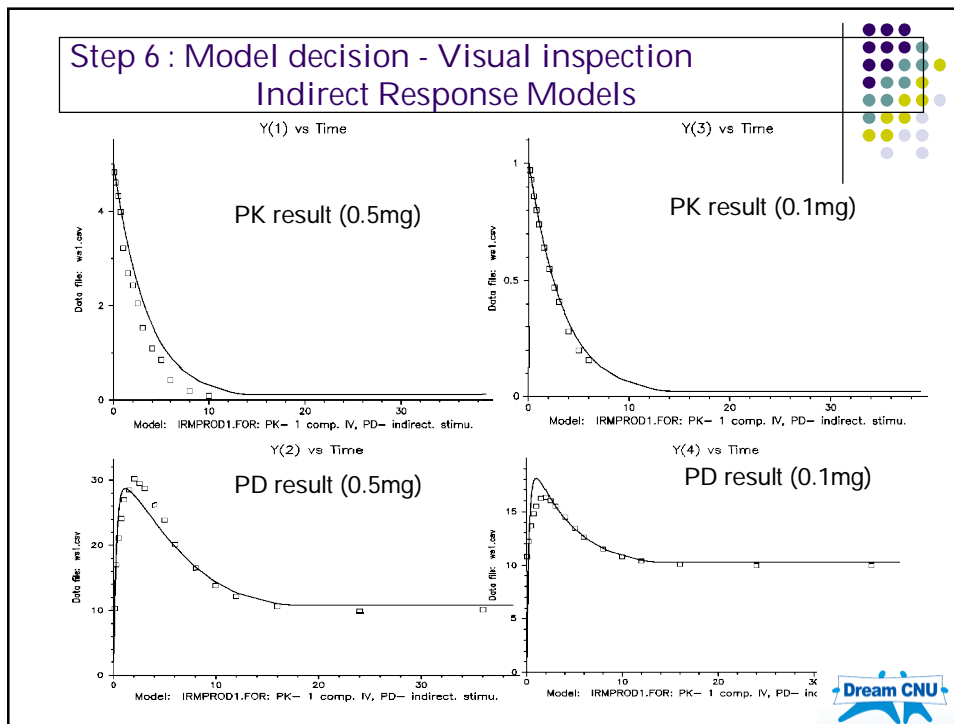
1. Visual examination: Goodness of fit
2. Akaike information criteria (AIC)
3. Bayesian information criteria (BIC)  
= Schwarz criterion (SC)
4. Sum of squares of residuals (SSR)
5. Standard deviation of parameter estimates
6. Correlations between parameters

The art of modeling: In Pharmacokinetic-pharmacodynamic modeling and simulation, Bonate PL. intext Springer, SA, 2006



## Step 6 : Model decision – Visual inspection Biophase distribution model





### Step 6 : Model decision – Final parameter comparison

[Biophase model]

- Final parameter

Parameter	Initial	Estimated
Kel	0.3	0.3145
V	100	99
E <sub>max</sub>	20	43.01
EC <sub>50</sub>	0.86	3.351
Keo	1.386	0.8786
E <sub>0</sub>	10.0	9.943

- Model Selection criteria
  - Goodness of fit
  - AIC : -24.912
  - SC : 4.8678

[Indirect response model, IDR]

- Final parameter

Parameter	Initial	Estimated
Kel	0.3	0.3145
V	100	99
K <sub>in</sub>	20	73.03
SC <sub>50</sub>	0.86	1.832
S <sub>max</sub>	1.386	2.104
R <sub>0</sub>	10.0	18.17
K <sub>out</sub>	0.75	0.99

- Model Selection criteria
  - Goodness of fit
  - AIC : 97.719
  - SC : 127.50

### Types of PK/PD model

Type of Drug effects	PK/PD model	Model characteristics ( E: empirical based model, M: mechanism-based model )
Reversible	Simple direct effects	E or M
	Biophase distribution	E
	Slow receptor-binding	M
	Basic and extended indirect effects	E or M
	Signal transduction	M
Irreversible	Cell or target inactivation	M
	Enzyme inactivation	M
	Signal transduction	M
Tolerance	Counter-regulation	M
	Desensitization	M
	Up- or down-regulation	M
	Precursor pool depletion	M

Donald E. mager, Minireview: Diversity of mechanism-based pharmacodynamic models, *Drug Metabolism and Disposition*, 31(5), 510-518 (2003)

