2012년
집단 약동/약력학 연구회
연례 학술대회

일시: 2012년 12월 6일(목)
장소: 서울아산병원 연구원 지하대강당

PAGK Population Approach Group in Korea

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PAGK Population Approach Group in Korea

인사말씀

제 1회 PAGK 연례학술대회 참석자 분들께

PAGK (대한 집단약동약력학연구회)가 2006년 창립한 지 어느덧 6년이 되었습니다. 창립 시 62명으로 출발한 연구회는 현재 157명의 회원을 확보하는 등 연구회의 학문적 특수성에 비해 그 동안 양적으로 괄목한 만한 성장을 하였습니다.

그러나 최근의 국제 동향은 우리에게 더 큰 도약을 요구하고 있습니다. 아시다시피 집단약동약력학 모델링 및 시뮬레이션이 비용과 시간을 단축시킬 수 있는 21세기 신약개발의 핵심기술로 떠오르면서 선진 제약 국가들은 이 분야의 육성 및 미래 전문가 확보에 많은 노력을 기울이고 있으며, 이는 PAGE (유럽 집단약동약력학 연례미팅)및 ACoP (북미 집단약동약력학 연례미팅)의 참석자 수가 최근 급격히 늘어 각기 600 명에 이른 사실에서 잘 나타나 있습니다.

이러한 흐름 속에 집단약동약력학에 대한 전 세계적인 발전을 도모하고자 창립된 WCoP (세계 집단약동약력학 학술대회) 의 초대 대회를 다른 지역을 제치고 지난 9월 서울에서 개최할 수 있었던 것은 매우 뜻 깊은 일이 아닐 수 없습니다. 이를 계기로 이 분야에서 우리나라가 아시아 나아가 세계의 선도국가로 발전하기를 바라며 이를 위하여 PAGK가 중심역할을 해주기를 기대해 봅니다.

이와 관련하여 PAGK는 올해부터 연례 학술대회를 개최하여 연구회의 학술 활동을 강화하고 나아가 약학대학 및 제약회사 등 관련 기관 연구자들의 참여를 넓혀 외연을 확장함으로써 연구회의 실질적 발전을 꾀하려고 합니다. 아울러 내년부터는 PAGJA (일본 집단약동약력학 연구회)와의 공동심포지엄을 개최하여 국제적 네트워크를 구축하고 회원들에게 국제적 학술 교류의 장을 제공하고자 합니다.

제 1회 PAGK 연례 학술대회를 열게 됨을 회원 분들과 함께 경축하면서 앞으로 연구회의 무궁한 발전이 있기를 기원합니다.

2012년 12월 6일

PAGK 회장 **박 경 수**

2012년 집단 약동/약력학 연구회 연례 학술대회

▌프 로 그 램▐

1:00-1:30	등 록	
1:30-1:40	Opening remark	연세의대 **박경수**
1:40-2:10	Phase I clinical trial of decitabine – An example of adaptive trial design using PK-PD M&S	가톨릭의대 임동석/ 2
2:10-2:40	Pharmacokinetic and pharmacodynamic modeling of a copper-selective chelator	차약대 조혜영/26
2:40-3:10	Population modeling tools	울산의대 배균섭/52
3:10-3:30	총 회	
3:30-4:00	*Coffee Break*	
4:00-4:30	Prediction of the tacrolimus population pharmacokinetic parameters considering genotypes and clinical factors in kidney transplant recipients	서울약대 김인화/81
4:30-5:00	Pharmacometrics research and application in the hospital setting	서울의대 정재용/100
5:00-5:30	Working as a pharmacometrician in US/UK/EU – What are they looking for? Hiring manager's perspective	GSK 김용호/119
5:30-5:40	Closing remark	울산의대 **배균섭**

CURRICULUM VITAE

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소 속 : 가톨릭대학교 의과대학

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Department of Clinical Pharmacology, Seoul St. Mary's Hospital, Seoul, Korea

▌Educations ▌

1992 M.D. Seoul National University College of Medicine, Seoul, Korea
1996 Ph.D. Clinical Pharmacology, Seoul National University College of Medicine, Seoul, Korea

▌Professional Experiences ▌

2001- Professor and Chairman, Department of Pharmacology, Catholic University College of Medicine, Seoul, Korea
2003-2005 Visiting Fellow, Center for Drug Development Sciences, Georgetown University, Washington DC, USA
2006 Establishment Promoter, PAGK (Population Approach Group in Korea)
2009-2011 President, PAGK

An Example of Adaptive Trial Design Based upon PK-PD Modeling

- Phase I Trial of Decitabine in Patients Undergoing Allogeneic Stem Cell Transplantation

Dong-Seok Yim[1], Yoo-Jin Kim[2]

[1]Department of Clinical Pharmacology,
[2]Department of Hematology, Seoul St. Mary's Hospital

Allogeneic stem cell transplantation is the only known curative therapy for myelodysplastic syndromes (MDS). Transplant outcome of the advanced MDS is poor due to higher relapse rate and substantial transplant-related mortality (TRM). Myeloablative conditioning regimen leads to lower relapse rates but its beneficial effects upon relapse is offset by high TRM. The introduction of stem cell transplantation (SCT) with nonmyeloablative or reduced intensity conditioning allowed extension of allogeneic SCT to a much wider patient population by reducing the toxicity and exploiting the graft-versus leukemia (GVL) effect. High relapse rate, however, remains an obstacle to long-term disease control and further approaches to reduce the risk of relapse after allogeneic SCT are needed.

Decitabine has been shown to be effective for treatment of MDS and associated with very limited extramedullary toxicity at the lower doses. Furthermore, the hypomethylating effects of decitabine require an extended period of therapy and are likely to be more beneficial in the setting of a minimal residual disease after transplantation. We hypothesized that post-transplant maintenance therapy with decitabine may reduce relapse rate.

For the patients who finish the above transplant procedure and meet the enrollment criteria, decitabine will be given at a dose of 5 mg/kg/day ~ 15 mg/kg/day iv over 1 hour for 5 consecutive days. The drug will be repeated every 4 weeks for up to 4 cycles. Dose escalation strategy between cohorts and between cycles in the same cohort patients will be based upon the quantitatively measured hematological toxicity (e.g., ANC or platelet count at nadir). In other words, a mechanism-based pharmacokinetic / phamacodynamic model developed using sparsely sampled patients' PK data and toxicity response will be used to titrate next cycle doses for the patients and initial doses for new cohort patients. The model to predict the time course of bone marrow suppression by anticancer drugs has been published elsewhere. However, there are no reports on its application to individual dose titration and dose-escalation between cohorts in early phase anticancer drug trials. This study is the first case of PK/PD modeling-based adaptive clinical trial.

Incorporation of PK &Biomarkers in clinical trials

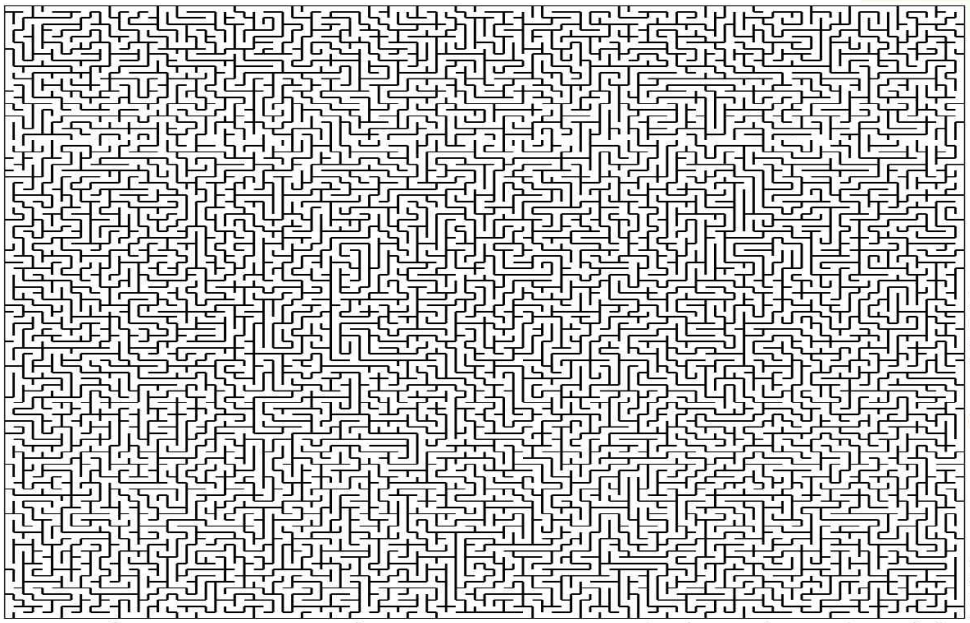
An Example of Adaptive Trial Design Based upon PK-PD Modeling

Seunghoon Han, Dong-Seok Yim, Yoo-Jin Kim*
Dept. Clinical Pharmacology and *Hematology
Seoul St. Mary's Hospital

원래는 이런 사진...

Background

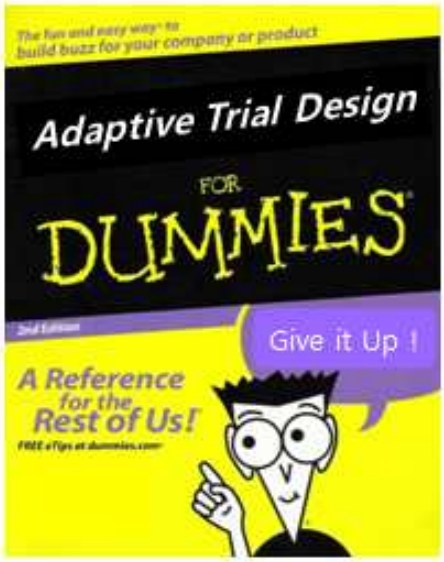
Adaptive trial design papers in the eyes of non-statisticians



$$\propto \exp\left[\sum_{j=1}^{K}\sum_{i=1}^{n_j}\left\{k_{ij}(\boldsymbol{\beta}^T\mathbf{x}_{ij}+b_{ij})-\lambda_{ij}^{y_{ij}}\exp(\boldsymbol{\beta}^T\mathbf{x}_{ij}+b_{ij})\right\}\right].$$

ming language) for the MCMC computations is available by request.

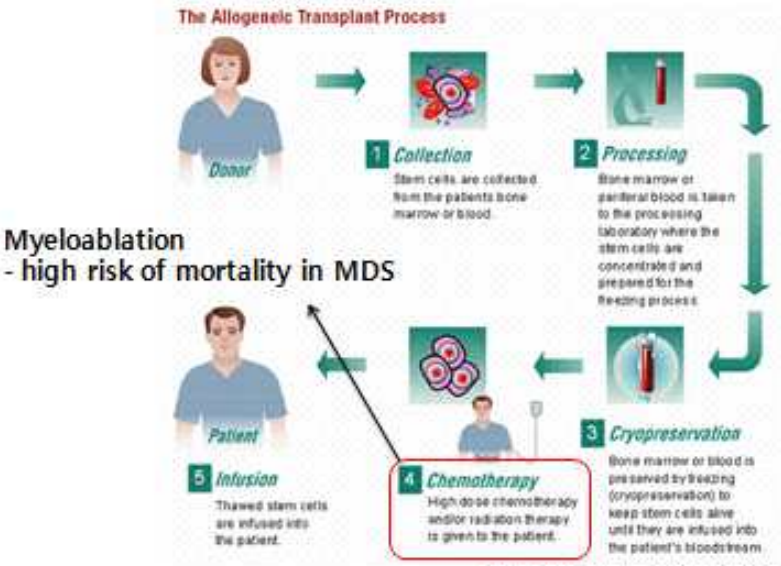
No easy guides to design adaptive trials at all.



The story begins at a discussion with a hematologist (Prof. Kim).

- Myelodysplastic syndrome (MDS)
  - Fatal bone marrow disorder with inefficient production of myeloid cells
  - Chemotherapy
    - Lenalidomide, Azacytidine, Decitabine …
  - Allogeneic stem cell transplantation (SCT)
    - the only curative therapy
    - Another person's bone marrow stem cells are transplanted

Allogeneic SCT



Myeloablation
- high risk of mortality in MDS

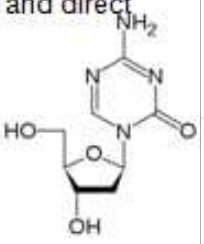
http://biomed.brown.edu/Courses/BI108/BI108_2007_Groups/group07/stemcells/img/Allogenic_big.gif

Non-myeloablative SCT for MDS

- Non-myeloablative or reduced intensity conditioning
  - Widening of SCT indications
  - but higher relapse rate
- Any ways to reduce relapse ?
  - ????
  - Is Decitabine useful to reduce the relapse rate after SCT?

Decitabine

- One of chemotherpy choices for MDS
  - inhibit DNA methyltransferase following phosphorylation and direct incorporation into DNA.
- Dosage regimen:
  - 20 mg/m^2/day iv over 1 hour for 5 consecutive days.
  - repeated every 4 weeks for up to 4 cycles.



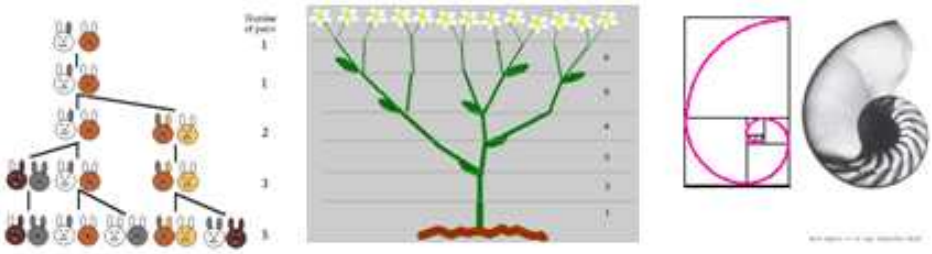
- Toxicity
  - Thrombocytopenia, Neutropenia

Considerations to design phase I trial of decitabine in post-SCT patients

- If we use the modified Fibonacci design
  - Many patients may be exposed to subtherapeutic doses for more than 4 cycles
- No quantitative exposure – toxicity relationship of decitabine is known.
  - Optimal phase II dose in Korean post-SCT patients may be determined based upon PK-PD model

Fibonacci

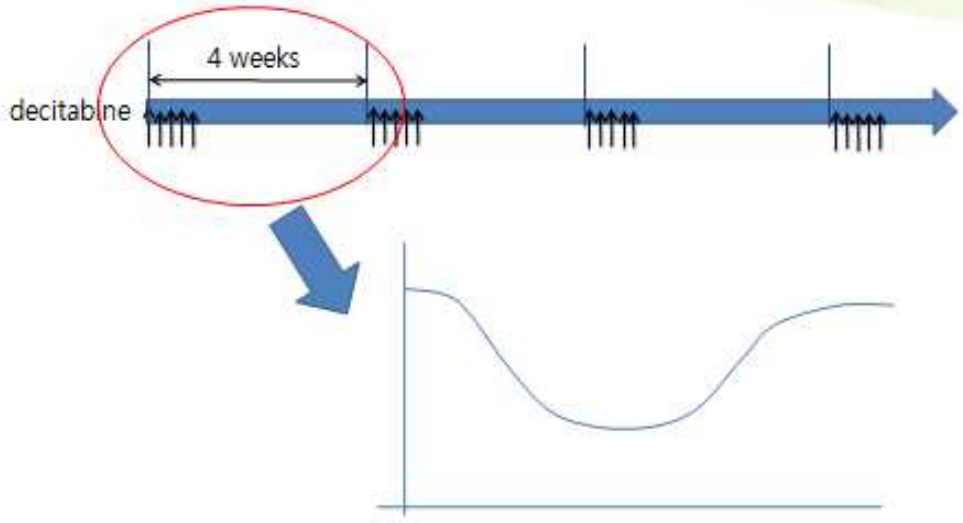
- Fibonacci Sequence
  1, 2, 3, 5, 8 ,13, 21, ...



Classical Dose escalation

- Fibonacci Sequence
  1, 2, 3, 5, 8 ,13, 21, ...
- Modified Fibonacci dose multiples
  Initial dose, 2.00, 1.67, 1.50, 1.40, 1.33, 1.33...
- MTD (Maximum Tolerable Dose)
  Dose at DLT (Dose Limiting Toxicity) in 30% of patients
- Expect to reach MTD in 3-4th dose
- RPTD (Recommended Phase II Dose)
  The next lower dose level of MTD

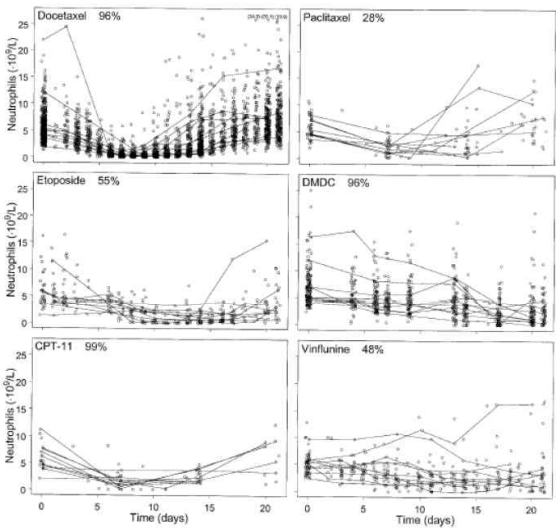
- Dose titration based upon toxicity



Neutrophils and platelets are recovered within 4 weeks

General PK-PD model for All Anticancer Drugs

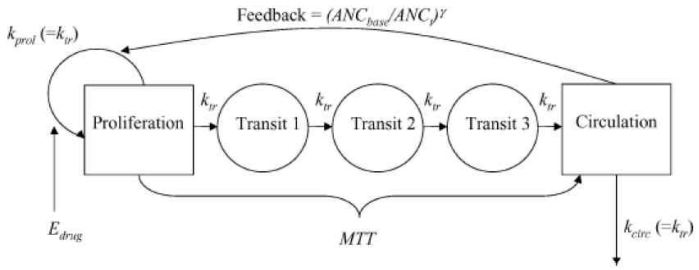
- DOSE – CONCENTRATION – TOXICITY
- But not that simple



J Clin Oncol 20:4713-4721. © 2002

Semi-physiological model

- To describe the time delay of toxicity
  - NONMEM (Ver. 7.1)



$$dProl/dt = k_{prol} \cdot Prol \cdot (1 - E_{Drug}) \cdot (Circ_0/Circ)^{\gamma} - k_{tr} \cdot Prol$$

$$dTransit1/dt = k_{tr} \cdot Prol - k_{tr} \cdot Transit1$$

$$dTransit2/dt = k_{tr} \cdot Transit1 - k_{tr} \cdot Transit2$$

$$dTransit3/dt = k_{tr} \cdot Transit2 - k_{tr} \cdot Transit3$$

$$dCirc/dt = k_{tr} \cdot Transit3 - k_{circ} \cdot Circ$$

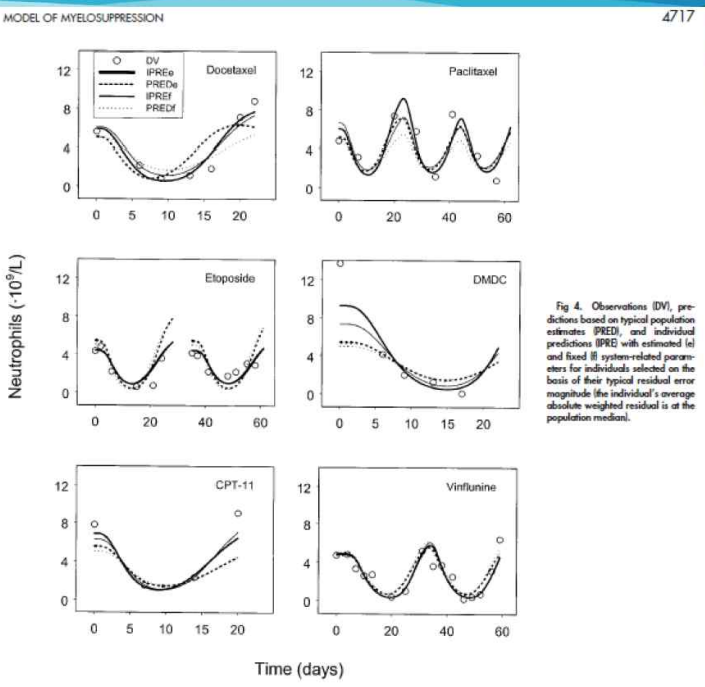


Fig 4. Observations (DV), predictions based on typical population estimates (PRED), and individual predictions (IPRE) with estimated (e) and fixed (f) system-related parameters for individuals selected on the basis of their typical residual error magnitude (the individual's average absolute weighted residual is at the population median).

J Clin Oncol 20:4713-4721. © 2002

The same model also works for platelets.

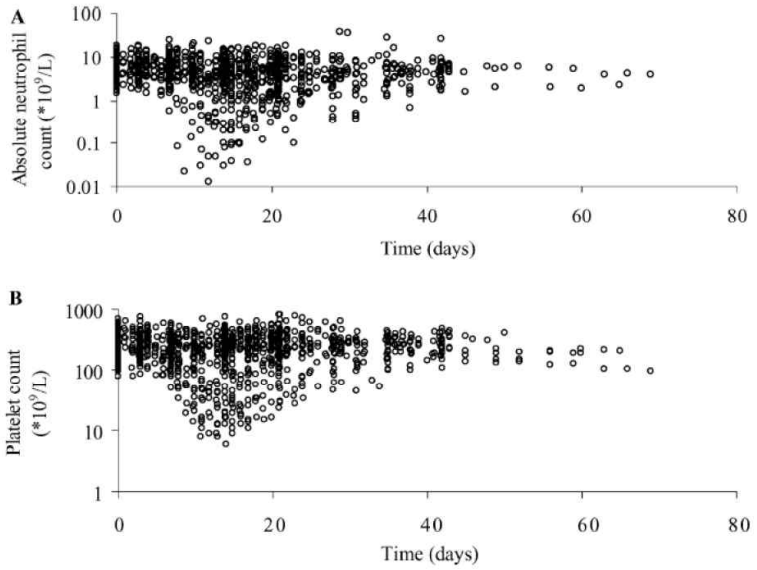


Figure 2. Observed cell count versus time for neutrophils (panel A) and platelets (panel B).

Investigational New Drugs **23:** 225–234, 2005.

If we develop a PK-PD model for decitabine

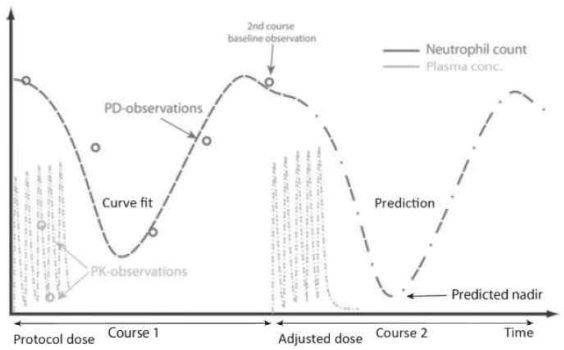


Fig. 2. Pharmacokinetic and/or pharmacodynamic information from first course used for prediction and dose adjustment of subsequent course.

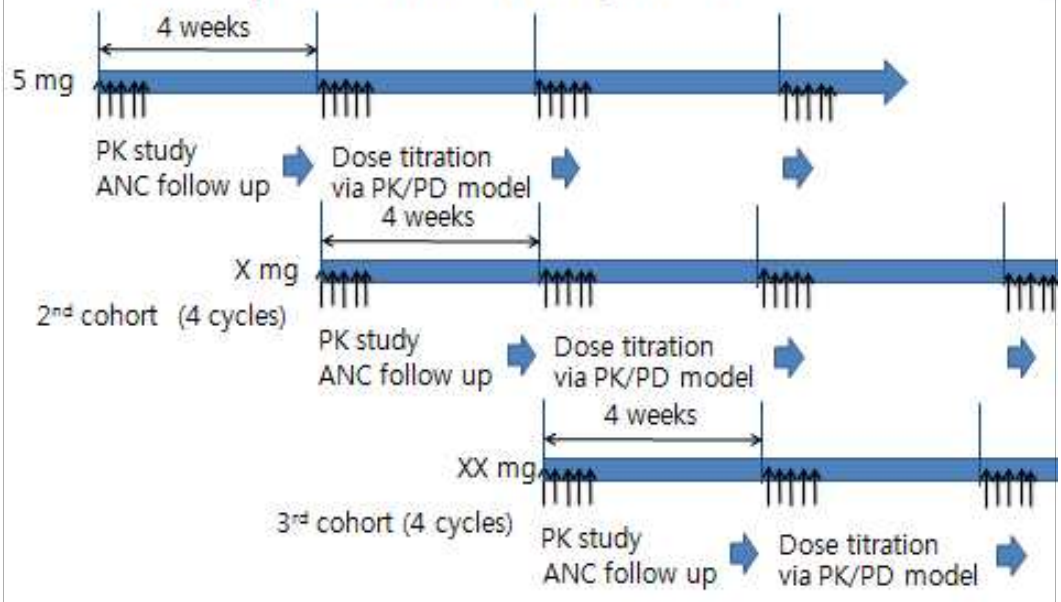
 Basic & Clinical Pharmacology & Toxicology, **106**, 234–242

Target level of toxicity

- Based upon NCI CTC (Grade 0~4)
- "Grade 3"
  - Neutropenia : 500 -1000/mm^3
  - Thrombocytopenia: 10,000 - 50,000/mm^3
  - E.g., 95% of simulated nadirs should be higher than the center of Grade 3 ranges.

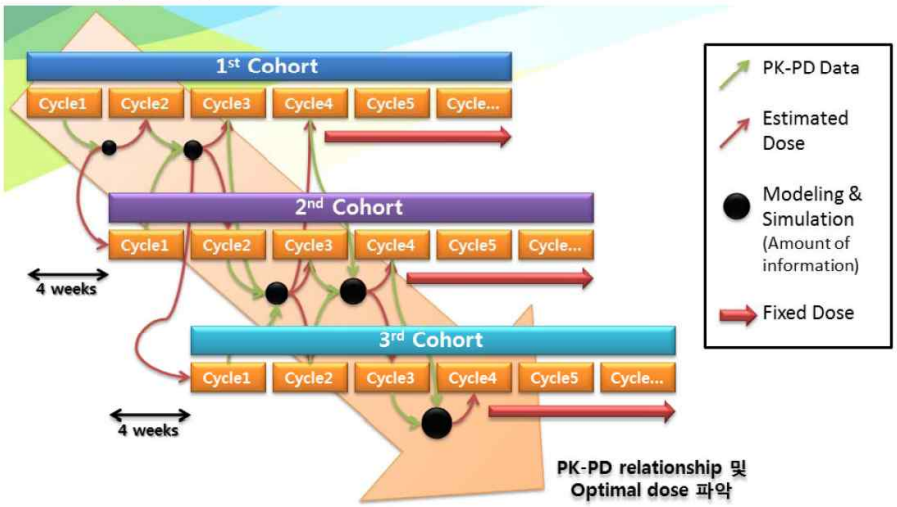
We may apply the model to design phase I

- Dose titration between cycles and cohorts instead of giving fixed dose pre-determined in the protocol



Subject Enrollment (M&S-based dose titration)

- 9 subjects, 3 cohorts



METHODS

Initial study plan

- Observation
  - PK
    : measure drug concentration at 20, 40, 60 (just before infusion end), 90, 120, 180 min
  - PD
    : measure platelet count (PLT) and absolute neutrophil count (ANC) weekly
- Dose optimization
  - Dose escalation
    : PK-PD 분석을 통한 호중구 혹은 혈소판 최대 감소의 90% CI가 NCI-CTC grade4 이상반응을 보이지 않을 것으로 판단되는 최대 용량을 다음 주기에 적용
    이전 주기 용량의 2배를 초과하지 않음
  - 감량 혹은 투여 지연
    - 혈액학적 이상반응(grade 4) 혹은 비혈액학적 이상반응(grade 3) 발생 시
    - 혈액학적 회복(3일 이상의 G-CSF 투약 없이 ANC≥ 1,000/μL, 3일 이상의 수혈 없이 혈소판≥ 30,000/μL)까지 투여 지연
    - 투여 지연의 원인이 된 이상반응이 발생하지 않은 최대용량으로 다음 주기 진행

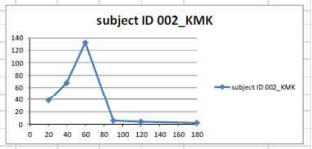
Initial study plan

- Fixed dose maintenance
  - 피험자 별 용량의 증량은 3회에 한하여 조정
  - 4주기의 용량을 최종 결정된 용량으로 정하여 고정용량으로 12주기까지 투약
  - 고정 용량으로 치료 중 상기의 감량 혹은 투여 지연의 사유가 발생한 경우, 당시까지의 약동-약력 분석 결과에 따라 2회에 한하여 상기 '감량 혹은 투여 지연의 원칙'에 따라 용량을 재조정할 수 있다. 유지 용량은 20mg/m^{2}을 초과할 수 없다.

Data Acquisition

- Pharmacokinetic data
  : blood sampling at 20, 40, 60 (just before infusion end), 90, 120, 180 min after infusion initiation

Time(min)	subject ID 002_KMK
0	NQ
20	38.95
40	67.73
60	132
90	5.415
120	3.431
180	2.376



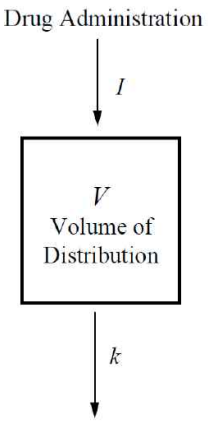
* NQ: not quantifiable, < 0.5 ng/ml
* NS : no sample

- Pharmacodynamic data
  : routine weekly monitoring of platelet count (PLT) and absolute neutrophil count (ANC)

Visit	Day	Lab	
V1, Screening		PLT	ANC
BMT			
V2, C1D1	2012.01.17	128.000	4,470
V3, C1D8	2012.01.26	99.000	3,530
V4, C1D15	2012.01.31	64.000	2,580
V5, C1D22	2012.02.07	81.000	750
V6,C1D29	2012.02.14	134.000	1,570
V7,C1D36			
Next Cyle DOSE	6mg/m2		
V2, C2D1	2012.02.21	132.000	2,980
V2, C2D8	2012.02.28	84.000	1,800
V2, C2D15	2012.03.05	65.000	2,009
V2, C2D22	2012.03.13	92.000	750
V2, C2D29	2012.03.19	124.000	630
Next Cyle DOSE	5.5mg/m2		
V2, C3D1	2012.03.27	112.000	1170
C3D8	2012.04.02	103.000	1,900
C3D15	2012.04.09	82.000	2,320
C3D22	2012.04.16	90.000	1,230

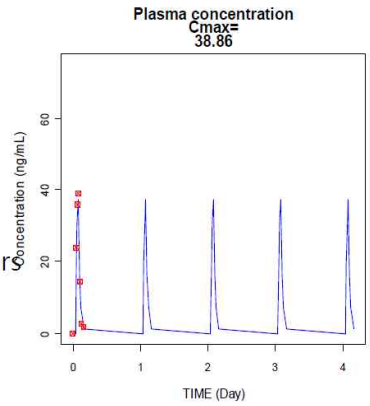
Individual Dose Titration – *Step1. PK model*

- PK model development based on the time-concentration profile



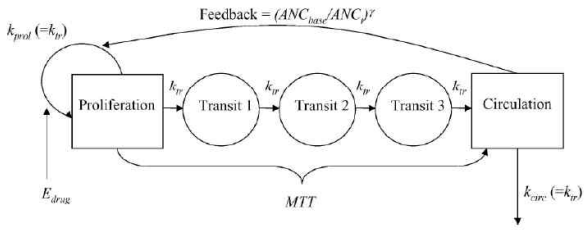
$$\text{Infusion: } C(t) = \text{Rate} \times \frac{C}{\lambda}\left(1 - e^{-\lambda t_1}\right) e^{-\lambda t_2}$$

Estimated PK parameters
CL: 133 L/hr, V: 81.6 L

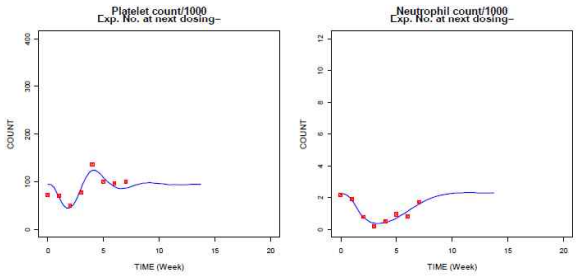


Individual Dose Titration – Step2. PD model

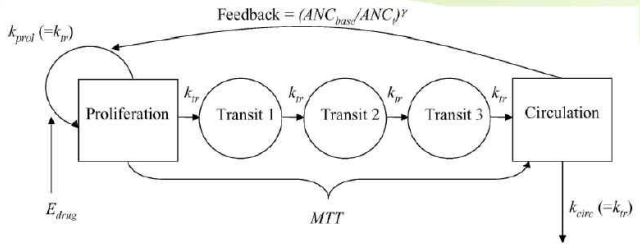
- Link drug concentration to the drug effect shown as decrease in cell count



	PLT	ANC
K_{tr}	0.026	0.0163
SLOPE	0.165	0.549
BASE*	94.9	2.25
GAMMA	0.252	0.109



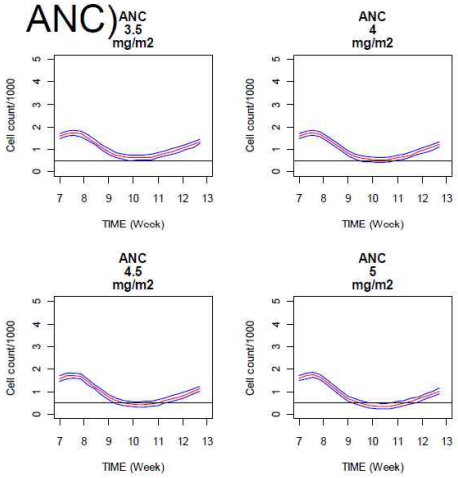
A part of NONMEM code




```
$DES
 CE = A(1)/V
 PE = A(2)
 NE = A(7)
 DADT(1) = - KE*A(1)
 DADT(2) = PKT * A(2) * ((1-PSL*CE) * (PBA/A(6))**PGAM - 1)
 DADT(3) = PKT * (A(2) - A(3))
 DADT(4) = PKT * (A(3) - A(4))
 DADT(5) = PKT * (A(4) - A(5))
 DADT(6) = PKT * (A(5) - A(6))
 DADT(7) = NKT * A(7) * ((1-NSL*CE) * (NBA/A(11))**NGAM - 1)
 DADT(8) = NKT * (A(7) - A(8))
 DADT(9) = NKT * (A(8) - A(9))
 DADT(10) = NKT * (A(9) - A(10))
 DADT(11) = NKT * (A(10) - A(11))
```

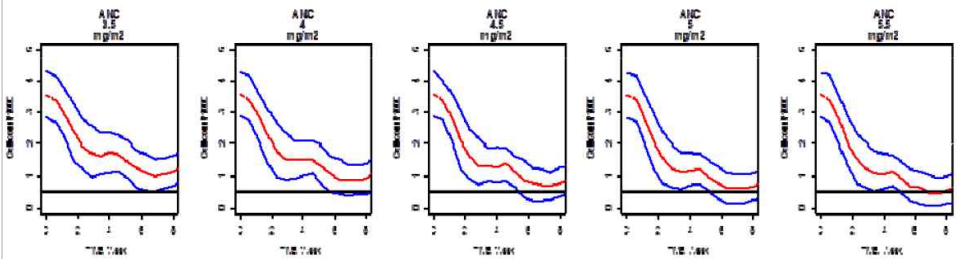
Individual Dose Titration – *Step3. Simulation*

- Simulate next cycle time-effect profile using 500 simulation datasets
  (Performed only for more sensitive cell type: usually ANC)



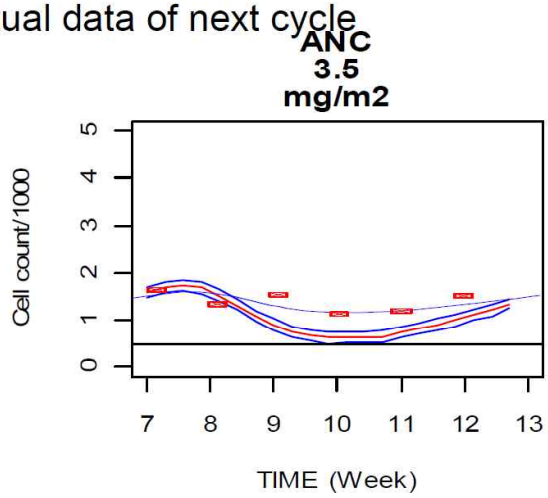
Recommended Dose
: 3.5 mg/m²/day (50% CI)

- Select a maximum dose expected not to exert grade IV toxicity
  (PC > 25,000/mm³, ANC > 500/mm³)
  using median & 50% confidence interval



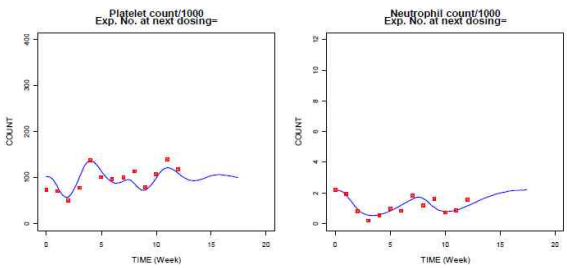
Individual Dose Titration – Step4. Validation

- Compare the simulation result from the prior cycle to the actual data of next cycle



Individual Dose Titration – Step5. Dose titration

- Estimate new parameter values from all of the previous data from that individual



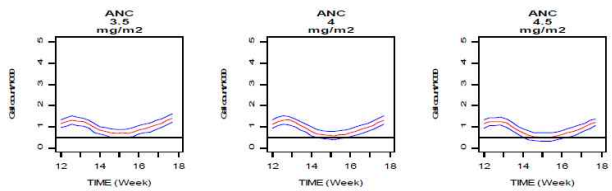
previous

	PLT	ANC
K_{tr}	0.026	0.0163
SLOPE	0.165	0.549
BASE*	94.9	2.25
GAMMA	0.252	0.109

current

	PLT	ANC
K_{tr}	0.0236	0.0152
SLOPE	0.140	0.389
BASE*	104	2.08
GAMMA	0.347	0.113

- Perform simulation with new estimates



RESULTS

Determined Dose levels

COHORT	INITIAL DOSE (mg/m^2/day)
1	5
2	4
3	5
4	5.5
5	5 (planned)

Mean time to nadir

Subject	Mean time to nadir (week)	k_{tr} (hr^{-1})	Expected Time to Nadir
2	3.2	0.0229	2.88
3	3.75	0.0127	5.20
7	4	0.0143	4.62
8	4	0.0147	4.49
9	4.3	0.00869	7.59
15	3.5	0.0130	5.08
13	3	0.0152	4.34
14	3	0.0152	4.34
17	4	0.0119	5.55
19	3	0.0323	2.04
20	4	-	-
21	3	0.0370	1.78
Mean	**3.595455**	**0.017499**	**4.503**

Safety profile

- Number of Dose-limiting toxicity occurred

Cycle	1 ~2 (No M&S)	2~ (M&S)
Total number of cycles	15	30
Mean number of cycles per patients	1.25	2.5
Total number of cycles with DLT	6	2
Proportion of DLT cycle	40 %	6.7 %

Clinical Outcomes

COHORT	CASE	DOSE (mg/m²/day)		CYCLE	Maintenance TREATMENT	SURVIVAL
		Initial	Fixed			
1	PEY	5	1.5	12	Finished	Alive (D645, CR)
	KMK	5	6	4	Withdrawn (refusal)	Dead (D421, BO)
	KJH	5	NR	1	Withdrawn (death)	Dead (D118, Pn)
	LJL	5	4	5	Withdrawn (refusal)	Alive (D506, AML)
2	KHB	4	7	11	Ongoing	Alive (D482, CR)
	JYS	4	12	12	Finished	Alive (D481, CR)
	KJG	4	5.5	10	Ongoing	Alive (D362, CR)
3	KJY	5	7	9	Ongoing	Alive (D366, CR)
	CHY	5	4.5	9	Ongoing	Alive (D366, CR)
	KYM	5	9	7	Ongoing	Alive (D294, CR)
4	LJB	5.5	NR	2	Withdrawn (refusal)	Alive (D268, CR)
	JSG	5.5	8	5	Ongoing	Alive (D240, CR)
	SYK	5.5	8	6	Ongoing	Alive (D239, CR)

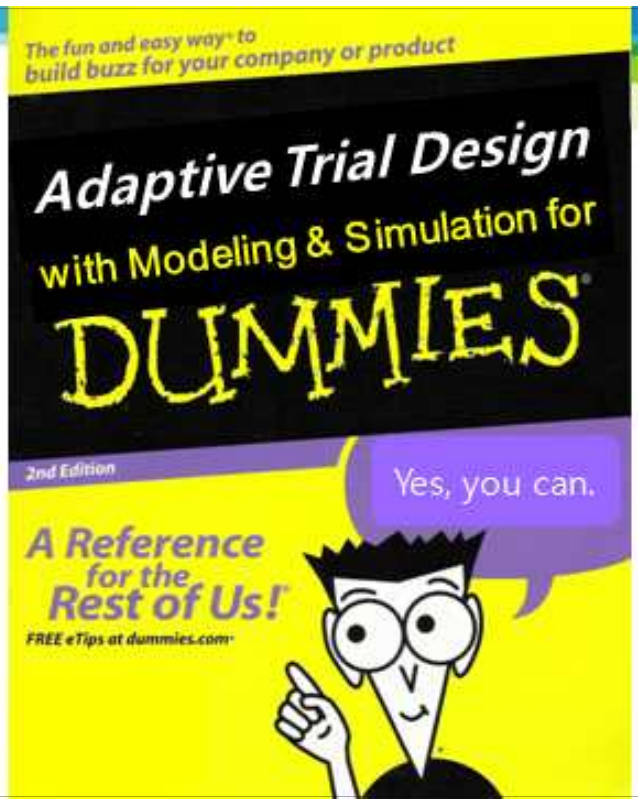
Compared with traditional Phase I trials

- Individualized dosage regimen for each patient was given
  - Without being exposed to subtherapeutic doses or unnecessarily high doses
- Longer study periods
  - Phase I participants can be directly benefited by the trial drug.

Remaining Questions

- Are decitabine doses causing grade 3 toxicity really better than lower doses ?
  - Fundamental questions on the mechanism of decitabine used for this indication.
    - If its effect is not by cytotoxicity, its optimal dose may be lower…
- But before we get convincing evidences for the optimal dosage, current "grade 3 toxicity-causing" dosage regimen seems the best one we may give.

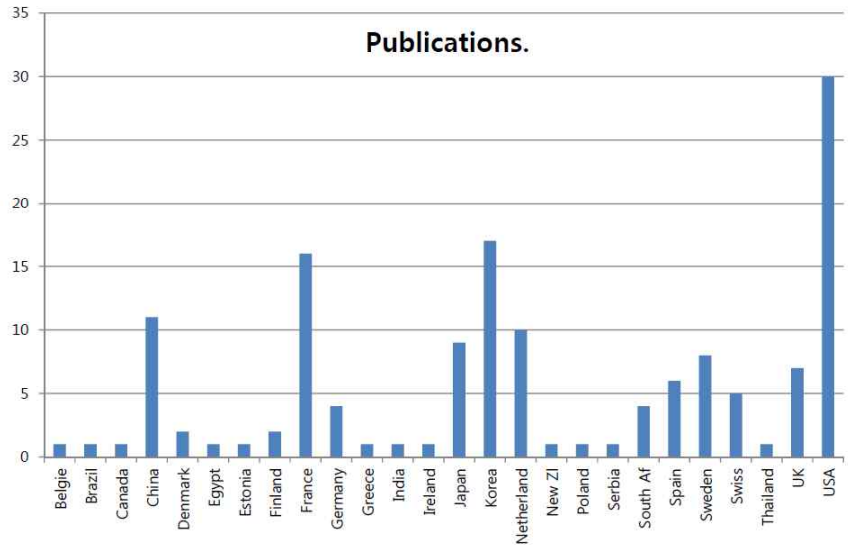
-



Pubmed search

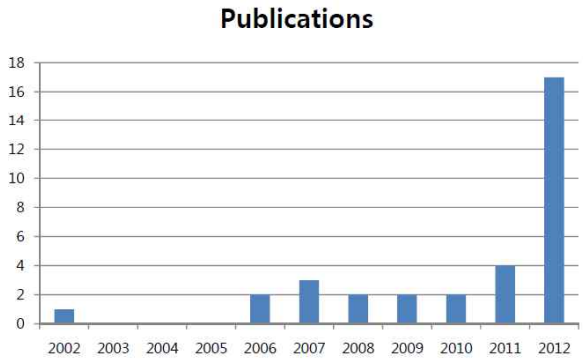
- Keyword: NONMEM, MONOLIX or NLME
  - Publication date: 2012/01/01-2012/11/25
- 147 articles
  - Only 12 were from industry (publication bias)
  - 8 used MONOLIX, 5 NLME, others NONMEM
- Topics
  - Methodology: 8
  - PK-PD: 20 / PD: 12 / Pop PK: others

41



42

ESPERANZA ES MI DESTINACION.



43

CURRICULUM VITAE

성 명 : **조 혜 영**
소 속 : 차의과대학 약학대학

▌Educations▐

Post-doctoral fellowship (School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo)
Ph.D. in Biopharmaceutical Science (Chonnam National University)
M.S. in Biopharmaceutical Science (Chonnam National University)
B.S. in College of Pharmacy (Chonnam National University)

▌Experiences▐

2012.02. – present Director of Clinical Research Division, CHA Group
2012.01. – present Associate Professor of BioPharmaceutics
College of Pharmacy, CHA University
2006.08. – 2011.12. Deputy Director of Clinical Trials Management Div.
Korea Food & Drug Administration
2006.03. – 2006.08. Research Professor,
Clinical Trial Center, Chonnam National University Hospital
2003.03. – 2004.02. Teaching Assistant
College of Pharmacy, Chonnam National University
1998.09. – 2002.02. Researcher, Research Institute of Drug development
Chonnam National University
1994.08. – 1997. 06. General Manager Embiel Co. Ltd
1987.02. – 1990.05. Pharmacist / IlYang Pharm. Co. Ltd /DAEWON Pharm. Co. Ltd
2012.05. – present Committee Member, Experts Committee on PBPK Working Group,
National Institute of Food and Drug Safety Evaluation (NIFDS)
2010.01. – present Committee Member, Clinical Trials Training Academy (CTTA), Korea
National Enterprise for Clinical Trials (KoNECT)
2009.01. – present Associate Editor/Science Secretary, The Korean Society of Food,
Drug and Cosmetic Regulatory Sciences
2006.01. – present Associate Editor/Editor, The Korean Society of Pharmaceutical Sciences and Technology
2009.01. – 2010.12. Promotional Staff, The Korean Society of Applied Pharmacology

Pharmacokinetic and Pharmacodynamic Modeling of a Copper-Selective

Hea-Young Cho, Ph.D.