## What is Good and Useful Model

1. Ability to characterize the observed data and to include the most of the important features of the data
2. Makes accurate and precise prediction
3. Increases understanding of the system
4. The model is actually used
5. The model is completed on time
6. Logically consistent, plausible
7. Validated by empirical observations
8. Robust to small changes in the data
9. Appropriate level of precision and detail
10. As simple as possible
11. Judged on what it is intended to do
12. Has flexibility
13. Is effective as a communication tool
14. Serves many different purposes
15. May allow for extrapolation outside the data range

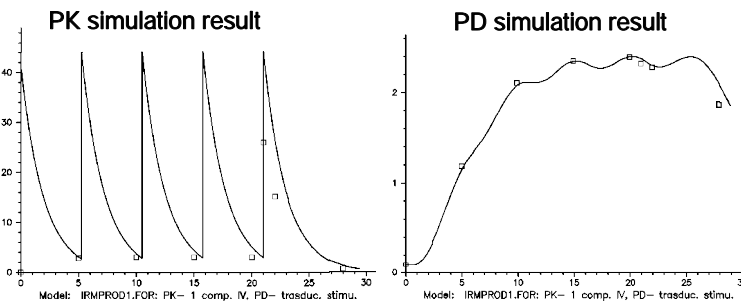
The art of modeling: In Pharmacokinetic-pharmacodynamic modeling and simulation, Bonate PL. intext Springer, SA, 2006



## Step 7 : Simulation from developed PK/PD model -Individual simulation-

1. Individual PK & PD parameter optimization using PK/PD model
2. Perform the individual PK/PD simulation after fixing PK & PD parameter using ADAPT II program or WinNonlin.
3. Obtain only the individual simulated mean profile. (No confidence interval)

<Individual simulation example using signal transduction PK/PD model>



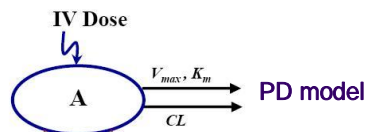
## Step 7 : Simulation from developed PK/PD model -Population simulation-

1. Population PK & PD parameter (mean & S.E.) optimization using ADAPT or NONMEM
  - ✓ STS method: ADAPT II program
  - ✓ NONMEM method: NONMEM program
2. Population PK/PD simulation based on the Monte-Carlo simulation, so we have to need the population mean and S.E. value of PK & PD parameters
3. Perform thousands of the population PK/PD simulation using estimated population mean & S.E. values through simulation mode of ADAPT II or NONMEM
4. Obtain both population mean profiles and confidence interval.



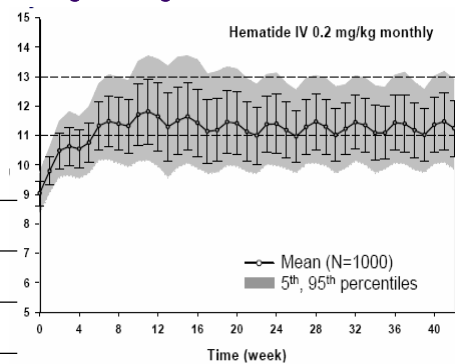
## Simulation from developed PK/PD model -Example of population simulation-

<Population PK simulation of Hematide>



PK and PD Parameters	Definition	Population mean(%SE)
Vmax (ug/hr)	Michaelis-menten capacity constant	14.4(22.3)
Km (ng/ml)	Michaelis-mente affinity constant	96.1(34.4)
V (L)	Volumn of distribution	3.47(2.4)
CL (L/hr)	Clearance	0.0432(6.9)

Hemoglobin mg/dL



- Monte-carlo simulation 1000 times iteration
- Confidence interval was obtained using S.E.
- ADAPT II program

Woo et al. Population PK/PD modeling of a novel erythropoietin agonist, Hematide, in healthy volunteers, AAPS2006



### Example of PK/PD model Development - Cilostazol : Characteristics -

C1=NC2=C(C=C1)N(C2)CCCCOC3=CC=C4C(=O)NCC4=O (Cilostazol)
   
 $\xrightarrow{\text{CYP2C19, CYP3A4}}$ 
C1=NC2=C(C=C1)N(C2)CCCCOC3=CC=C4C(=O)NCC4=O (3,4-dihydrocilostazol)
   
 $\xrightarrow{\text{CYP3A4}}$ 
C1=NC2=C(C=C1)N(C2)CCCCOC3=CC=C4C(=O)NCC4=O (4'-trans-hydroxycilostazol)