College of Pharmacy, CHA University

The population pharmacokinetics (PK) and pharmacodynamics (PD) of triethylenetetramine (TETA) dihydrochloride (trientine) administered orally as 100 mg, 300 mg, 600 mg, or 1800 mg twice-daily doses were assessed in healthy adult male and female volunteers. This study was a randomized, double-blind, placebo-controlled, group-sequential, dose-escalating design. Forty participants, 10 per dose level (8 receiving TETA, 2 receiving placebo), received twice-daily doses for 14 consecutive days. A 2-compartment model for the PK and a linear direct effect model for drug-induced copper excretion (PD) were employed. The population PK/PD model was applied using the NONMEM software. Covariates tested were glomerular filtration rate (GFR), body weight, and gender. Multiple daily doses of TETA were safe and generally well tolerated. The linear 2-compartment model with first-order absorption well characterized the serum concentration data. Although its role was small, GFR had a statistically significant ($P < 0.05$) influence on systemic clearance (CL/F). The augmentation of copper excretion was well described by a direct linear model in which the slope was related to GFR and gender ($P < 0.001$). The intersubject coefficient of variation was 22.2% for slope (SL) and 82.5% for intercept (ER0). TETA has consistent single/multiple-dose pharmacokinetics and dose-proportional and serum concentration-proportional effects on enhancing copper excretion.

Key Words: *Triethylenetetramine, copper, pharmacokinetics, pharmacodynamics, human subjects*

Pharmacokinetic & Pharmacodynamic Modeling of a Copper-Selective Chelator (TETA)

Hea-Young Cho, Ph.D.

Lab. of Biopharmaceutics, College of Pharmacy
Division of General Research, Clinical Trial Center
CHA University

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Outline

- ❖ **Background**
  - **Copper homeostasis in human**
  - **Copper chelation and diabetes**
  - **Pharmacology of TETA**
- ❖ **Study Design and Data Collection**
- ❖ **PK and PD Modeling**
- ❖ **Population PK/PD Analysis**
- ❖ **Conclusions**

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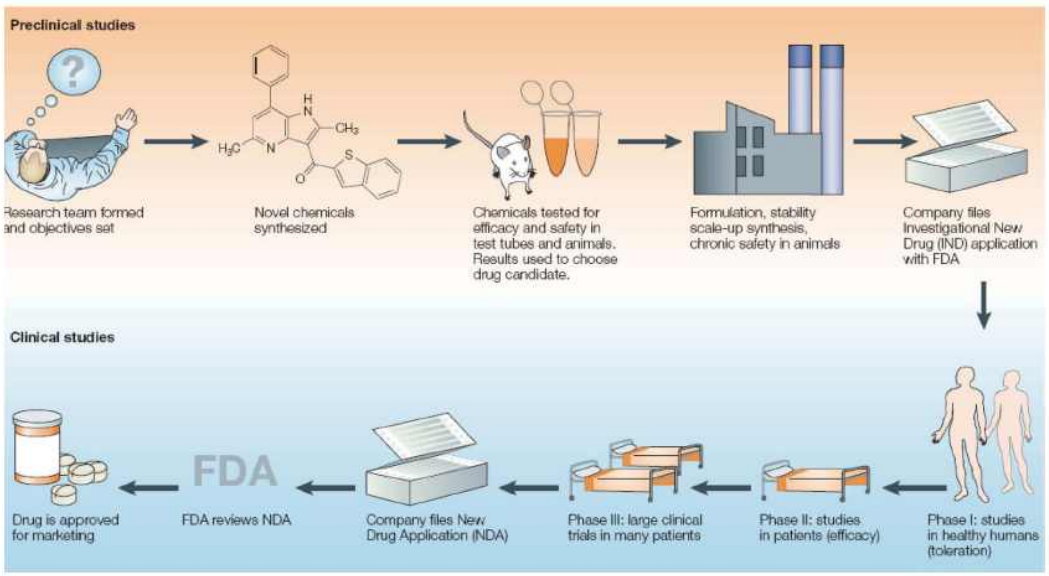
Stages in the drug discovery & development



Nature Reviews Drug Discovery 3, 853-862 (2004)

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Copper Homeostasis (Uptake and distribution)

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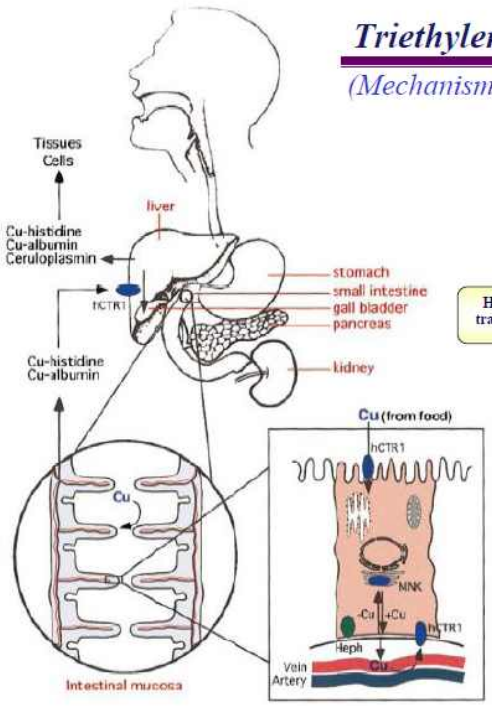
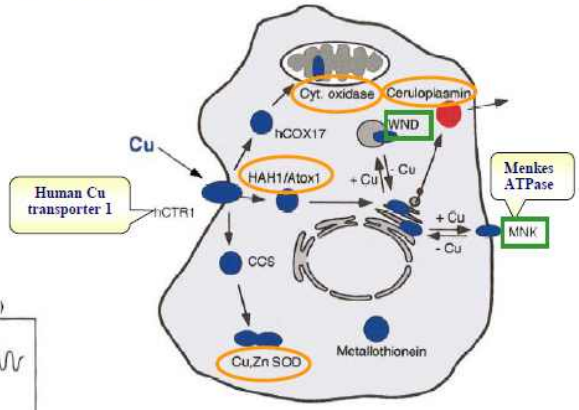
Triethylentetramin dihydrochloride (TETA)

(Mechanism of action)





Shap Int. J. Biochem. Cell Biol. 35:288-291, 2003

Pena et al J. Nutr. 129:1251-1260, 1999

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Copper-binding proteins

Common Name	Biological Function	Consequence of Deficiency or Defect
Cu/Zn SOD	Free radical detoxification	Oxidative damage of cell components
Cytochrome c oxidase	Electron transport in the mitochondria	Symptoms of deficiency of ATP: myopathy, ataxia, seizures
Lysyl oxidase	Crosslinking of collagen and elastin	Connective tissue symptoms: vascular rupture and torsion Loose skin and joints, emphysema
Dopamine β-hydroxylase	Catecholamine production	Hypothalamic imbalance : hypothermia, hypotension, dehydration, somnolence
Tyrosinase	Melanin production	Depigmentation
Peptidylglycine Monooxygenase	Bioactivation of Peptide hormones	Probable widespread effects through malfunction of several peptide hormones
Ceruloplasmin	Ferroxidase, Cu transport	Anemia
Clotting Factor, V, VIII	Blood clotting	Bleeding tendency
Angiogenin	Induction of blood vessel formation	Defective blood vessel development
Metallothionein	Cu-sequestration	Cu toxicity
Prion protein	Normal function currently unknown; Copper binding properties suggests potential role in Cu uptake	Altered sleep patterns and circadian rhythm in mice, Creutzfeld Jacob disease, Kuru, Gerstmann-Straussler-Scheinker disease, Fatal familial insomnia
β-amyloid precursor protein	Normal function currently unknown	Familial Alzheimer's Disease
Hephaestin	Iron egress from intestines	Sex-linked anemia

Ref. Maris et al J. Nutr. 129:1251-1260, 1999

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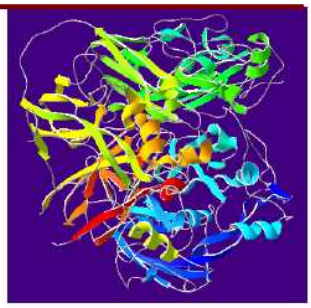
Ceruloplasmin (α-globulin protein)



- A copper containing protein which normally binds 80-90% of the copper present in plasma.
- Officially known as ferroxidase I
- Reference Interval
  - Male: 16.2-35.6 mg/dL
  - Female: 17.9-53.3 mg/dL
- Lower-than-normal ceruloplasmin levels may indicate:
  - Menkes' syndrome (Kinky Hair Sndrome); very rare
  - Wilson's disease
  - Malnutrition
  - Nephrotic syndrome
- Greater-than-normal ceruloplasmin levels may indicate:
  - Pregnancy
  - Lymphoma
  - Acute and chronic infections
  - Rheumatoid arthritis

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Functions of copper

- Copper has an essential role in several key physiological and biochemical functions.
  - compound of metalloenzymes (endogen antioxidative system)
  - compound of ceruloplasmin (transport of copper)
- It is required for:
  - normal infant development
  - red and white blood cell maturation
  - iron transport
  - bone strength
  - cholesterol metabolism
  - myocardial contractility
  - glucose metabolism
  - brain development
  - immune function
  - protection against oxidative stress

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Copper Chelation and Diabetes

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References for copper chelation & diabetes (cont'd)

Diabetes 53: 2501-2508 (2004)

Ref.1

Regeneration of the Heart in Diabetes by Selective Copper Chelation

Garth J.S. Cooper,[1,2] Anthony R.J. Phillips,[1] Soon Y. Choong,[1] Bridget L. Leonard,[1] David J. Crossman,[1] Dianne H. Brunton,[1] 'Etuate L. Saafi,[1] Ajith M. Dissanayake,[3] Brett R. Cowan,[2,4] Alistair A. Young,[4] Christopher J. Oecleshaw,[5] Yih-Kai Chan,[1] Fiona E. Leahy,[1] Geraldine F. Keogh,[1] Gregory D. Gamble,[2] Grant R. Allen,[6] Adèle J. Pope,[7] Peter D.W. Boyd,[6] Sally D. Poppitt,[2] Thomas K. Borg,[8] Robert N. Doughty,[2] and John R. Baker[3]

Diabetes 54: 1468-1476 (2005)

Ref.2

Demonstration of a Hyperglycemia-Driven Pathogenic Abnormality of Copper Homeostasis in Diabetes and Its Reversibility by Selective Chelation

Quantitative Comparisons Between the Biology of Copper and Eight Other Nutritionally Essential Elements in Normal and Diabetic Individuals

Garth J.S. Cooper,[1,2,3,4] Yih-Kai Chan,[1,4] Ajith M. Dissanayake,[3] Fiona E. Leahy,[1,4,6] Geraldine F. Keogh,[1,4] Chris M. Frampton,[7] Gregory D. Gamble,[3] Dianne H. Brunton,[1] John R. Baker,[5] and Sally D. Poppitt[3,4]

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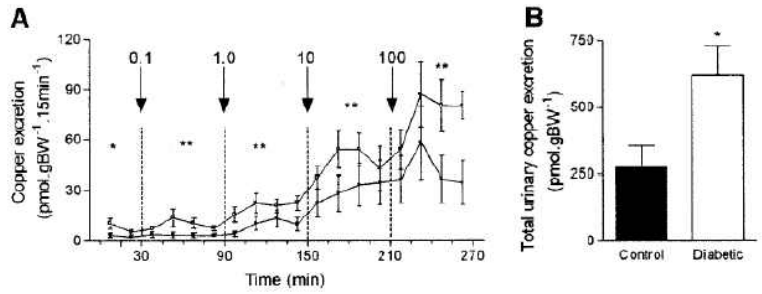
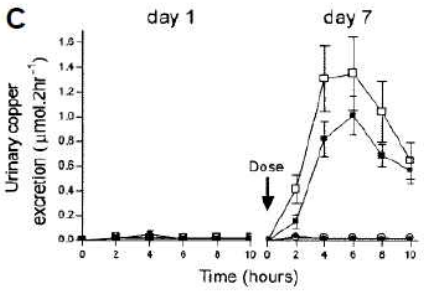
Selective copper chelation & diabetes

Ref.1



A: Urinary Cu after IV trientine in control (n=7) and diabetes (n=7) rats.
B: Total urinary Cu (■ ; control, □ ; diabetes).



C: Effects of oral trientine were compared with placebo between men with type 2 diabetes and age-matched control subjects.

- Basal Cu output was significantly greater in type 2 diabetes than control (P<0.001).
- Trientine elicited more Cu from type 2 diabetes than from control (P<0.05).

Cooper et al Diabetes 53:2501-2508, 2004

TETA

(Triethylentetramin dihydrochloride)

Phase I Study

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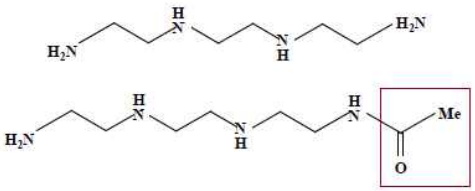
Triethylentetramin dihydrochloride (TETA)

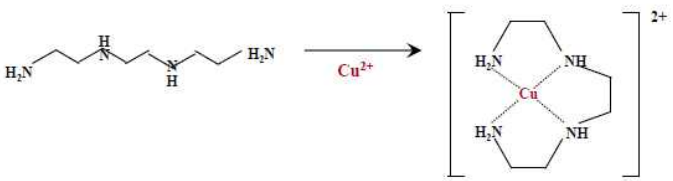
❖ **Physicochemical properties**

- **Chemical structure and metabolism pathway**



- Rapid acetylator (F/F)–Intermediate (S/F)-Slow acetylator (S/S)

❖ **A potent copper-chelator**



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Phase I (Study design)

Drug	**TETA**	
Dose	**200**	**ays**
No. Subjects (Genotyping)		
	Day	
Sampling	**Plasma**	**0, 5 90, and 3, 4 16, 2 60, 12, and 48 hr**
	Urine	**0-2, 2-4, 4-6, 6-8, 8-10, 10-12, and 12-24 hr**
Measurements		**Plasma – TETA, N-acetyl TETA, urine – copper, Serum – copper & ceruloplasmin (for safety)**

Genotype	Acetylator phenotype
*NAT2*5A/NAT2*5B*	Slow (S/S)
*NAT2*5A/NAT2*6A*	Slow (S/S)
*NAT2*5B/NAT2*5B*	Slow (S/S)
*NAT2*5A/NAT2*6A*	Slow (S/S)
*NAT2*6A/NAT2*6A*	Slow (S/S)
*NAT2*4/NAT2*5B*	Intermediate (S/F)
*NAT2*4/NAT2*6A*	Intermediate (S/F)
*NAT2*4/NAT2*4*	Rapid (F/F)

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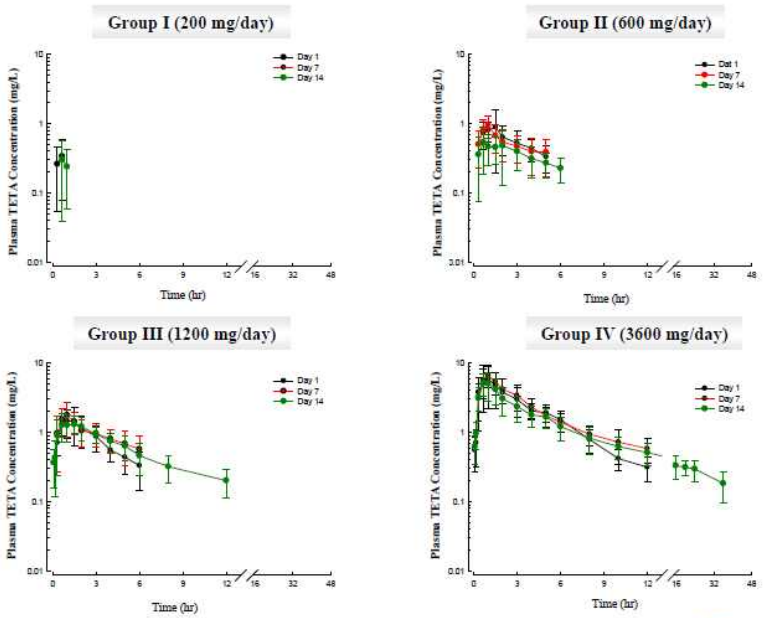
Mean concentration time profiles by dose



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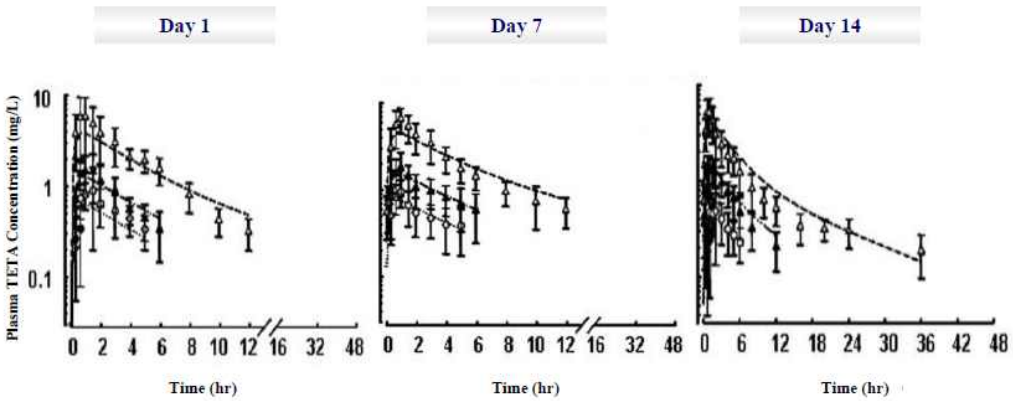
Pharmacokinetic profiles: Dose-proportionality



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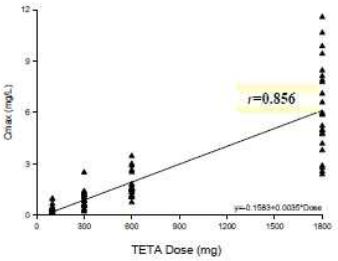
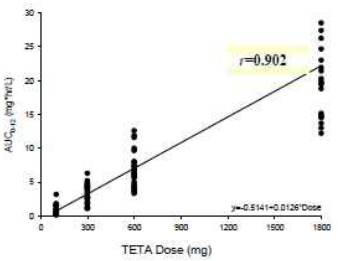
PK parameters in relation to dose: NCA

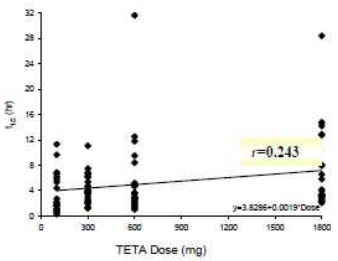
C_{max} vs. Dose (n=32)



$AUC_{0\text{-}12}$ vs. Dose (n=32)



$t_{1/2}$ vs. Dose (n=32)



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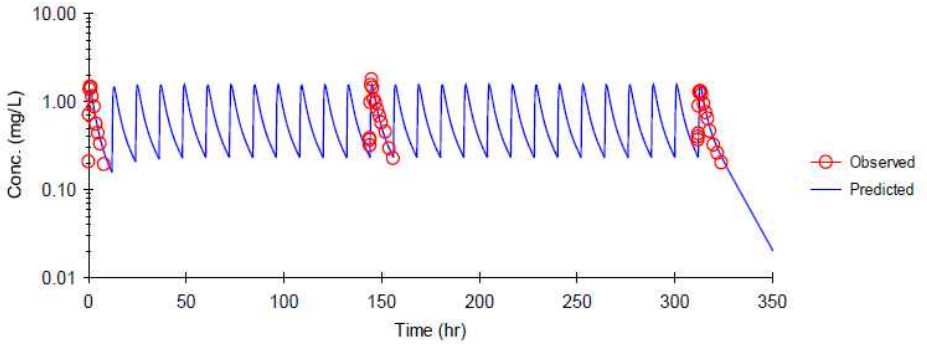
Pharmacokinetics (600 mg/12 hr): *WinNonlin Fitting*



k_a = 2.77 (hr)	$t_{1/2}$ = 7.52 (hr)
V_C/F = 330.0 (L)	Cl/F = 77.39 (L/hr)
V_Z/F = 249.4 (L)	Cl_D/F = 45.03 (L/hr)
Accumulation Index (AUC Ratio) = 1.30	

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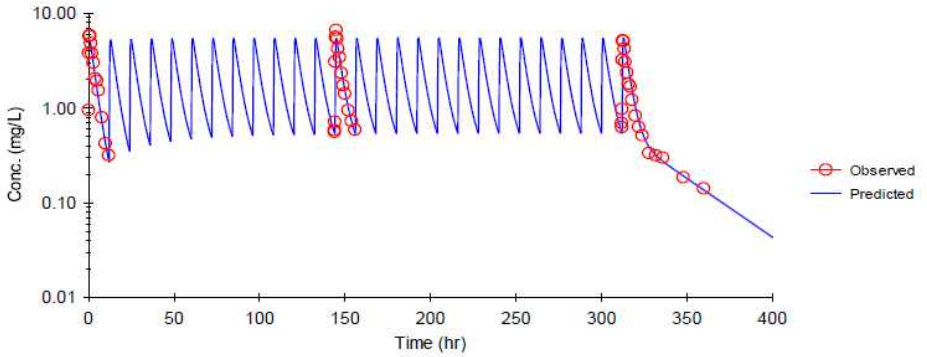
Pharmacokinetics (1800 mg/12 hr): *WinNonlin Fitting*



k_a = 4.30 (hr)	$t_{1/2}$ = 24.3 (hr)
V_C/F = 293.4 (L)	Cl/F = 73.42 (L/hr)
V_Z/F = 452.8 (L)	Cl_D/F = 16.12 (L/hr)
Accumulation Index (AUC Ratio) = 0.90	

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Summary: *Pharmacokinetics*

- TETA was rapidly absorbed and pharmacokinetics were essentially linear based on doses evaluated.
- No accumulation, consistent stationary profiles over time were observed with multiple-dosing for 600, 1200, and 3600 mg/day dosing for 14 days.
- While a biexponential model may be appropriate to characterize the drug's elimination profile, the late phase appears to be unimportant.
- Consistent pharmacokinetic behavior was observed for all subjects and doses.

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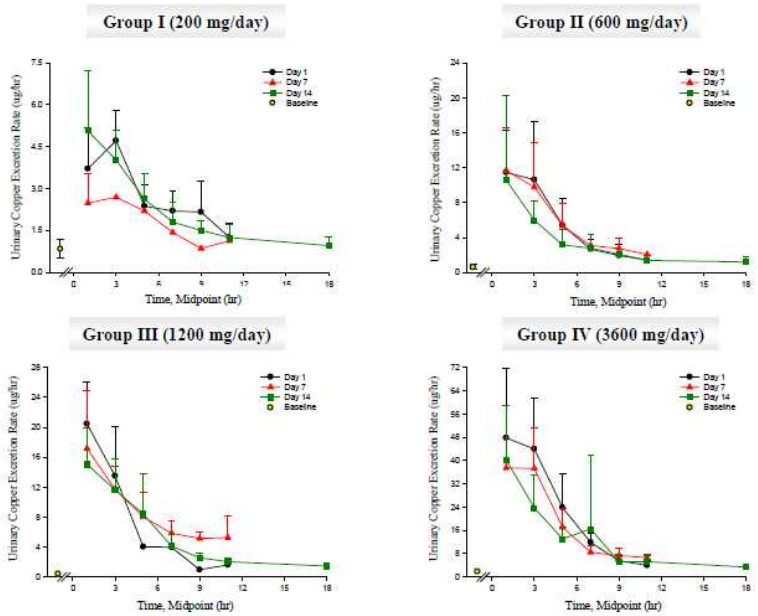
Mean urinary copper ER- time profiles by dose



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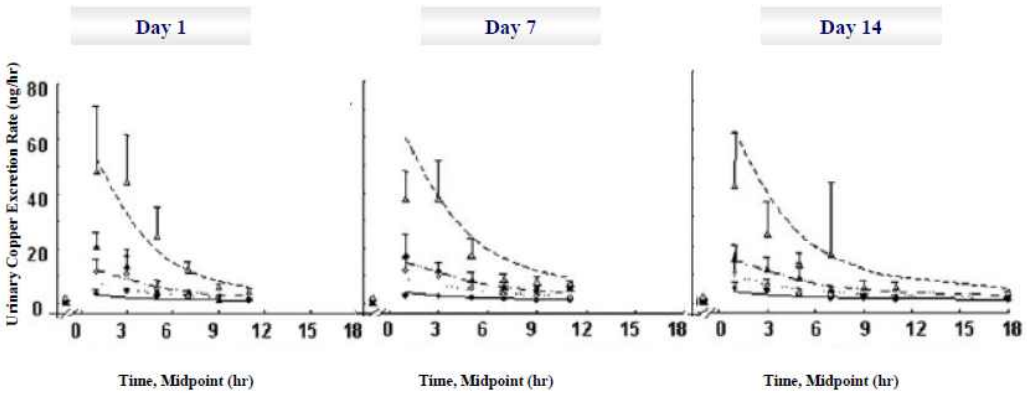
Pharmacodynamic profiles: Dose-proportionality



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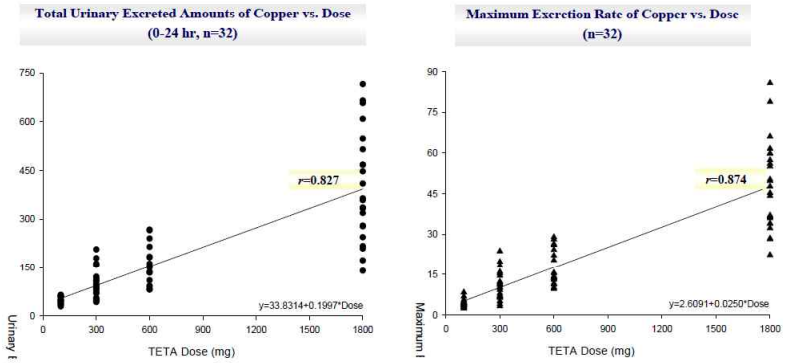
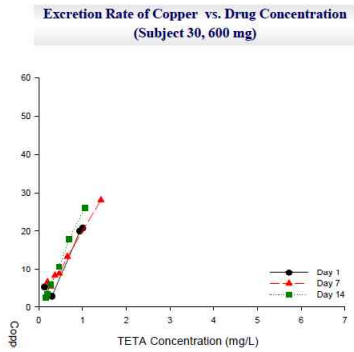
Copper excretion in relation to dose

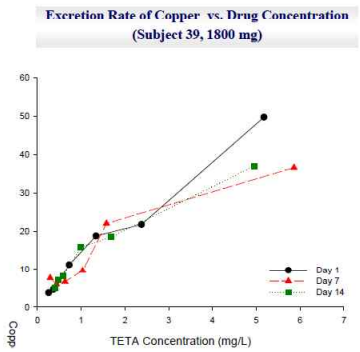


Summary: *Pharmacodynamics*

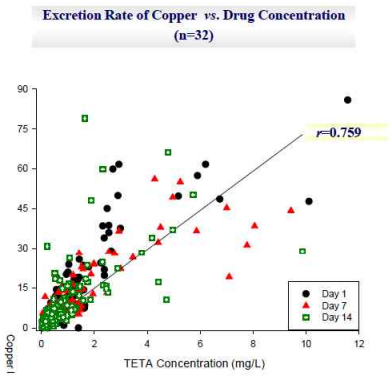
- Urinary copper excretion was nearly dose proportional over the dose range of 200 to 3600 mg/day.
- The rate and extent of copper excretion following TETA dosing showed similar patterns following single-dose (Day 1) and steady-state (Day 7 and 14) dosing.
- Copper was excreted at the highest rate in the 0-2 h interval following TETA dosing, and the excretion rate decreased in each subsequent 2-h interval .
- The mean 0-4 h cumulative urine copper excretion (94.43 ng) accounted for approximately 72% of the mean total cumulative urine copper excretion (131.69 ng) prior to the second daily dose (0-12 h interval)

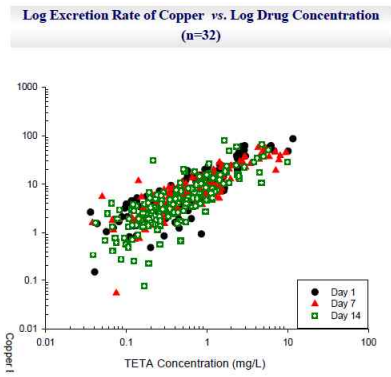
PK-PD link profiles:
TETA Conc.-Urinary copper excretion rate



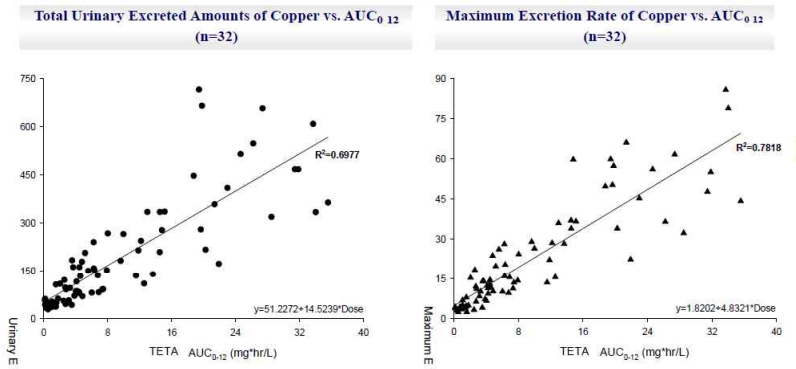


PK-PD link profiles:
TETA Conc.-Urinary copper excretion rate





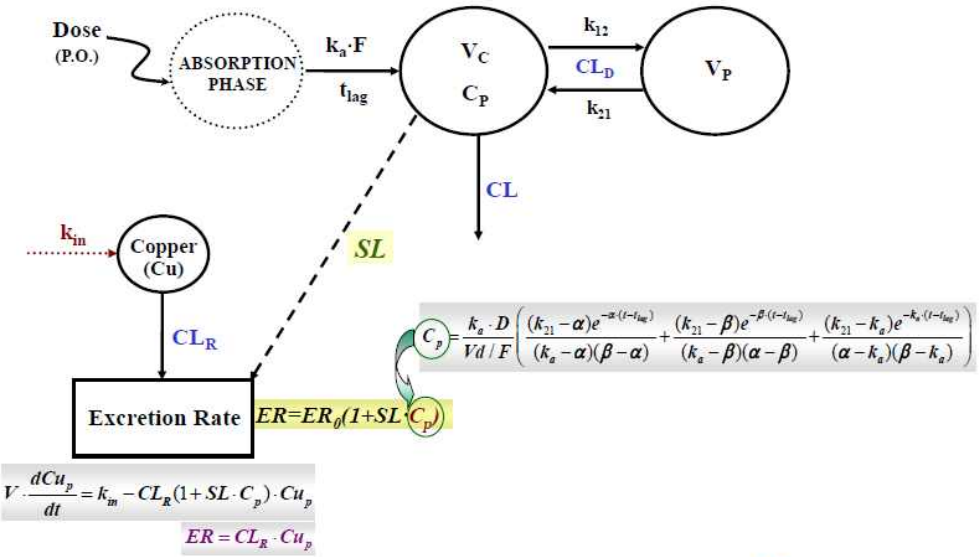
Copper excretion in relation to AUC



Summary: *PK/PD*

- A preliminary examination of plasma TETA concentrations *versus* urine copper excretion rate (adjusted for baseline) by day and dose demonstrates a direct linear relationship and consistency across days and doses.
- Urine cupruresis appeared to increase in a dose and drug exposure (plasma concentration &AUC) dependent manner.

Proposed PK and PD model for fitting



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Population PK/PDAnalysis

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Data

PK: 1234 plasma concentration of TETA
PD: 663 urinary copper excretion rate

Characteristic	TETA doses			
	200 mg/day (n=8)	600 mg/day (n=8)	1200 mg/day (n=8)	3600 mg/day (n=8)
Age (years)	34.8 ± 15.0 (18 ~ 57)	26.8 ± 6.5 (22 ~ 42)	38.1 ± 10.7 (23 ~ 53)	28.6 ± 11.1 (18 ~ 44)
Gender, M/F†	6/2	4/4	3/5	6/2
Height (cm)	174.9 ± 8.4 (162.6 ~ 190.5)	168.6 ± 11.3 (154.9 ~ 185.4)	168.9 ± 10.1 (157.5 ~ 190.5)	171.8 ± 8.7 (162.6 ~ 185.4)
Body weight (kg)	78.3 ± 14.9 (63.5 ~ 104.8)	74.1 ± 14.5 (56.2 ~ 109.3)	87.3 ± 10.6 (68.0 ~ 101.6)	87.3 ± 16.5 (71.2 ~ 122.9)
GFR (ml/min)	113.4 ± 19.1 (90.9 ~ 148.1)	144.3 ± 37.5 (110.4 ~ 220.1)	139.6 ± 26.8 (97.3 ~ 185.3)	144.7 ± 26.1 (106.7 ~ 175.1)
Baseline serum copper (μg/L)	914.4 ± 158.0 (762 ~ 1250)	1026.4 ± 253.9 (740 ~ 1461)	1375.8 ± 309.1 (770 ~ 1748)	958.4 ± 156.7 (772 ~ 1183)
Baseline serum ceruloplasmin (mg/dL)	21.5 ± 3.1 (18 ~ 27)	20.1 ± 3.7 (14 ~ 25)	31.8 ± 4.9 (23 ~ 37)	25.6 ± 4.0 (20 ~ 31)

†M, male; F, female; GFR, Glomerular Filtration Rate.

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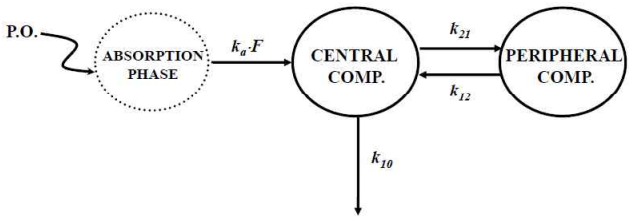
Model development (cont'd)

- Population PK analysis was performed using the computer software package NONMEM (Version V, Level 1.1).
- S-plus 6.0 and SigmaPlot 8.0 for Windows were used to visually evaluate fits and to produce graphs.
- The minimum value of the NONMEM objective function (MOF) was used to discriminate between various models during the model-building process.
- A difference in MOF of 3.84 for 1 degree of freedom (P<0.05) was considered statistically significant during the full model building.

Model development (cont'd)

Population PK model

- The pharmacokinetic model employed for this analysis was a two-compartment model with first-order absorption, and first-order elimination from central compartment.
- This model was employed using ADVAN4 and TRANS4 PREDPP subroutines within NONMEM.



Model development (cont'd)

Variability model

- Interindividual variability: Exponential models

$$P_i = \hat{P} \cdot \exp(\eta_i) \qquad \eta \sim N(0, \omega_\eta^2)$$

- The residual variability: a constant coefficient of variation equation.

$$Y_{ij} = F(P_i, x_{ij}) \cdot (1 + \varepsilon_{ij}) \qquad \varepsilon_i \sim N(0, \sigma_{\varepsilon_i}^2)$$

- The first-order conditional estimation (FOCE) with interaction method was tested for the estimation for the population pharmacokinetic parameters, interindividual variability in these parameters, and residual variability between observed and predicted plasma concentrations.

Model development (cont'd)

Covariates model:

- ❖ **Assessment of additional covariate effects was then performed starting from the 'basic model'.**
- ❖ **Gender, body weight, and glomerular filtration rate (GFR) were examined for their influence on the PK and PD.**
- ❖ **Covariate selection was based on the drop in objective function value (ΔMOF). Only covariates producing a decrease in MOF>3.84 (P<0.05) on inclusion were incorporated in the model.**

Model development

Covariates selection: Parameter-Covariates Correlation

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Model building step for the PK model

No	Model Name	Model	OBJ	c.f.	Significance
1	PROMW1COM (Start Model)	TVCL = THETA(1) TVV = THETA(2) TVKA = THETA(3)	-1042.777		
2	PROMW (Base Model)	TVCL = THETA(1) TVV2 = THETA(2) TVQ = THETA(3) TVV3 = THETA(4) TVKA = THETA(5)	-1588.515	Start M.	$P<0.001$
3	PROMWL	TVCL = THETA(1) TVV2 = THETA(2) TVQ = THETA(3) TVV3 = THETA(4) TVKA = THETA(5) ALAG1 = THETA(6)	-1691.547	Base M. (PROMW)	$P<0.001$
4	PROMWLG-C1 (Final Model)	TVCL = THETA(1) × (GFR/133)**THETA(7) TVV2 = THETA(2) TVQ = THETA(3) TVV3 = THETA(4) TVKA = THETA(5) ALAG1 = THETA(6)	-1696.939	PROMWL	$P<0.05$
5	PROMWLGW-C1	TVCL = THETA(1) × (GFR/133)**THETA(7) TVV2 = THETA(2) TVQ = THETA(3) × (WGT/81)**THETA(8) TVV3 = THETA(4) TVKA = THETA(5) ALAG1 = THETA(6)	-1700.365	PROMWLG-C1	N.S.

Model building step for the sequential PK/PD model

No	Model Name	PK & Error Model	OBJ	c.f.	Signifi-cance
1	PROPKPD1 (Start Model)	TVBASE = THETA(1) TVSL = THETA(2) ER = BASE+SL×F Y2 = ER+EPS(2)	921.384		
2	CHOPKPD (Base Model)	TVBASE = THETA(1) TVSL = THETA(2) ER = BASE+SL×F Y2 = ER × EXP(EPS(2))	-56.307	Start M.	$P<0.001$
3	CHOPKPDG-1	TVBASE = THETA(1) TVSL = THETA(2) × (GFR/133)**THETA(3) ER = BASE+SL×F Y2 = ER × EXP(EPS(2))	-63.568	CHOPKPD	$P<0.01$
4	CHOPKPDGS-1 (Final model)	TVBASE = THETA(1) TVSL = THETA(2) × (GFR/133)**THETA(3)+SEX*THETA(4) ER = BASE+SL×F Y2 = ER × EXP(EPS(2))	-94.951	CHOPKPDG-1	$P<0.001$
5	CHOPKPDGSW-1	TVBASE = THETA(1) × (WGT/81)**THETA(5) TVSL = THETA(2) × (GFR/133)**THETA(3)+SEX*THETA(4) ER = BASE+SL×F Y2 = ER × EXP(EPS(2))	-95.010	CHOPKPDGS-1	N.S.

Final Model

$$CL/F = (\theta_1 \cdot (GFR/133)^{\theta_7}) \cdot \exp(\eta_{CL/F})$$
$$V_2/F = \theta_2 \cdot \exp(\eta_{V_2/F})$$
$$Q/F = \theta_3 \cdot \exp(\eta_{Q/F})$$
$$V_3/F = \theta_4 \cdot \exp(\eta_{V_3/F})$$
$$k_a = \theta_5 \cdot \exp(\eta_{k_a})$$
$$Alag1 = \theta_6$$
$$ER_0 = \theta_8 \cdot \exp(\eta_{ER_0})$$
$$SL = \left[\theta_9 \cdot (GFR/133)^{\theta_{10}} + Gender \cdot \theta_{11}\right] \cdot \exp(\eta_{SL})$$

For this model,

k_{12}, k_{21} and k_{10} were reparameterised to more physiologically relevant parameters as follows:

$$k_{12} = Q/V_C \qquad k_{21} = Q/V_P \qquad k_{10} = CL/V_C$$

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Estimated PK/PD parameters

Parameter (units)	Definition	Population mean value (SE%)	Interindividual variability, CV% (SE%)
CL/F (L/hr)[a]	Clearance/F	69.5 (4.42)	13.4 (23.8)
V_c/F (L)	Central Volume	393 (11.5)	48.2 (23.2)
CL_D (L/hr)	Distribution Clearance	21.3 (45.1)	65.5 (62.0)
V_p/F (L)	Peripheral Volume	252 (19.6)	79.5 (119)
k_a (hr^{-1})	Absorption Rate Constant	3.99 (22.8)	97.0 (70.4)
t_{lag} (hr)	Lag-time	0.0759 (1.06)	-
V_{ss} (L)	Steady-state Volume	645	
Baseline (ER_0, µg/hr)	Copper Excretion	0.721 (20.3)	82.5 (69.6)
SL[b]	Slope Factor	12.6 (8.73)	12.2 (28.5)
Intraindividual residual variability, % (SE%)			
PK sigma		42.9 (5.98)	
PD sigma		49.7 (10.6)	

[a] $CL/F = 69.5 \cdot (GFR/133)^{0.516}$

[b] $Slope = 12.6 \cdot (GFR/133)^{0.266} - Gender \cdot 3.62$

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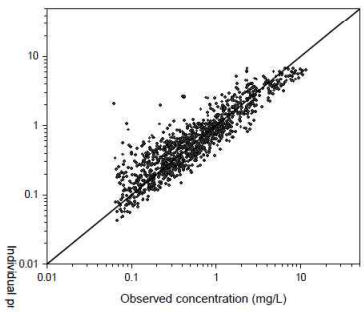
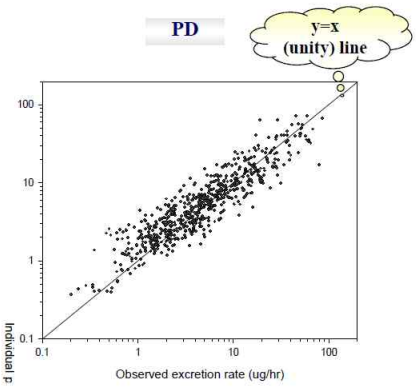
Goodness-of-fit (cont'd)

PK



Observed TETA concentrations (DV)
versus
individual predicted concentrations (IPRED)

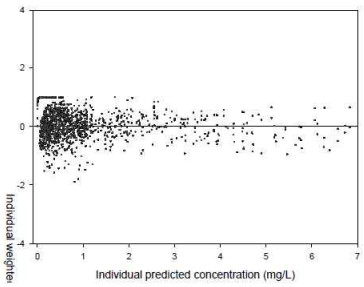
PD



Observed copper excretion rate (DV)
versus
individual predicted excretion rate (IPRED)

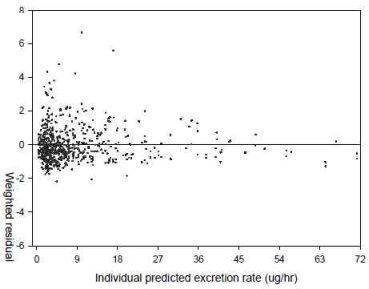
Goodness-of-fit

PK



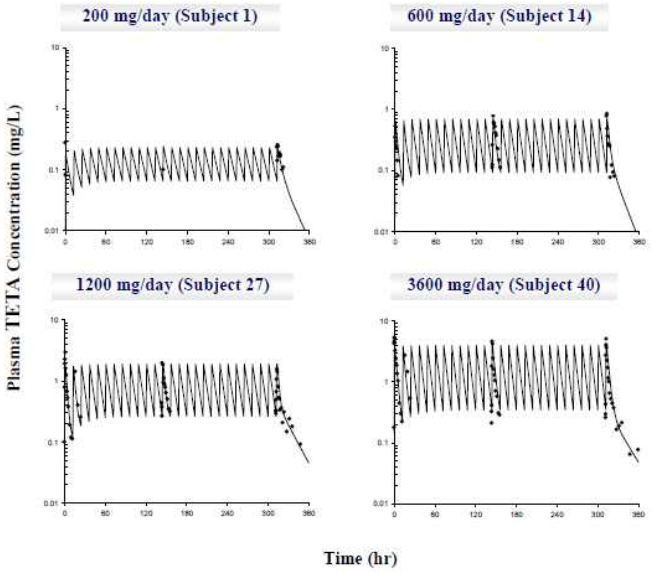
Individual weighted residuals (IWRES)
versus
individual predicted concentrations (IPRED)

PD



Weighted residuals (WRES)
versus
individual predicted excretion rate (IPRED)

Individual fitting PK profiles



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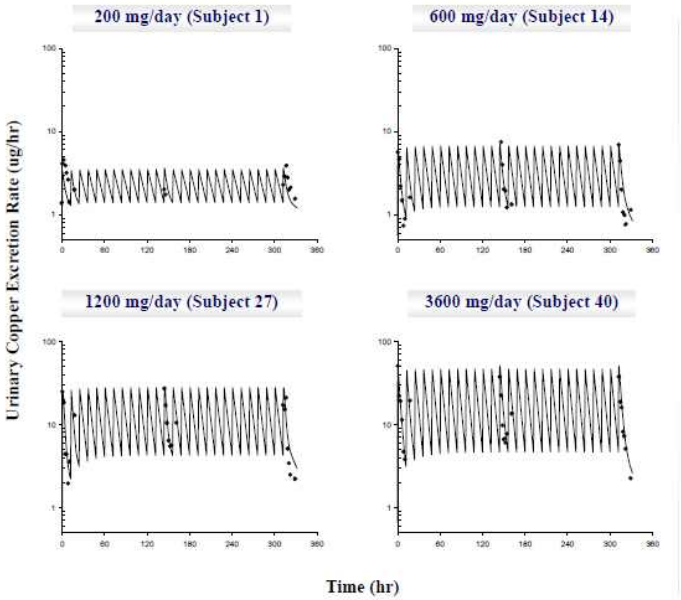
Individual fitting PD profiles



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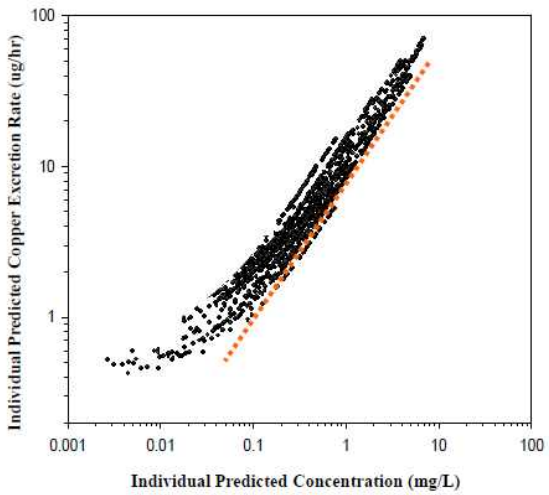
Conclusions: *Population PK/PD analysis*

- The weighted residuals versus predicted data as well as individual weighted residuals versus individual predicted data were generally distributed around zero and were relatively symmetric.
- The individual predicted time profiles of TETA from the final model were shown good agreement between observed and predicted concentrations.
- The PK and PD of TETA can be considered to be linear with dose and variability is modest among this group of subjects.

Relationship between conc. of TETA and urinary copper excretion rates predicted the final population PK/PD model



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Thank you for your attention

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CURRICULUM VITAE

성 명 : Kyun-Seop Bae M.D. Ph.D.

소 속 : 울산대학교 의과대학

Department of Clinical Pharmacology and Therapeutics, Asan Medical Center,
University of Ulsan
- 88, Olympic-ro 43-gil, Sonpa-gu, Seoul 138-736, Republic of Korea

▌Current Positions▐

Chair, Department of Clinical Pharmacology and Therapeutics, Asan Medical Center
Executive Secretary, Institutional Review Board, Asan Medical Center
Director, Division of Data Management, Clinical Trial Center, Asan Medical Center
Expert Advisor, Central Pharmaceutical Affair Committee, Korea Food and Drug Administration
Director of Education & Training, Korean Society for Clinical Pharmacology and Therapeutics

▌Education▐

University	Major	Degree	Year
Seoul National University, Korea	Medicine	M.D.	1994
Seoul National University, Korea	Clinical Pharmacology	M.S.	2000
Seoul National University, Korea	Clinical Pharmacology	Ph.D.	2002

▌Career▐

2010.10 – present	Associate Professor, Asan Medical Center/University of Ulsan, Korea
2009.1 – 2009.7	Visiting Scholar, University of Southern California, USA
2008.1 – 2009.1	International Fellow, Pfizer Global Research and Development – La Jolla, USA
2004.9 – 2010.9	Assistant Professor, Asan Medical Center/University of Ulsan, Korea
2002.6 – 2004.9	Clinical Lecturer, Asan Medical Center/University of Ulsan, Korea

Population Modeling Tools

Kyun-Seop Bae M.D. Ph.D.