- Cilostazol(Pletal): Phosphodiesterase(PDE) inhibitor anti thrombotics: Anti-platelet aggregation
- Dosage: 100mg twice a day
- Metabolism: hepatic CYP 2C19, CYP3A4
- 3,4-dihydrocilostazol: active metabolite, 4~7 times potent than cilostazol
- 4'-trans-hydroxy-cilostazol: active metabolite, effective 20% compared with cilostazol effect

Ikeda Y. *Thrombosis and Haemostasis*, 82(2): 435-438 (1999)  
Ikeda Y et al. *EJP*, 314: 197-202 (1996)

### Example of PK/PD model Development -Cilostazole : Study design-

- Study design (Single oral dose)

Dose	Cilostazol 100mg(Pletal) single dose
volunteers	n=20
PK sampling time	0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 32, 48 hr(total 13point)
PD sampling time	0, 1, 2, 3, 4, 6, 8, 10, 12, 24 hr(total 10point)
Pharmacokinetic	Analyzed by HPLC/UV
Pharmacodynamic	Platelet aggregation test

### Example of PK/PD model Development -Platelet Aggregation Test-

Blood : Sod. Citrate (9 : 1)  $\xrightarrow{\text{Centrifuge (160g/10min.)}}$  Platelet rich plasma (PRP)  $\xrightarrow{\text{Centrifuge (2000g/10min.)}}$  Platelet poor plasma (PPP)

Platelet rich plasma (PRP)  $\xrightarrow{\text{37°C, 3 min Spike the inducer (ADP, Arachidonic acid)}}$  Aggregation 5 min

- Platelet aggregation(%) = (PRP turbidity/PPP turbidity) × 100
- Set the baseline between 70% and 100%

### Example of PK/PD model Development - Cilostazol : PK data -

#### Oral two-Compartment model

Model dependent parameter		
PK Parameter	Value (mean±SD)	Population mean
$K_a$ (hr <sup>-1</sup> )	0.187 ± 0.146	0.153
$K_{cp}$ (hr <sup>-1</sup> )	0.175 ± 0.112	0.202
$K_{pc}$ (hr <sup>-1</sup> )	0.086 ± 0.002	0.076
$K_{el}$ (hr <sup>-1</sup> )	0.264 ± 0.123	0.268
$V_c/F$ (L)	17.730 ± 10.522	20.352

PK profiles of cilostazol 100mg after a single oral dose. (n=20, mean±SD) Closed circles are observed values and solid line is the fitted line using PK/PD model

### Example of PK/PD model Development - Cilostazol : Model selection -

- Biophase model
  - ✓ Goodness of fit is not good
- Receptor-binding model
  - ✓ Goodness of fit is good
  - ✓ AIC = -10.232
  - ✓ SC = -2.345
- Platelet aggregation effect model
  - ✓ Goodness of fit is good
  - ✓ AIC = -15.234
  - ✓ SC = -6.328

[Final model scheme]