Department of Clinical Pharmacology and Therapeutics, Asan Medical Center
University of Ulsan

Population Modeling Tools

Kyun-Seop Bae MD PhD
Dept of Clinical Pharmacology and Therapeutics
Asan Medical Center
University of Ulsan

Population Modeling Tools

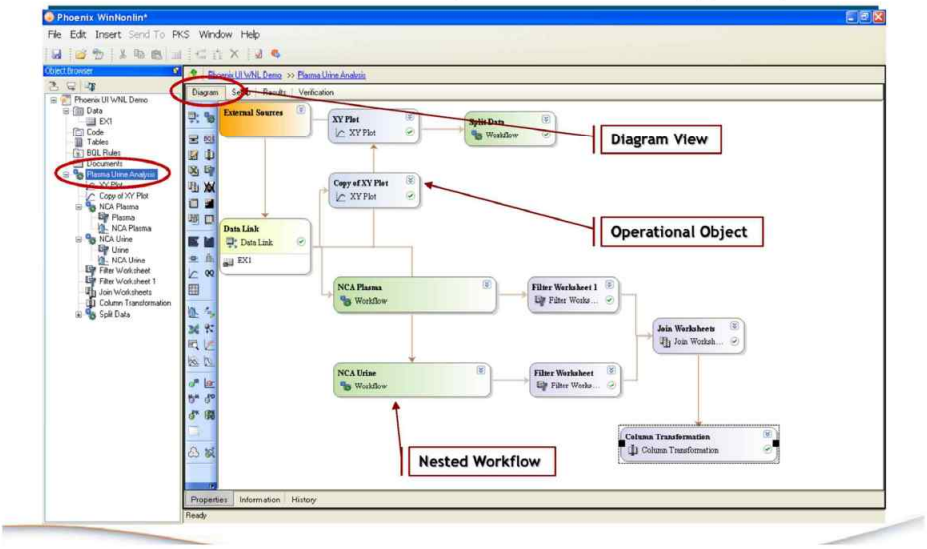
Software	Third party	Price	Version	Homepage
NONMEM		$515	7.2	http://www.iconplc.com/technology/products/nonmem/
	PDx-Pop	$280	5	http://www.iconplc.com/technology/products/pdx-pop/
	PIRANA	Free for Academia	2.6.1	http://www.pirana-software.com
	Xpose	Free	4.4.0	http://xpose.sourceforge.net/
	PsN	Free	3.5.3	http://psn.sourceforge.net/
	WFN	Free	720	http://wfn.sourceforge.net/
NLME		>$1000	1.2	http://www.pharsight.com/products/prod_phoenix_nlme_home.php
Monolix		Free	4.2.0	http://www.lixoft.com/
ADAPT II		Free	5	http://bmsrs.usc.edu/Software/
	R	Free	2.15.1	http://www.r-project.org/

Test Items

- Single Run: Execution & Diagnostics
- Covariate Modeling: Methods & Execution
- Validation: Methods & Execution
- Help & Other Functionalities
  - Speed, Parallelizing, Distributed Computing
  - OS Supporting, Syntax Highlighting
  - Template/Example Library
  - History Management/Archiving
  - Set-up/Installation, Data Preparation/Exploration

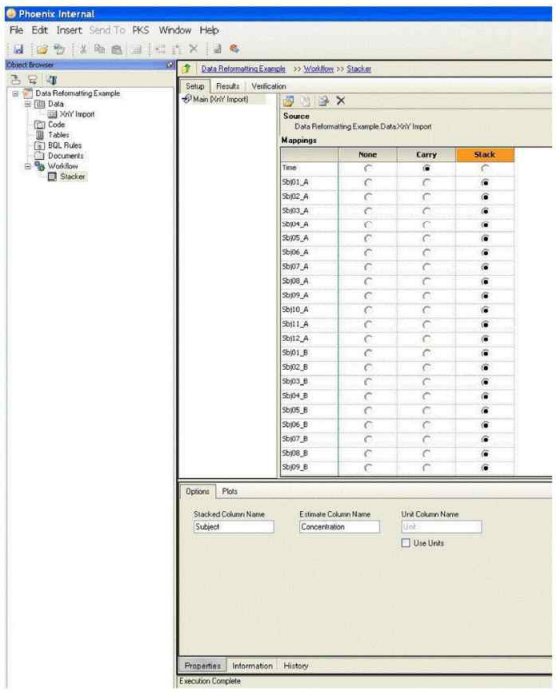
Phoenix NLME

Phoenix: Main Window (Workflow: Diagram)

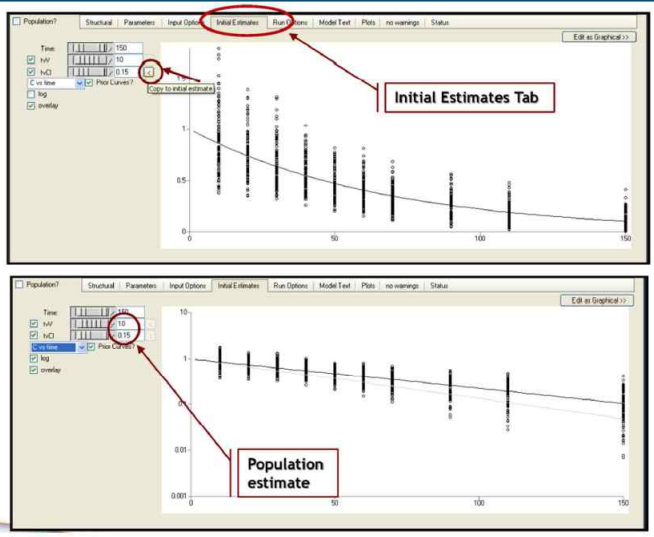


WinNonlin like – Phoenix Integrated Interface

Stacking

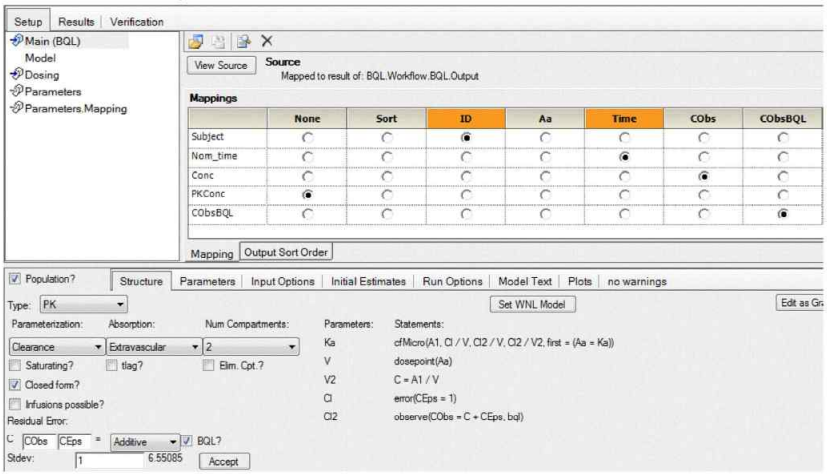


Initial Estimates Tab



Visual Initial Estimate Finding

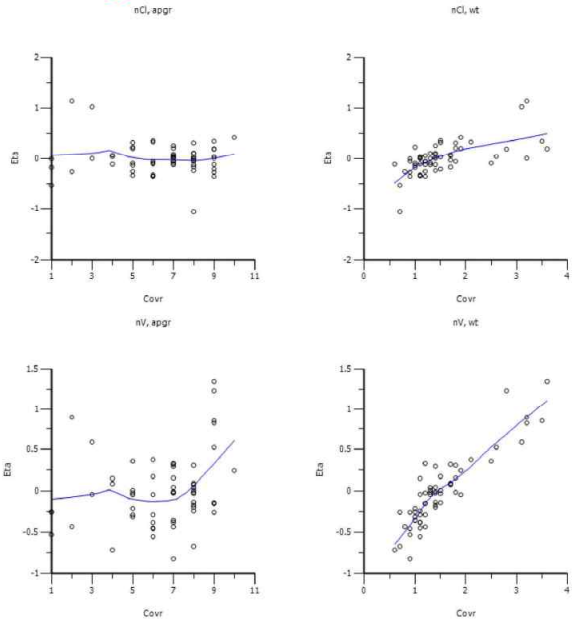
19. Make the following selections. Be sure to check the "BQL?" checkbox.



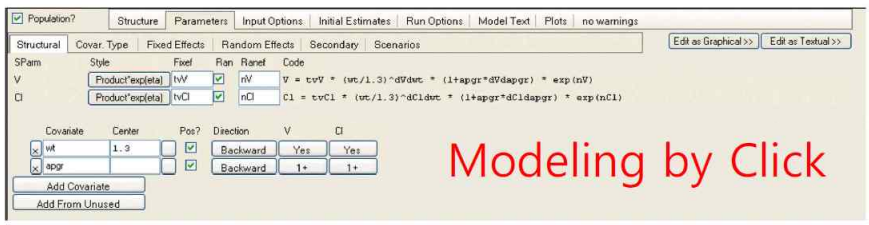
NOTE: If 'BQL?' is selected, a column can be mapped to the CObsBQL context in the Main Mappings panel. This column can contain two values: nonzero numeric (BQL) or 0/blank (non-BQL). If a concentration value is marked as BQL, then the cumulative distribution function evaluated at BQL is used to calculate the li) the interval (0 to BQL). If a concentration value i ction is used to calculate the likelihood in the us

Easy BQL Modeling

Extensive Diagnostic Plot



34. View the Parameters tab>Structural tab. Click the buttons (more than once if necessary) to add interaction terms into the model (apgr and wt effects on V and Cl) as shown.

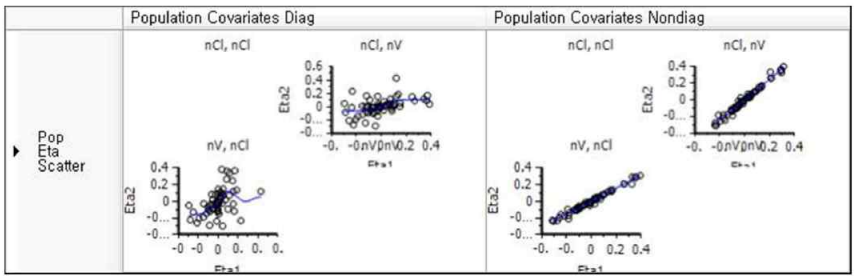


Modeling by Click

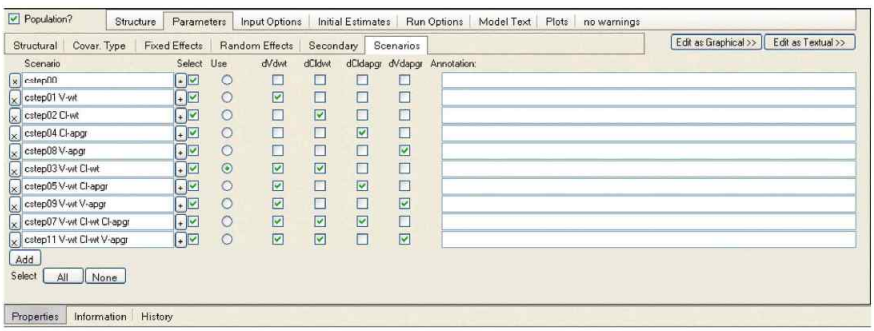
35. View the Run Options tab. Select 'Cov. Srch Stepwise' listed under 'Run Mode'.

Very Convenient & Powerful Covariate Searching

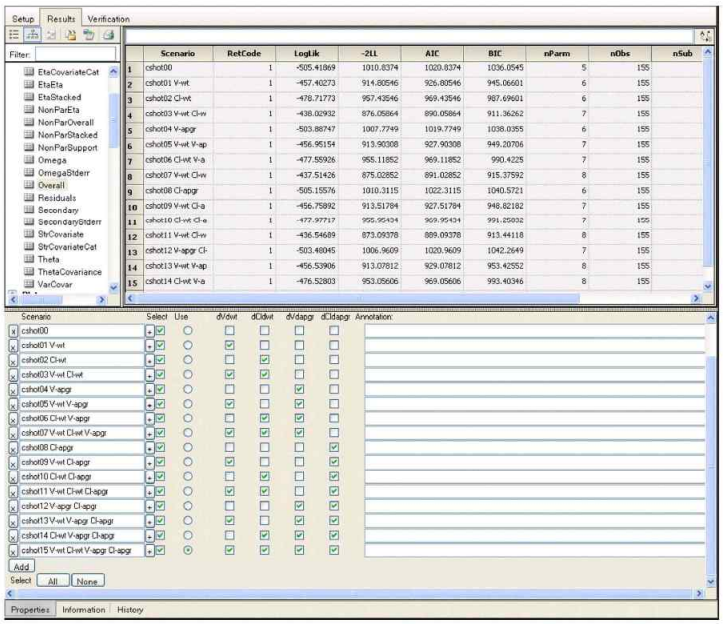
Model Comparison by Plot



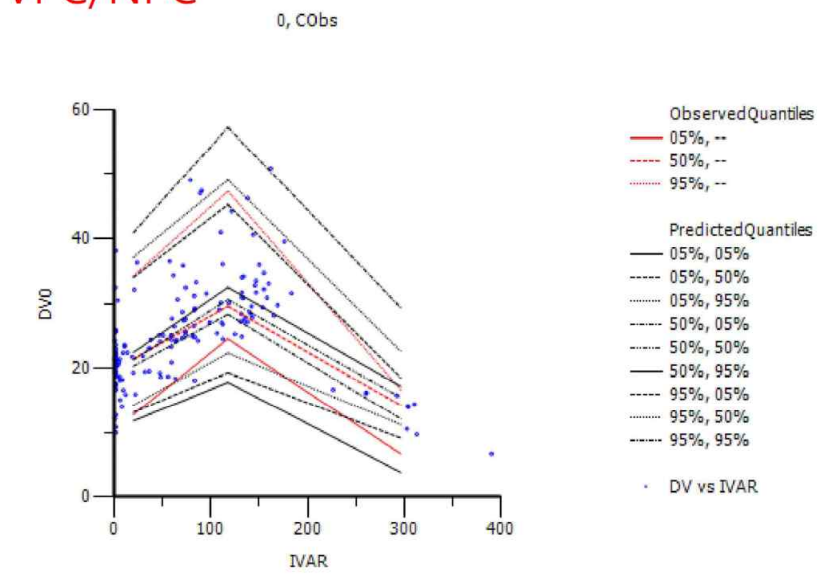
38. After the run has been completed successfully, save the project, and view the Parameters Tab>Scenarios Tab, along with the Overall worksheet in the Results Tab. Notice that Phoenix has created new scenarios, and determined a best model (wt effects on V and Cl), indicated by the "Use" button.

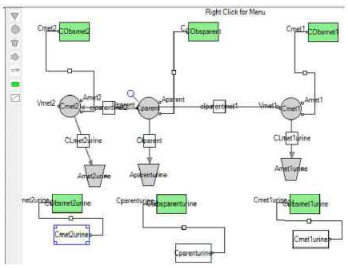


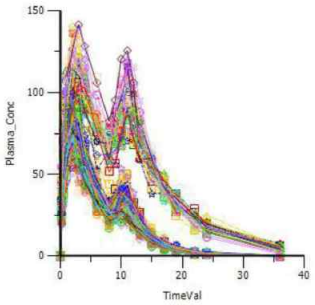
Scenarios for Model Comparison



Easy Model Comparison by Numbers and Graphics



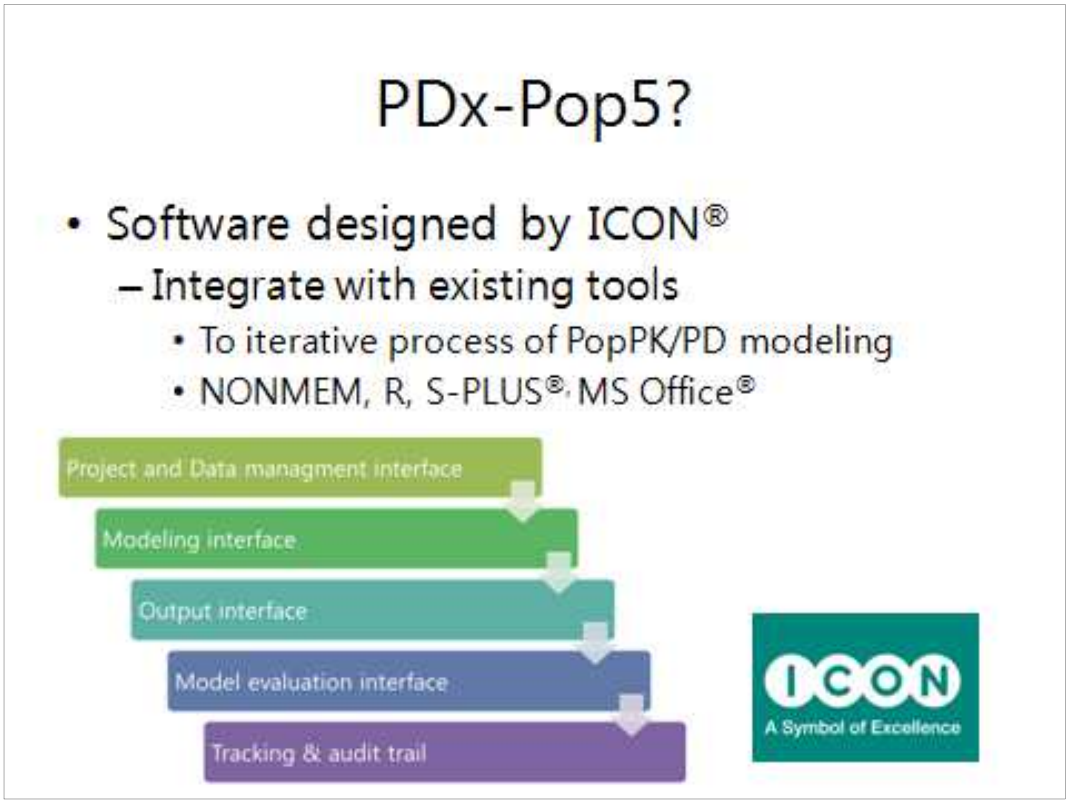


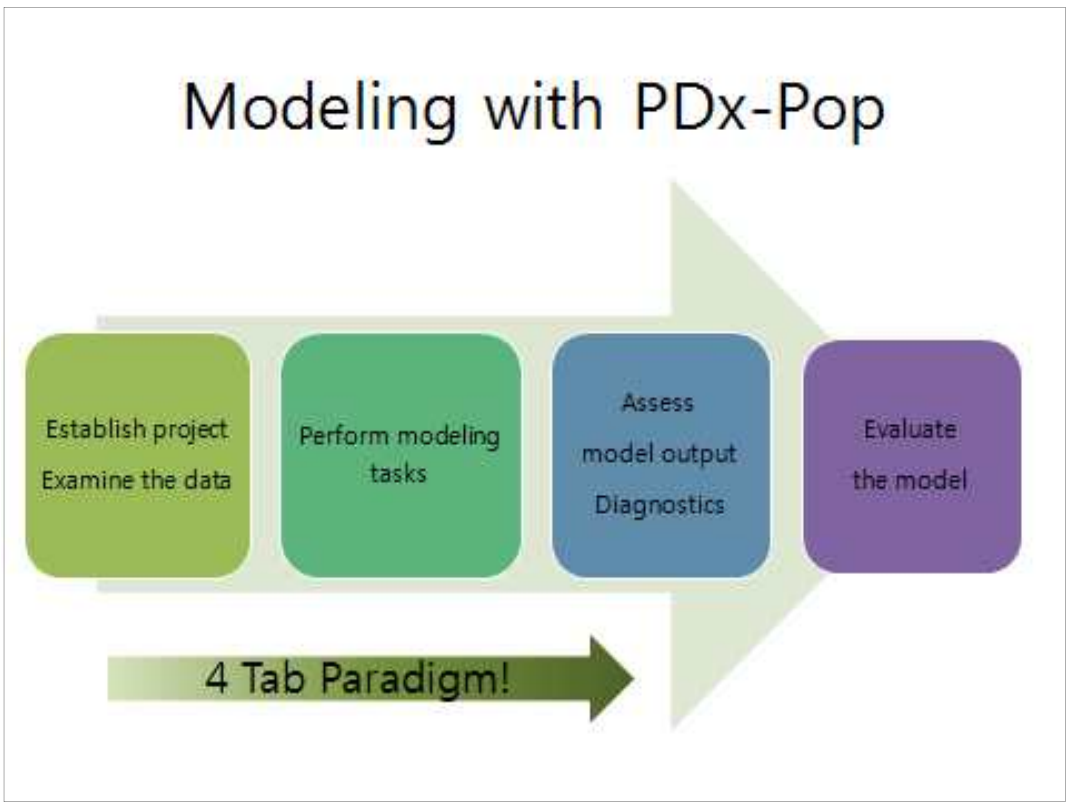



```
test(){
    deriv(A1 = - (Cl * C))
    C = A1 / V
    dosepoint(A1, duration = (Tinf))
    error(CEps = 0.5)
    observe(lnCObs = log(C) + CEps)
    stparm(V = (tvV) * exp(nV))
    stparm(Cl = (tvCl) * exp(nCl))
    stparm(Tinf = (tvTinf) * exp(nTinf))
    fixef(tvV = c(0, 90, 300))
    fixef(tvCl = c(0, 5, 20))
    fixef(tvTinf = c(1, 2.5, 5))
    ranef(diag(nCl, nV, nTinf) = c(0.15, 0.15, 0.15))
}
```

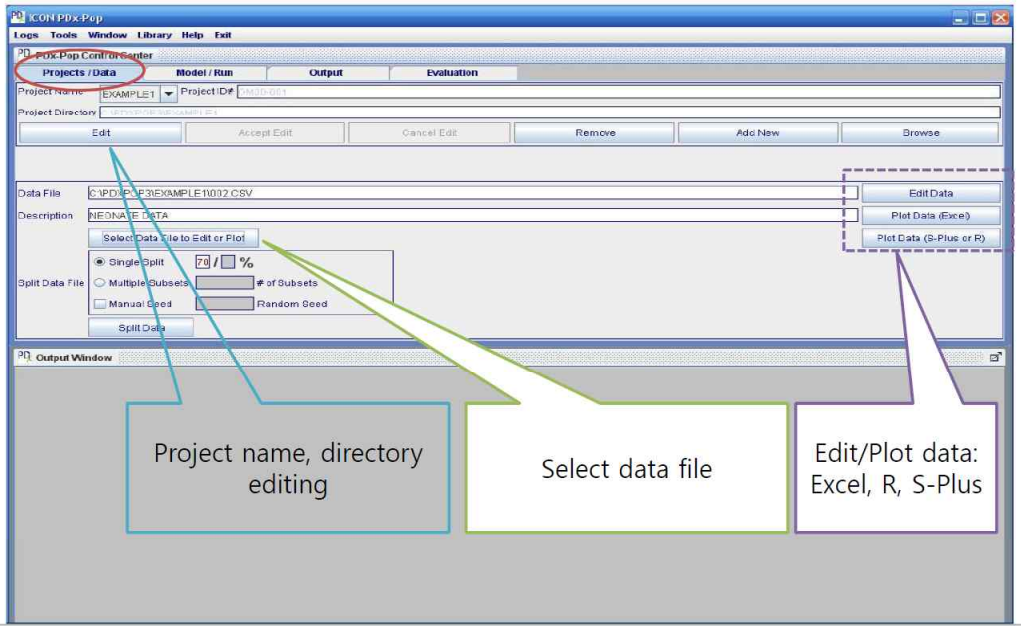
Seamless Integration of
WinNonlin -> NLME -> Trial Simulator
By Phoenix Modeling Language

PDx-Pop

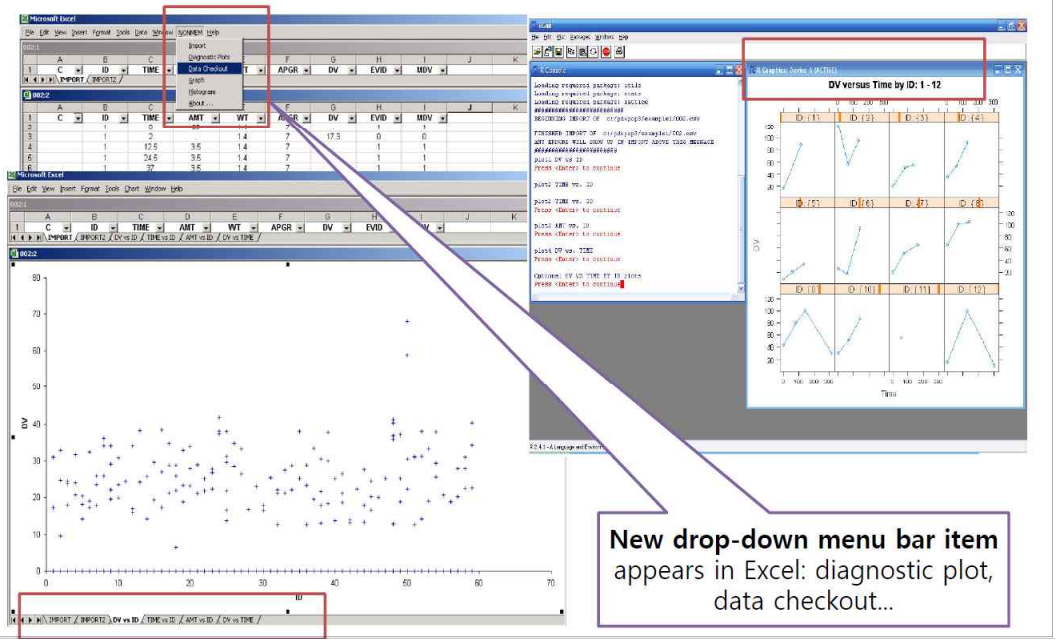

PDx-Pop5?
• Software designed by ICON®
– Integrate with existing tools
• To iterative process of PopPK/PD modeling
• NONMEM, R, S-PLUS®, MS Office®
Project and Data managment interface
Modeling interface
Output interface
Model evaluation interface
Tracking & audit trail
ICON
A Symbol of Excellence


Modeling with PDx-Pop
Establish project
Examine the data
Perform modeling tasks
Assess model output
Diagnostics
Evaluate the model
4 Tab Paradigm!

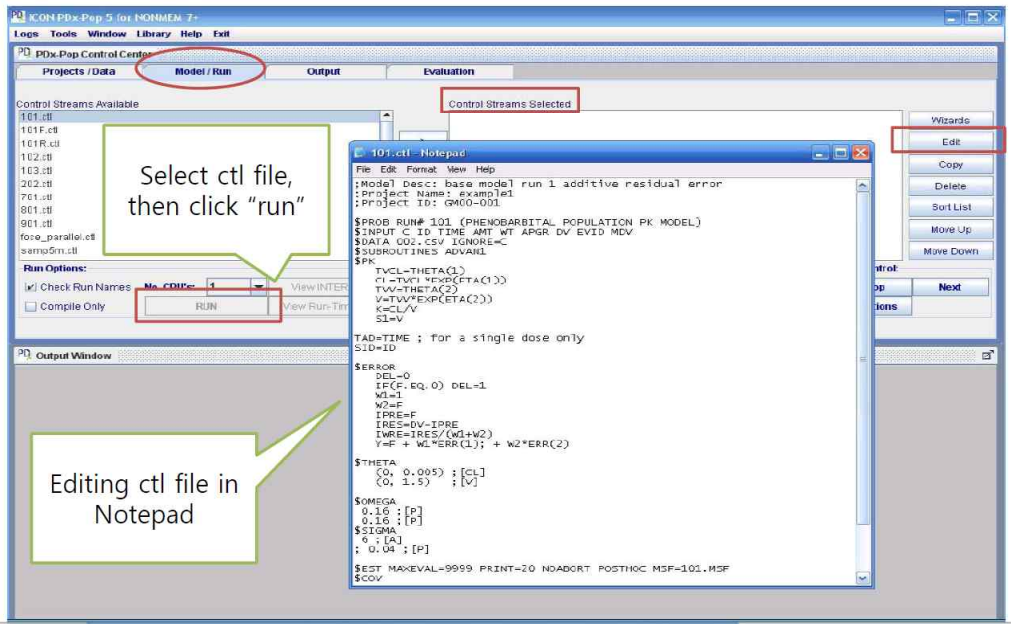
Establish project



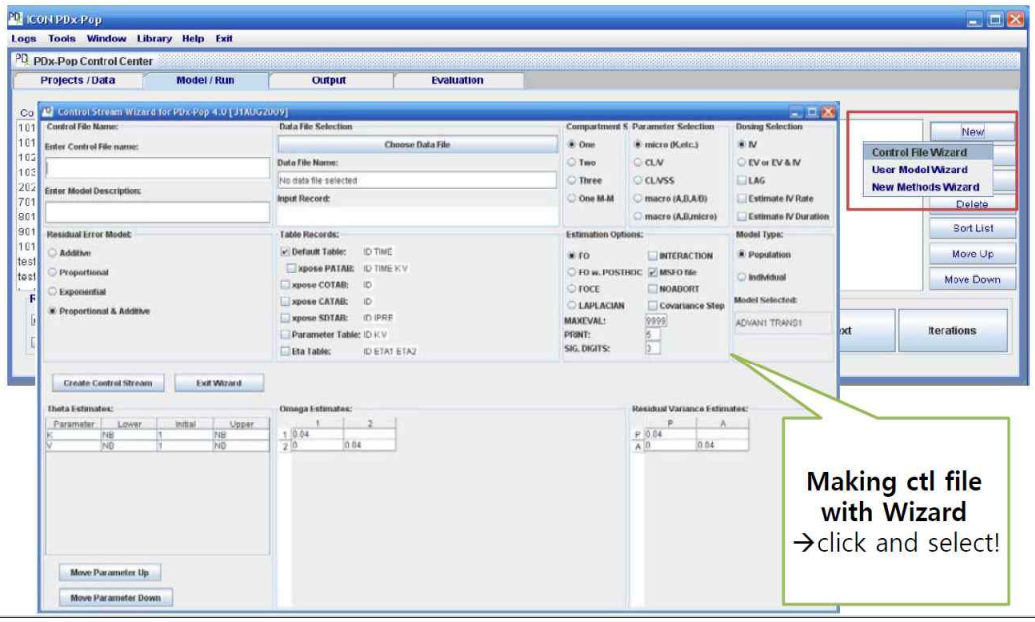
Examine the data



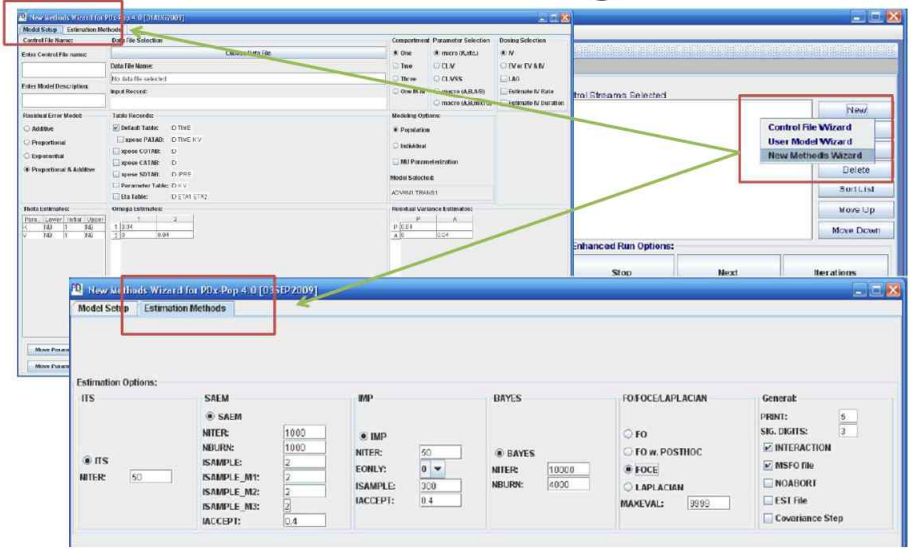
Perform Modeling Tasks



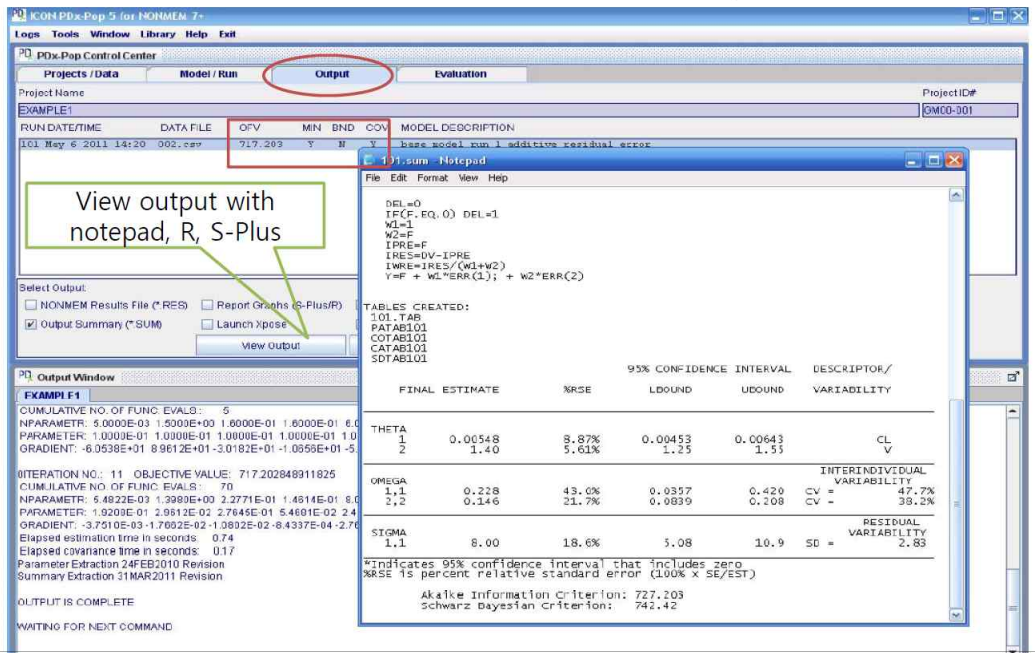
Perform Modeling Tasks



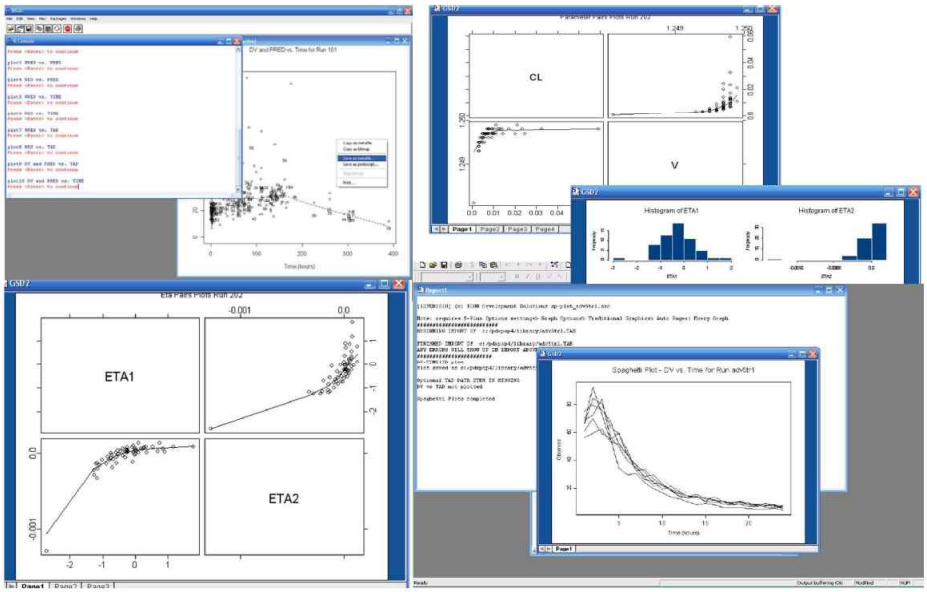
Perform Modeling Tasks



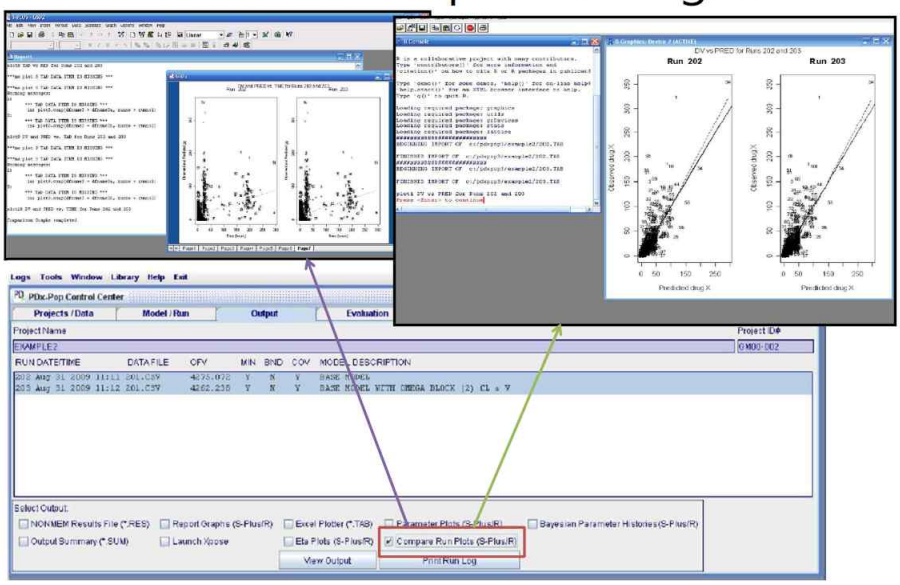
Assess Model Output



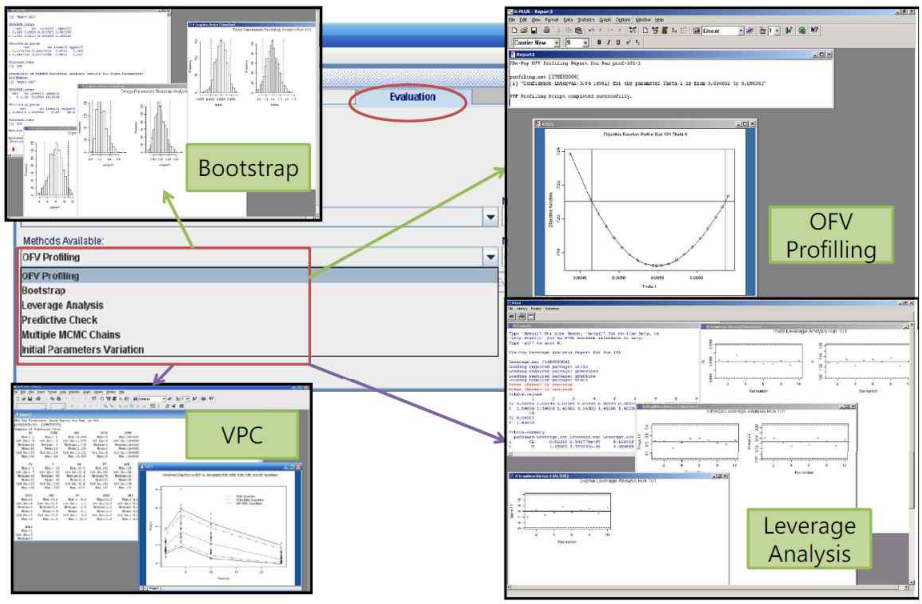
Assess Model Output & Diagnostics



Assess Model Output & Diagnostics

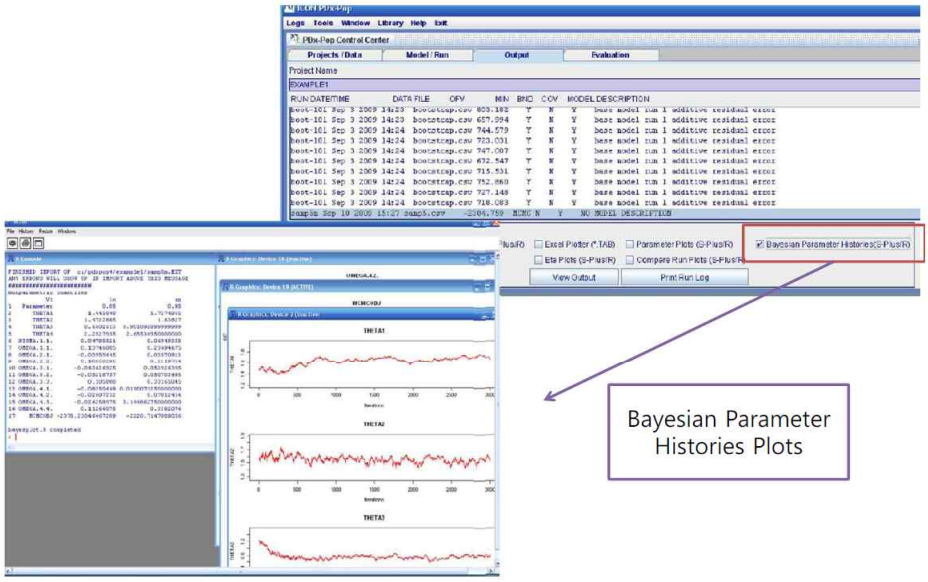


Evaluate the Model

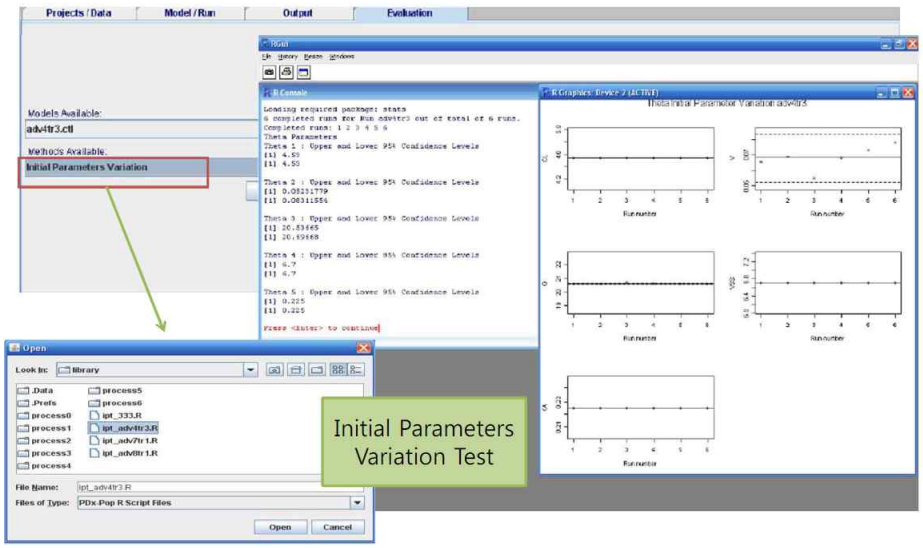


Evaluate the Model

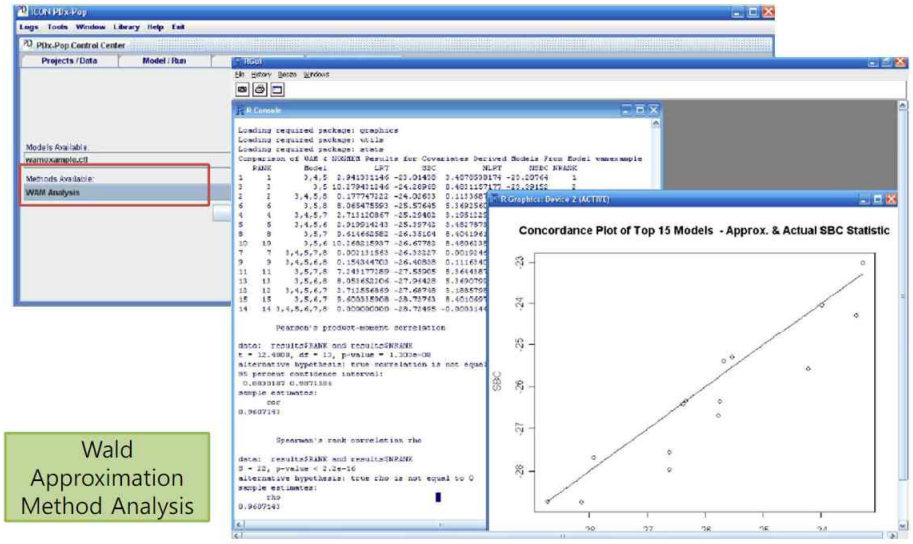
Evaluate the Model



Evaluate the Model

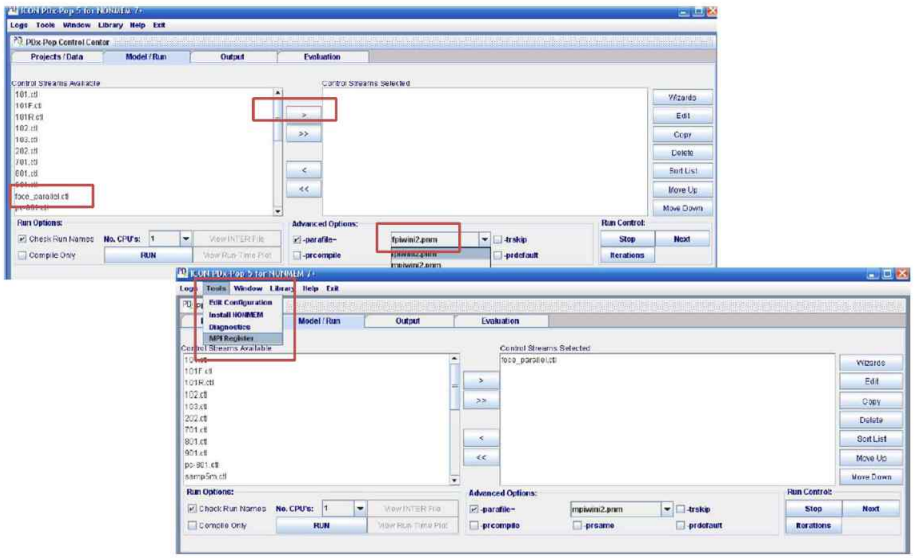


Evaluate the Model



Wald Approximation Method Analysis

Others: MPI Registration



Features of PDx-Pop5

Strengths	Weaknesses
Compatibility and Flexibility	Cannot read files without valid filename/format for PDx-Pop5
Easy for beginners: Just click!	Difficult to edit plots to taste by using R or S-Plus: All results are automatically controlled
Automated creation, error proofing of control files	Need background knowledge for R, S-Plus, Excel to use
Efficiently utilize outputs, perform analyses	Cost (license renewal every 1 year)

Summary of PDx-Pop 5

- Single Run
  - Data Prep 기능 없음
  - MS-Excel로 넘겨 Data Exploration
  - Basic control file을 click만으로 만들 수 있음
  - Initial Parameter Variation 기능 있음
  - User supplied post-processing script 실행할 수 있음
  - 결과/plot PDF 자동저장 기능 없음
  - 기본 Diagnostics에 CWRES없음
  - OFV profiling이 특징적임
- Covariate Modeling
  - 모형간 비교 formal test 없음
  - WAM 지원
- Validation
  - Bootstrapping, Leverage Analysis(CDD) 지원
- Help & Others
  - 외장 Editor사용할 수 있음
  - Parallel/Distributed Computation 지원(다른 SW에서도 기본)
  - History Management 지원, Archiving은 따로 없음
  - Set-up시 다른 SW(예를 들어, Pharsight사 SW)와 path 충돌 주의
  - 오류가 흔히 발생함, Control file restriction이 많아 매우 까다로움

PIRANA

"What's with the name?"