Cilostazol PK model

Platelet aggregation effect model

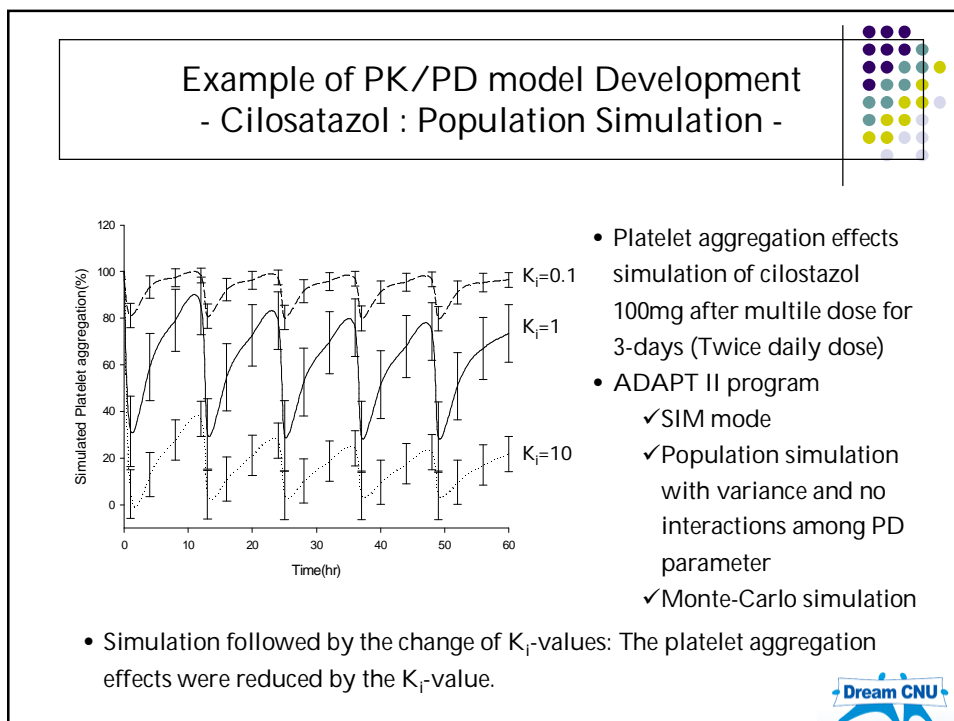
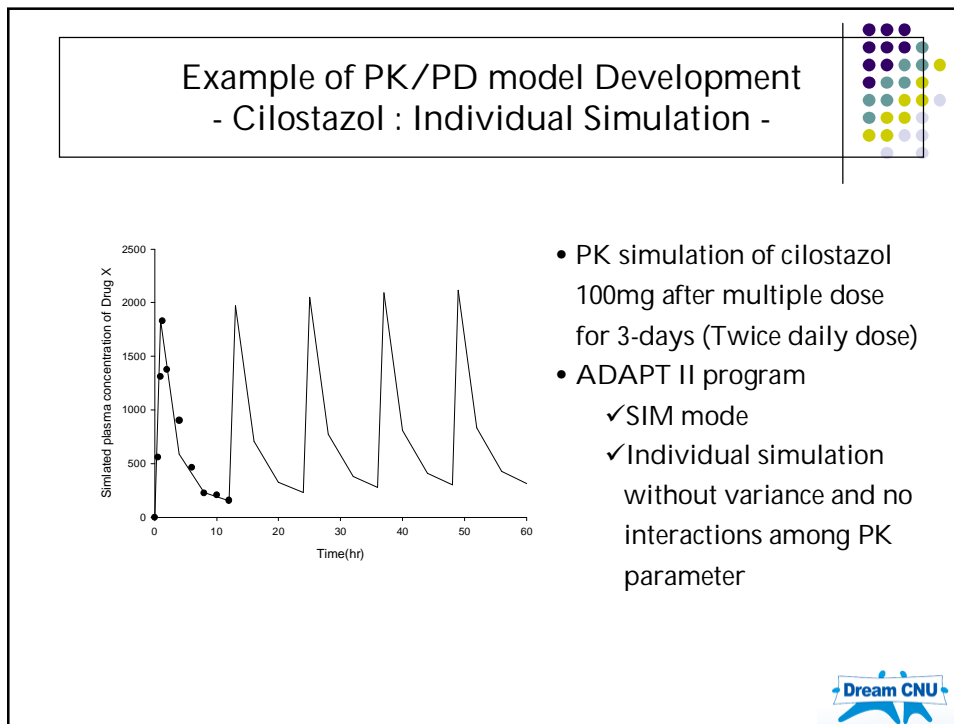
$K_s$  = Active-form of platelet synthesis rate constant  
 $K_{el-PRP}$  = Apparent platelet disappearance rate constant  
 $K_i$  = Apparent platelet aggregation inhibition rate constant

### Example of PK/PD model Development - Cilostazol : PD data -

#### Platelet aggregation effect model

PD profiles of cilostazol 100mg after a single oral dose. (n=20, mean±SEM) Closed circles are observed values and solid line is the fitted line using PK/PD model

PD Parameter	Mean±SD	Population mean
$K_i$ (ml/ng/hr)	1.025 ± 0.953	1.058
$K_s$ (hr <sup>-1</sup> )	0.0067 ± 0.0021	0.0046
$K_{el-PRP}$ (hr <sup>-1</sup> )	0.0076 ± 0.0032	0.0087



## Summary

- Successful PK/PD model verifies both of PK and PD data
- Mathematical PK/PD relationship can be utilized for simulation, for example, PK/PD model from phase I study can be used for the study design of Phase II, III clinical trials.
- The drug mechanism and the mode of activity can be estimated through PK/PD model.
- Biomarker qualification (Clinical validation) can be achieved through PK/PD modeling.
- PK/PD model enrich the BE results with extra PD data

In conclusion, PK/PD modeling is essential for new drug development in designing clinical trials and also for labeling. It is also very effective for government examination for approval and for policy guidance.



Thank you

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