Pirana
Is a
Resourceful
Assistant in
NONMEM
Analyses

PIRANA

- NONMEM과 PsN을 위한 모형화 환경 제공
  - 지원되는 OS: Mac OSX (Mountain Lion 10.8, Snow Leopard 10.6), Windows, Linux (32-bit Ubuntu)
  - 필수 요구사항: NONMEM
  - 권장 사항: R, PsN, Xpose
  - 지원 사항: Clusters, WFN, NMQual

특징 1

- NONMEM 사용
  - 설치된 모든 NONMEM 관리 가능
  - nmfe를 사용한 모형화 지원
  - PsN-toolkit 모두 지원
  - 지원되는 Cluster infrastructure: SGE (Sun Grid Engine), MOSIX and PCluster

특징 2

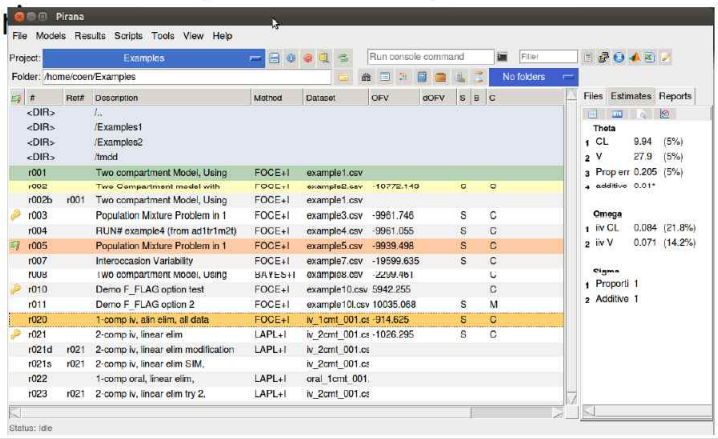
- 한번에 여러 가지 모형화 작업 가능하며, 실행번호로 목록화가 가능하고, 트리 형태의 작업 환경 관리
  - 모형과 결과에 메모를 남기거나 색깔로 구분가능
  - 내장된 혹은 선호하는 에디터(Emacs [http://ess.r-project.org/, http://esnm.sourceforge.com/], PSPad [www.pspad.com], ConTEXT [http://www.contexteditor.org/], Acroedit [http://www.acrosoft.pe.kr])를 사용하여 control file을 열어 자유롭게 편집 가능
  - 모형 복제가 쉬움(이전 결과를 자동으로 인식하여 넣어줄 수 있으며, 모형 파일 내의 번호도 자동으로 수정 가능)
  - 자료세트를 바로 열거나 찾아볼 수 있으며, 즉석에서 R 혹은 excel 등으로 수정 및 확인 가능

특징 3

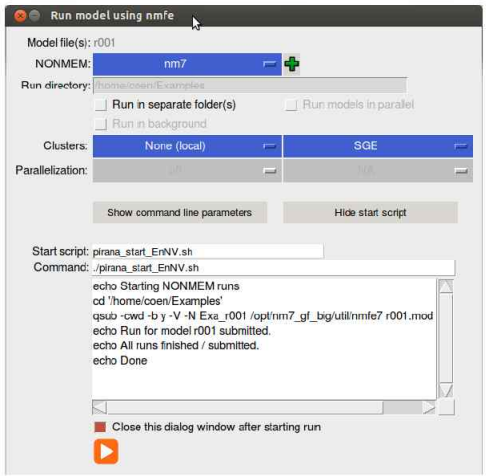
- 결과 생성
  - 모형 결과에 따른 적합한 R 구문으로 모형의 적합성 판단 가능 (예, goodness of fit plots 혹은 VPCs 등). 많은 유용한 R 구문이 내장되어 있음.
  - 내장된 R 구문으로 Xpose의 모든 기능 사용 가능
  - NONMEM 결과 파일에서 HTML- 혹은 LaTeX-요약본을 출력 가능
  - Data Inspector 기능을 사용하여 자료세트를 확인하거나 모형 실행 결과를 도표화 가능

Screenshots

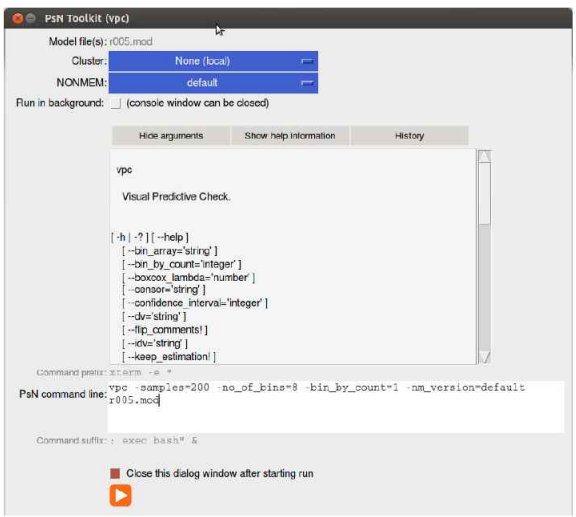
- Main screen (overview of models)
  - Model descriptions, results, notes
  - Datasets, output tables, Xpose datasets, R sc



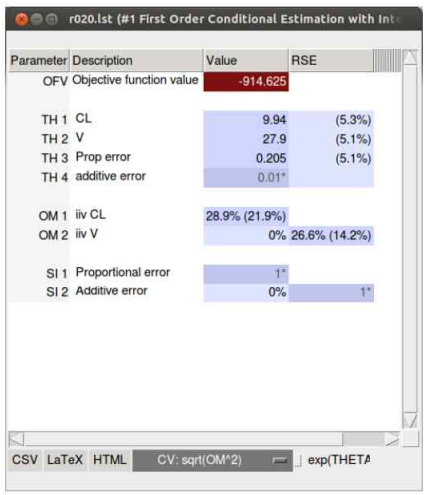
- Running NONMEM
  - Extensive running models, with support for clusters and parallelization



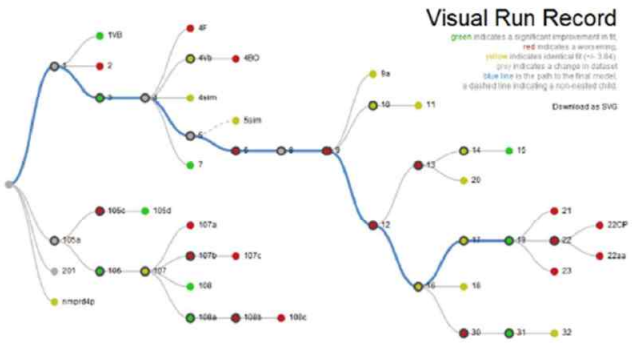
- PsN toolkit
  - vpc, npc, sse, scm, etc.
  - Basic information/help in the PsN dialog window



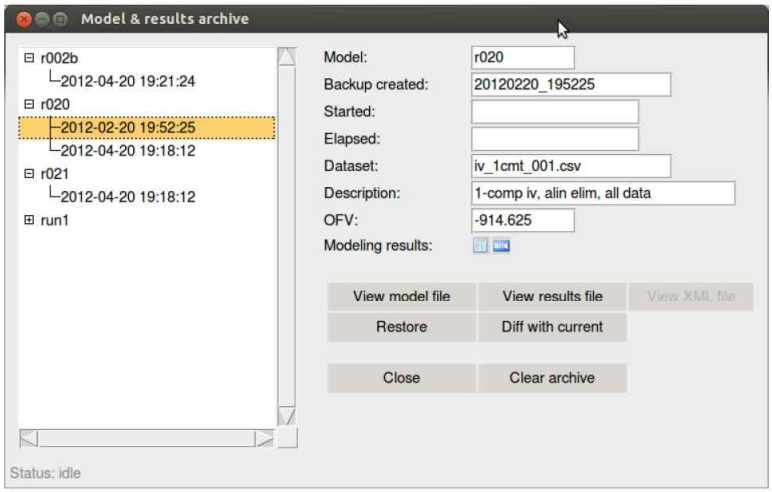
- Results
  - Viewing of parameter estimates
  - Comparing of other models' estimates



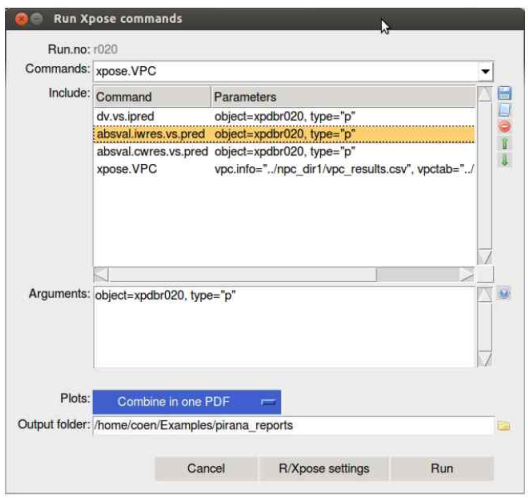
- Visual Run Record of NONMEM Results
  - Hierarchical fashion model development history



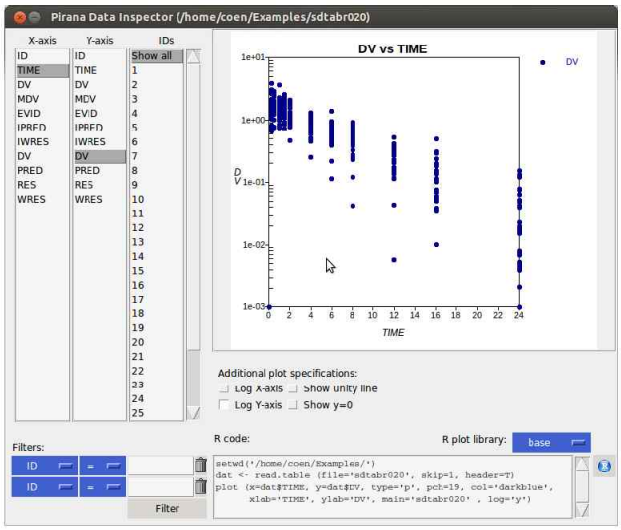
- Model archive
  - Comprehensive archiving/backup tool



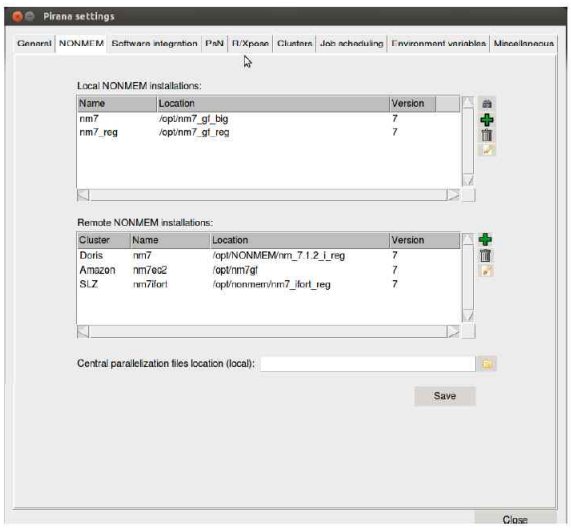
- Xpose
  - Multiple Xpose commands are provided
  - Plots or R code are provided



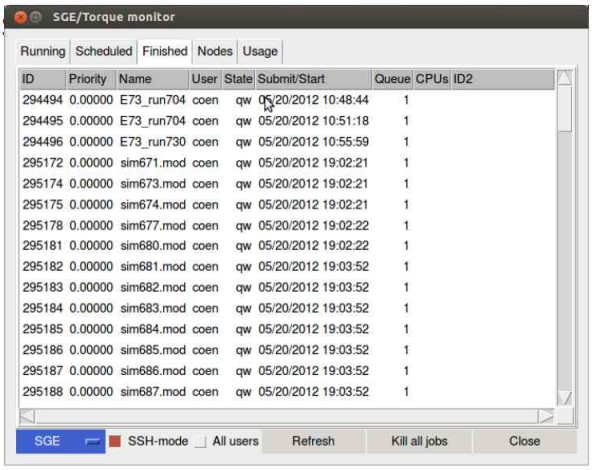
- Data inspector
  - Quick plots for datasets



- Settings
  - Settings and preferences easily adapted to the preferences of the user



- Job schedulers
  - Can run and manage jobs on the Sun Grid Engine and Torque.
  - Easily view cluster load, intermediate results, or stop jobs



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  - 1 year for 1 copy: €500 (5 copy: €2,000; 10 copies: €3,500; 20 copies: €6,000; unlimited: €12,500)

PDx-Pop과의 차이

- 무료 소프트웨어(학계에서 사용 시)
- 내장된 R 구문의 자유로운 수정 가능(PsN과 Xpose에서 사용하는 R 구문 포함)
- Cluster 기능 지원으로 네트워크를 통한 다중 실행 가능
- 여러가지 OS 지원(다양한 환경에서 사용 가능)
- PsN의 강력한 분석 기능(covariate searching[scm], code generating[update code], bootstrapping, VPC, random permutation test) 및 Xpose의 plotting 기능 완벽 지원

Summary of PIRANA

- Single Run
  - Data Exploration 기능 좋음
  - Initial Value Perturbation 가능
  - 풍부한 R script 제공 – post-processing, diagnostics
  - Click만으로 결과/plot을 PDF/HTML/Latex 등으로 저장
  - Click만으로 basic control file 작성 가능
- Covariate Modeling & Validation
  - PsN, Xpose 기능(bootstrap, cdd, scm, vpc/npc, sse, lasso, …)을 쉽게 모두 쓸 수 있음 -강력한 validation
  - Covariate search기능은 scm사용 – NLME보다 불편
- Help & Others
  - 다양한 distributed computing(cluster) 제공
  - 다양한 OS 제공, 비교적 자주 update – Uppsala group에서 만들고 사용
  - 모형간 비교기능 좋음
  - Template/Library 좋음
  - History 관리, Archiving 기능 좋음
  - 외장 Editor 가능(Syntax highlighting 가능)
  - 많은 다른 SW와 integration 좋음

Summary

Software Set	Functions	Convenience	Stability	Strength
Pirana+ PsN+Xpose+ NONMEM	★★★★★	★★★★	★★★★	Validation
PDx-Pop+ NONMEM	★	★★	★	OFV Profiling
Phoenix NLME	★★★★	★★★★★	★★★★★	Covariate
Monolix	★★	★★★	★	

CURRICULUM VITAE

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1990	B.Sc. Sookmyung Woman's University, Korea. Pharmacy.
1997	M.Sc. Sookmyung Woman's University, Korea. Pharmacy.
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1990-94	Pharmacist / Kangnam Sacred Heart Hospital, Seoul, Korea.
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1996-97	Research Assistant / Samsung Medical Center Clinical Research Institute, Seoul, Korea.
2000-01	Researcher / Research Institute for Development of Pharmaceutical Resources, Cheonju, Chungbuk, Korea.
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03/2008-02/2010	Research Professor / Department of Medicine, University of Ulsan College of Medicine, Seoul, Korea.
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Prediction of the Tacrolimus Population Pharmacokinetic Parameters Considering Genotypes and Clinical Factors in Kidney Transplant Recipients

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Prediction of the Tacrolimus Population Pharmacokinetic Parameters Considering Genotypes and Clinical Factors in Kidney Transplant Recipients

1st PAGK Annual Meeting

Jung Mi Oh/In-Wha Kim
Seoul National University

*Introduction

Introduction

*Tacrolimus

- Tacrolimus is a competent immunosuppressant used for the prevention of rejection after organ transplantation usually with mycophenolate and steroids (1).
- It is known that trough levels of tacrolimus, especially of the first 3 months, are significantly associated with clinical outcome.
- Tacrolimus has a rather narrow therapeutic range, but it is still hard to predict tacrolimus level precisely due to high individual variability of tacrolimus clearance (2-3).

1) Plosker GL, *et al.*, Drugs, 2000; 59: 323-389
2) Staatz CE & Tett SE, Clin Pharmacokinet, 2004; 43: 623-653
3) Kershner RP, *et al.*, Transplantation, 1196; 62: 920-926

Introduction

*Factors affecting tacrolimus concentrations

- Several clinical factors are known to be related with tacrolimus pharmacokinetics (1-2).
  - Age, Sex, Body weight, Ethnicity, Hematocrit, Albumin, Scr level, Post-operative days (POD)
  - Concomitant immunosuppressants and other drugs (3)
- Some genotypes are also considered as responsible for tacrolimus level.
  - *CYP3A5* metabolites tacrolimus in the liver and small intestine (4)
  - *ABCB1*

1) Staatz CE, *et al.*, Clin Pharmacokinet, 2007; 43(10): 623–653
2) Kim IW, *et al.*, Eur J Clin Pharmacol, 2012; 68: 657-669
3) Venkataramanan R, *et al.*, Clin Pharmacokinet, 1995; 29: 404-430
4) Iwasaki K, *et al.* Drug Metab Pharmacokinet, 2007; 22: 328-335

Introduction

*Tacrolimus population pharmacokinetic studies in kidney transplants

Authors	Subjects	Results	Remarks
Han, *et al.* (2012)	KTPL, Adults N=80, Korean (first 400 days)	*CL*: POD, *CYP3A5*, Hematocrit V_d: Body weight	k_a 4.5 h^{-1} fixed
Woillard, *et al.* (2010)	KTPL, Adults N=32 (first 6 mo) N=41 (after 12 mo)	*CL*: *CYP3A5*, Hematocrit V_d, k_a: no significant covariates	Week 1, 2, 4, 12, and 24 for 32 pts
Zhao, *et al.* (2009)	KTPL, Pediatrics N=50, French (first 2 mo)	*CL*: *CYP3A5*, Hematocrit, Body weight V_d, k_a: no significant covariates	Lag time, k_a estimated Dose proposed
Antignac, *et al.* (2007)	KTPL, Adults N=83 (first 2 mo)	*CL*: increased with POD and the dose of prednisone (>25 mg) V_d, F: no significant covariates	FOCE k_a 4.5 h^{-1} fixed
Musuamba, *et al.* (2009)	KTPL candidates, Adults N=19 (before operation)	*CL*: *CYP3A5*, *ABCB1* genotype k_a: time of drug administration	1 day dense

*To establish a population pharmacokinetic (PK) model of tacrolimus and evaluate the influence of clinical covariates, including the genetic polymorphisms of the cytochrome P450 3A5 (*CYP3A5*) and gene encoding ABCB1, on the PK parameters in adult Korean kidney transplant recipients.

*Objectives

*Methods

Methods

*Patients

- Inclusion criteria
  - Received kidney transplantation at Seoul National University Hospital
  - Between March 2007 to July 2010
  - Administered with Prograf® (Astellas Pharma US, Inc.)
- Exclusion criteria
  - Younger than 18 years old
  - Multi-organ transplantation
  - More than 2nd transplantation
  - Administered with Tacrobell® (CKD Pharmaceutical Corp.)

Methods

***Sampling of tacrolimus concentrations**

- Dense sampling
  - Just before and 0.5, 1, 2, 4, 6, 8, and 12 hr after administration of tacrolimus during 10 to 15 days after post-operation
- Trough level sampling
  - Collected all tacrolimus trough levels till around 14 days after transplantation
- Tacrolimus concentrations were determined by LC-MS/MS

Methods

***Genotyping**

- DNA was extracted from the whole blood samples (5 mL)
- Genotype
  - *CYP3A5* 6986A>G (intron 3, rs776746)
  - *ABCB1* 1236C>T (exon 12, rs1128503), 3435C>T (exon 26, rs1045642)
- TaqMan allelic assay
- Hardy-Weinberg equilibrium test using Chi-squared test

Methods

*Data collection

- Demographic data
  - Age, Sex, Dialysis duration, Type of dialysis before transplantation, Type of kidney disease, Donor type, Graft weight, post-operative days
  - Concomitant immunosuppressants and other drugs dosage
- Clinical/Laboratory data
  - Hemoglobin, Hematocrit, Body weight, Serum creatinine, AST/ALT, Total bilirubin, Cholesterol, Albumin, Total protein

Methods

*Modeling method

- Program: NONMEM® version 6.1
- Model building
  - ADVAN2 TRANS2 (One-compartment pharmacokinetic model with linear absorption and elimination)
  - First-Order Conditional Estimation with Interaction
  - Inter-individual variability: Exponential relationship
  - Residual variability: Proportional relationship
- Covariates Selection
  - Forward selection ($p<0.05$, OFV decrease > 3.84)
  - Backward elimination ($p<0.001$, OFV increase > 10.83)

Methods

*Model validation

- Bootstrap: 2000 times
  - Program: Perl-speaks NONMEM (PsN® ver. 3.1.0)
- Visual Prediction Check: 200 times
  - Program: Perl-speaks NONMEM (PsN® ver. 3.1.0)

*Covariates evaluation

- Program: IBM SPSS statistics ver. 19

*Results

Results

*Patients and data collection

- 122 patients received first kidney transplantation were enrolled to the study
- Total numbers of collected tacrolimus level: 3356 points
  - Dense sampled points: 481 points from 61 patients

Results

*Demographic data (n=122)

Patient characteristics		Patient characteristics	
Age (years)	40.9 (19-69)	**Graft Weight (g)**	160.2 ± 35.6
Sex, n(%)		**Type of kidney disease, n(%)**	
Female	55 (45.1)	Diabetes	9 (7.4)
Body Weight (kg)	58.3 ± 10.6	Hypertension	5 (4.1)
Donor type, n(%)		Glomerular nephropathy	44 (36.1)
Living donor	80 (65.6)	Unknown	43 (35.2)
Deceased donor	42 (34.4)	Others	21 (17.2)

Results

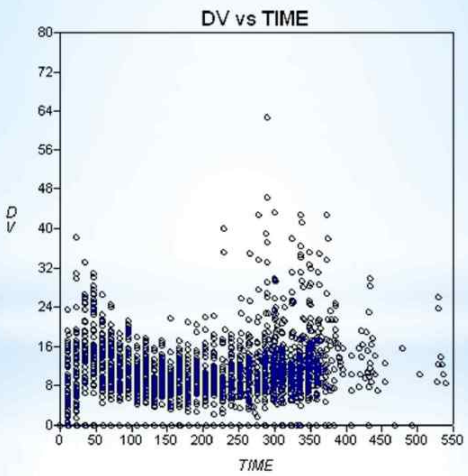
*Allelic frequencies (n=122)

Genes		Frequency (%)		
ABCB1	1236C>T	CC	CT	TT
		36 (29.5)	63 (51.6)	23 (18.9)
	3435C>T	CC	CT	TT
		23 (18.9)	71 (58.2)	28 (22.9)
CYP3A5	6986A>G	AA (*1/*1)	AG (*1/*3)	GG (*3/*3)*
		12 (9.8)	40 (32.8)	70 (57.4)

* Poor metabolizer

Results

*Tacrolimus concentration profiles (n=122)



Results

*Modeling – forward selection

Covariate		Model	OFV	ΔOFV
Base model			7857.528	-
CL/F	POD	$CL=\Theta1*(1+POD*\Theta2)$	7789.933	-67.595
	Hematocrit	$CL=\Theta1*(1+HCT*\Theta2)$	7833.216	-24.312
	Albumin	$CL=\Theta1*(ALB+0.0001)^{\Theta2}$	7850.894	-6.634
	Weight	$CL=\Theta1*(1+WTKG*\Theta2)$	7847.482	-10.046
	Total protein	$CL=\Theta1*e^{(TPRT*\Theta2)}$	7849.848	-7.68
	CYP3A5	$CL=\Theta1*e^{(CYP1*\Theta2+CYP2*\Theta3)\dagger}$	7831.934	-25.594
V/F	POD	$V=\Theta1*e^{(POD*\Theta2)}$	7847.94	-9.588
	Hematocrit	$V=\Theta1*e^{(HCT*\Theta2)}$	7846.292	-11.236
	Weight	$V=\Theta1*e^{(WTKG*\Theta2)}$	7843.15	-14.378
	Albumin	$V=\Theta1*(ALB+0.0001)^{\Theta2}$	7853.508	-4.02
	Total protein	$V=\Theta1*(1+TPRT*\Theta2)$	7853.126	-4.402
	Age	$V=\Theta1*e^{(AGE*\Theta2)}$	7847.492	-10.036
Ka	Hematocrit	$Ka=\Theta1*(1+HCT*\Theta2)$	7849.549	-7.979

† CYP1=*CYP3A5* *1, CYP2=*CYP3A5* *3/*3

Results

*Modeling – backward elimination

Covariate		Model	OFV	ΔOFV
Full model		**CL**=$\Theta1*(1+POD*\Theta2)*(1+HCT*\Theta3)*(ALB+0.0001)^{\Theta4})*(1+WTKG*\Theta5)*e^{(TPRT*\Theta6)}*e^{(CYP1*\Theta7+CYP2*\Theta8)}$ **V**=$\Theta9*e^{(POD*\Theta10)}*e^{(HCT*\Theta11)}*e^{(WTKG*\Theta12)}*(ALB+0.0001)^{\Theta13})*(1+TPRT*\Theta14)*e^{(AGE*\Theta15)}$ **Ka**=$\Theta16*(1+HCT*\Theta17)$	7681.367	-
CL/F	Albumin	**CL**=$\Theta1*(1+POD*\Theta2)*(1+HCT*\Theta3)*(1+WTKG*\Theta5)*e^{(TPRT*\Theta6)}*e^{(CYP1*\Theta7+CYP2*\Theta8)}$ **V**=$\Theta9*e^{(POD*\Theta10)}*e^{(HCT*\Theta11)}*e^{(WTKG*\Theta12)}*(ALB+0.0001)^{\Theta13})*(1+TPRT*\Theta14)*e^{(AGE*\Theta15)}$ **Ka**=$\Theta16*(1+HCT*\Theta17)$	7681.462	+0.095
	Total Protein	**CL**=$\Theta1*(1+POD*\Theta2)*(1+HCT*\Theta3)*(1+WTKG*\Theta5)*e^{(CYP1*\Theta7+CYP2*\Theta8)}$ **V**=$\Theta9*e^{(POD*\Theta10)}*e^{(HCT*\Theta11)}*e^{(WTKG*\Theta12)}*(ALB+0.0001)^{\Theta13})*(1+TPRT*\Theta14)*e^{(AGE*\Theta15)}$ **Ka**=$\Theta16*(1+HCT*\Theta17)$	7686.862	+5.4
	Weight	**CL**=$\Theta1*(1+POD*\Theta2)*(1+HCT*\Theta3)*e^{(CYP1*\Theta7+CYP2*\Theta8)}$ **V**=$\Theta9*e^{(POD*\Theta10)}*e^{(HCT*\Theta11)}*e^{(WTKG*\Theta12)}*(ALB+0.0001)^{\Theta13})*(1+TPRT*\Theta14)*e^{(AGE*\Theta15)}$ **Ka**=$\Theta16*(1+HCT*\Theta17)$	7693.894	+7.032
	Hemato-crit	**CL**=$\Theta1*(1+POD*\Theta2)*e^{(CYP1*\Theta7+CYP2*\Theta8)}$ **V**=$\Theta9*e^{(POD*\Theta10)}*e^{(HCT*\Theta11)}*e^{(WTKG*\Theta12)}*(ALB+0.0001)^{\Theta13})*(1+TPRT*\Theta14)*e^{(AGE*\Theta15)}$ **Ka**=$\Theta16*(1+HCT*\Theta17)$	7702.812	+8.918

Results

*Modeling – backward elimination

Covariate		Model	OFV	ΔOFV
V/F	Albumin	CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ7+CYP2*Θ8) V=Θ9*e^(POD*Θ10)*e^(HCT*Θ11)*e^(WTKG*Θ12)*(1+TPRT*Θ14)*e^(AGE*Θ15) Ka=Θ16*(1+HCT*Θ17)	7703.112	+0.3
	POD	CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ7+CYP2*Θ8) V=Θ9*e^(HCT*Θ11)*e^(WTKG*Θ12)*(1+TPRT*Θ14)*e^(AGE*Θ15) Ka=Θ16*(1+HCT*Θ17)	7709.254	+6.142
	Total protein	CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ7+CYP2*Θ8) V=Θ9*e^(HCT*Θ11)*e^(WTKG*Θ12)*e^(AGE*Θ15) Ka=Θ16*(1+HCT*Θ17)	7710.975	+1.721
	Hemato-crit	CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ7+CYP2*Θ8) V=Θ9*e^(WTKG*Θ12)*e^(AGE*Θ15) Ka=Θ16*(1+HCT*Θ17)	7712.184	+1.209
	Age	CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ7+CYP2*Θ8) V=Θ9*e^(WTKG*Θ12) Ka=Θ16*(1+HCT*Θ17)	7722.186	+10.002
Ka	Hemato-crit	CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ7+CYP2*Θ8) V=Θ9*e^(WTKG*Θ12) Ka=Θ16	7725.07	+2.884
Final Model		CL=Θ1*(1+POD*Θ2)*e^(CYP1*Θ3+CYP2*Θ4) V=Θ5*e^(WTKG*Θ6) Ka=Θ7	7725.07	-

Results

*Final Model

$$CL/F(L/h) = 16.2 \times (1 + (POD - 8.44) \times 0.018) \times e^{(CYP1 \times 0.437 + CYP2 \times 0.037)}$$
$$V/F(L) = 184 \times e^{(WTKG/57.50) \times 0.409}$$
$$k_a(h^{-1}) = 4.47$$
$$Lag\ time\ (h) = 0.25\ (Fixed)$$

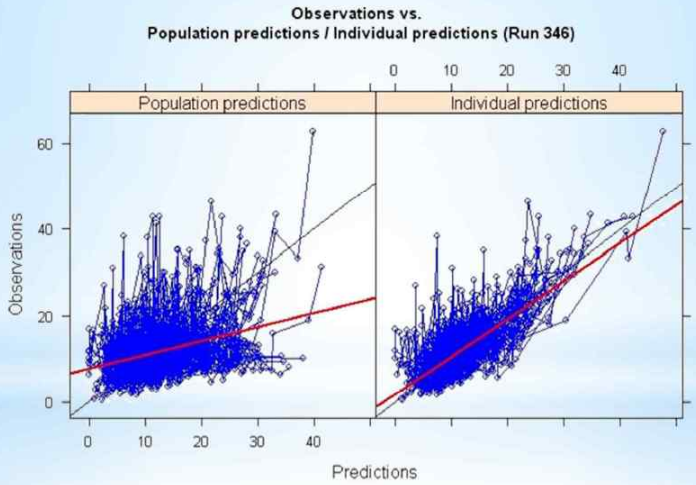
* CYP1= *CYP3A5* *1, CYP2= *CYP3A5* *3/*3

Results

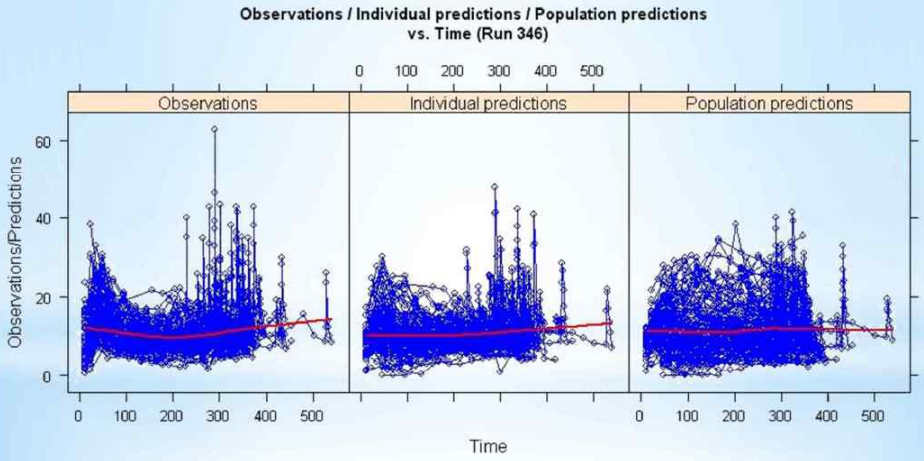
*Population pharmacokinetic parameters

Parameter	Pop. mean	%SEM	Inter-individual variability (%)
CL/F	16.2	5.1	34.9
POD	0.018	21.3	-
CYP3A5 *1	0.436	17.1	-
CYP3A5 *3/*3	0.0365	11.9	-
V_d/F	184	9.9	68.6
WTKG	0.409	22.9	-
k_a	4.47	10.7	65.8
Lag time	0.25 (fixed)	-	-
ω^2CL/F	33.9	8.1	-
ω^2V_d/F	62.1	10.5	-
ω^2k_a	60.0	24.9	-
σ^2	4.07	-	-
Random residual variability (%)	4.7	-	-

Results

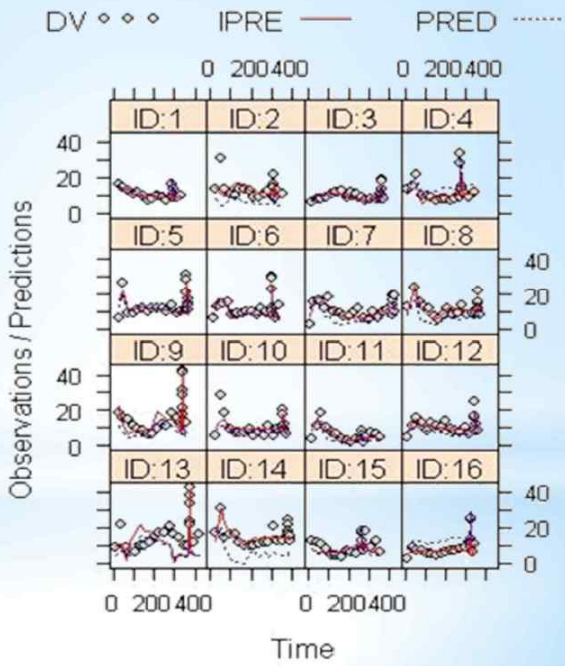


Results



Results

*Individual plots



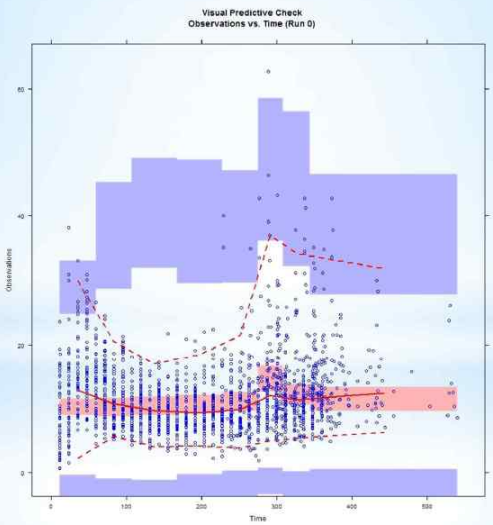
Results

* Bootstrap (n=2000)

Parameter	Pop. mean	5th percentile	95th percentile
CL/F	16.2	13.40	19.04
POD	0.018	0.011	0.024
CYP3A5 *1 carrier	0.437	0.286	0.632
CYP3A5 *3/*3	0.0365	-0.129	0.238
V_d/F	184	159	217
WTKG	0.409	0.270	0.564
k_a	4.47	3.74	4.38
Lag time	0.25 (fixed)	-	-
ω^2CL/F	33.9	28.3	38.6
ω^2V_d/F	62.1	49.5	72.3
ω^2k_a	60.0	29.9	81.2

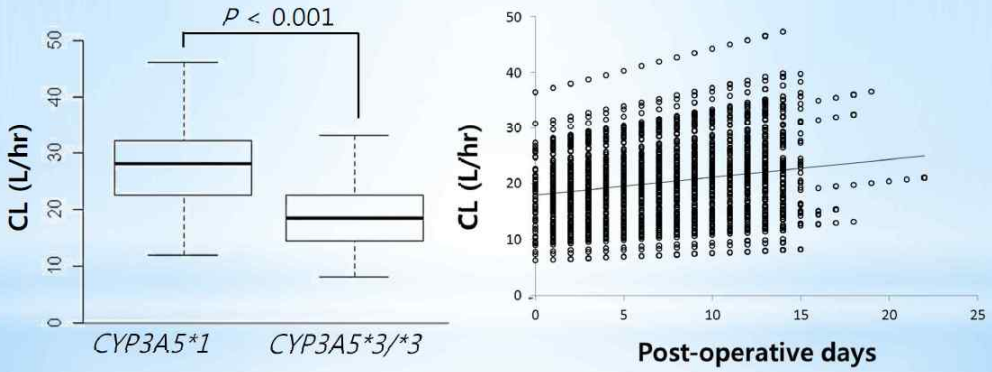
Results

* Visual predictive check (n=200)



Results

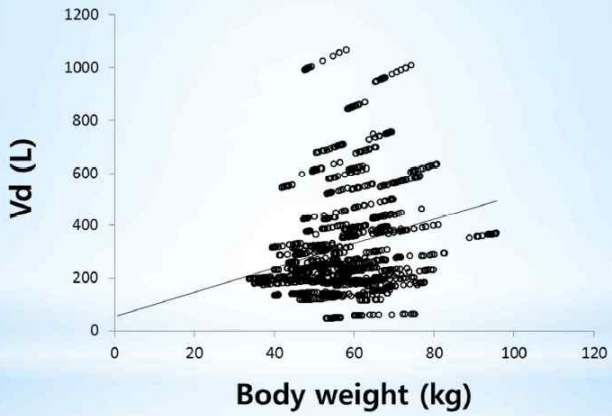
*Covariate evaluation



P < 0.001

Results

*Covariate evaluation



P < 0.001

Discussion

* The population estimated values of *CL/F*, *V/F*, and k_a were closed to those reported in other studies which also carried out population PK analyses on kidney transplant recipients.

* Numerous studies have shown that patients with *CYP3A5*3/*3* genotype have higher blood tacrolimus concentrations than those with the *CYP3A5*1*. However, *ABCB1* genotypes were found to have no effect on the PK parameters of tacrolimus.

* Many studies have demonstrated that *CL/F* increased with increasing number of post-operative days for the early days after transplantation.

* Other concomitant drugs, such as MMF and corticosteroids did not seem to have an influence on the PK of tacrolimus in this study.

Conclusion

* This study is to investigate the population PK of tacrolimus in Korean kidney transplants while both clinical and genetic factors as covariates.

* The *CYP3A5* genotype and post-operation days were identified as the main covariates that influence *CL/F* and body weight was found to have a significant effect on *V/F*.

* This tacrolimus population PK model will be a valuable tool in developing rational guidelines and provides a basis for individualized therapy after kidney transplantation.

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  - Soo Jung Ha, B.S.
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2001-2005 Research and teaching assistant, Department of Pharmacology, Seoul National University
2005-2008 Chief, Department of aerospace medicine, Aerospace Medical Center, ROKAF
2008-2009 Full time Lecturer, Department of Pharmacology, Yonsei University College of Medicine
2009-2012.2 Assistant Professor, Department of Pharmacology and Clinical Pharmacology, Yonsei University College of Medicine and Severance Hospital
2012.3~present Assistant Professor, Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital

▌Recent Publications▐

Oh ES, Lee SH, Park MS, Park K, Chung JY. Modeling of the LDL cholesterol-lowering effect of atorvastatin in Korean dyslipidemic patients and non-patient volunteers. Int J Clin Pharmacol Ther. 2012 Sep;50(9):647-56.

Cho SK, Oh ES, Park K, Park MS, Chung JY. The UGT1A3*2 polymorphism affects atorvastatin lactonization and lipid-lowering effect in healthy volunteers. Pharmacogenet Genomics. 2012 Aug;22(8):598-605. .

Kim CO, Cho SK, Oh ES, Park MS, Chung JY. Influence of ABCC2, SLCO1B1, and ABCG2 polymorphisms on the pharmacokinetics of olmesartan. J Cardiovasc Pharmacol. 2012 Jul;60(1):49-54.

Chung JY, Cho SK, Oh ES, Lee DH, Lim LA, Jang SB, Lee YJ, Park K, Park MS. Effect of HMGCR Variant Alleles on Low-Density Lipoprotein Cholesterol-Lowering Response to Atorvastatin in Healthy Korean Subjects. J Clin Pharmacol. 2012 Mar;52(3):339-46.

Cho SK, Yoon JS, Lee MG, Lee DH, Lim LA, Park K, Park MS, Chung JY. Rifampin Enhances the Glucose-Lowering Effect of Metformin and Increases OCT1 mRNA Levels in Healthy Participants. Clin Pharmacol Ther. 2011 Mar;89(3):416-21

Pharmacometrics research and application in the hospital setting

Jae Yong Chung, MD, PhD.

Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine
Clinical Trial Center, Seoul National University Bundang Hospital

The concept of modeling and simulation is not only useful in the drug development process but in the patient care and academic research. A range of pharmacometric approaches and tools to the care of patients in a wide variety of clinical settings including pediatrics, a population perhaps most in need of a careful approach to therapeutic drug use are now being applied. Core Function of Pharmacometrician in university hospital is mainly focusing on developing translational research methodology and teaching new students. There are several pharmacometrics cores in the hospital setting. For example, Kinetic Modeling and Simulation in Univ. Penn is at the forefront of bringing pharmacometrics to the bedside, with web-based “Dashboard” interface between clinicians, the electronic medical record, and sophisticated modeling. Some cases and experiences of academic research in the hospital setting using pharmacometrics approach will be shared. Multidisciplinary approach is necessary to achieve model based individual therapy in the patient care, dose optimization, personalized medicine and “therapeutic drug management”.

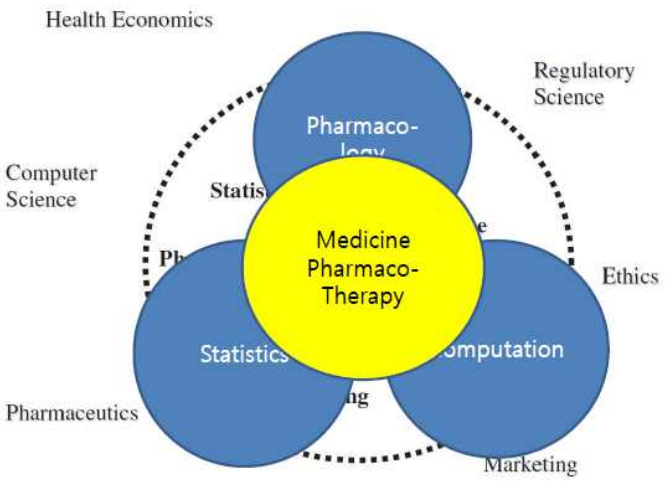
PAGK Annual Meeting, 6 Dec 2012

Pharmacometrics Research & Application in Hospital Setting

Jae Yong Chung

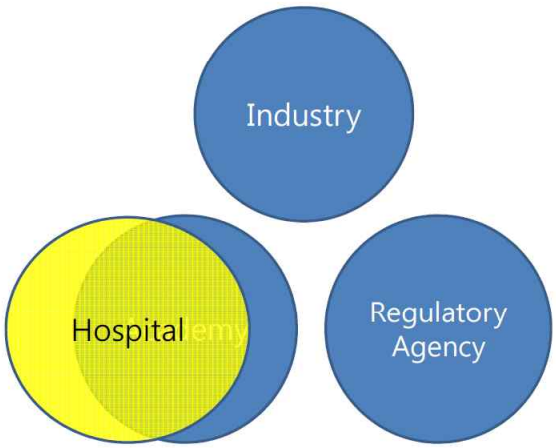
Seoul National University Bundang Hospital

Multidisciplinary influence on the field of PMx



J Clin Pharmacol 2008;48:632-649

Multi-professional Area



Core Function of Pharmacometrician in Academia

핵심역할	Impact	Collaborations
• Support/consult industry applications • Translational research • Methodology/IT • Developmental population PK/PD • Teaching new students	• **New biomarkers/endpoint** • **Disease process/progression** • **New tools** • **More trained Pmxians**	• Pmxian across institutions • Grant team members • Statisticians, programmers • Neonatologists, • Pharmacologists

J Clin Pharmacol 2008;48:632-649

SWOT 분석: 의약학계열 학생

Strengths	Weaknesses	Opportunities	Threats
Foundation in math, chemistry, physics, biology Principles of drug action, pharmacology, and biochemistry Anatomy and physiology Applied PK and PK/PD, and therapeutics Appreciation for drug delivery and input in general	Little experimentation No programming Only basic statistics understanding	Math electives easily accommodated as necessary Statistics, study design, programming, and simulation courses would fit well into existing curriculum	Competition for students by high-paying pharmacy jobs Often sparse funding opportunities

J Clin Pharmacol 2008;48:632-649

Hospital Setting 사례

- Pediatric hospitals: a setting and patient population perhaps most in need of a careful approach to therapeutic drug use.

Pharmacometrics Infrastructure Core

KINETIC MODELING AND SIMULATION

Kinetic Modeling and Simulation (KMAS)
Crucial infrastructure and Partnering with Univ. Penn. and Children's Hospital of Philadelphia Clinical & Translational Science Award (CTSA).
Director: Jeffrey S. Barrett, PhD is at the forefront of bringing pharmacometrics to the bedside, with his web-based "Dashboard" interface between clinicians, the electronic medical record, and sophisticated modeling.

(a) Aid in the development of drug assays
(b) Promote and assist in the performance of tracer kinetic studies
(c) Develop novel approaches to kinetic data analysis
(d) Provide pharmacokinetic (PK), PK– pharmacodynamic (PD), and tracer kinetic modeling
(e) Develop educational modules in pharmacokinetics and tracer kinetics to populate the educational initiatives pursued within the CTSA.

Staff: 11 MD, 14 PhD (5 PharmD, PhD), 3 MS

Sander Vinks, PharmD, PhD

Roger Jeliffe, MD: Founder of LAPK, USC*PACK

Michael Neely, MD: Pediatric physician and clinical pharmacologist (pharmacometrician)

Hospital Setting의 장점

- 풍부환 환자 자료
- 임상과와 다양한 공동연구
- 약물치료 Consult 와 병행 (TDM)
- 임상시험 자료 분석 (Phase 1 Unit)
- 환자치료에 직접 적용 가능한 연구 주제
- Clinical (Hospital) Pharmacology & Pharmacy 의 역할 확장

Example of Research

POPPK of Clinical Data

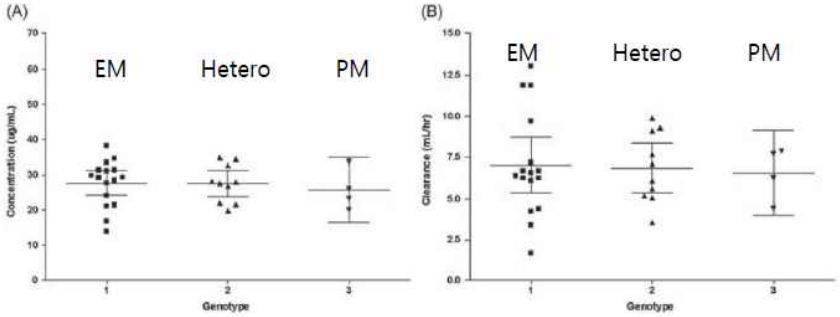
- Pharmacogenetics
  - Phenobarbital and CYP2C19
  - Theophylline and CYP1A2
- Aprotinin during cardiopulmonary bypass
- Vancomycin and Cystatin C

Phenobarbital PK in Neonates

- PB metabolism was affected by CYP2C19 polymorphisms in adults requiring dose adjustment.
- **Objective:** To evaluate the effect of CYP2C19 genetic polymorphisms on PB PK in neonates and infants with seizures.
- **Patients:** 52 neonates and infants (TDM data)
- **Covariates:** BWT, AGE, PB daily dose, CYP2C19 genotypes, laboratory findings

*Lee and Chung et al. Arch Dis Child 2012;**97:569–572***

Phenobarbital PK in Neonates



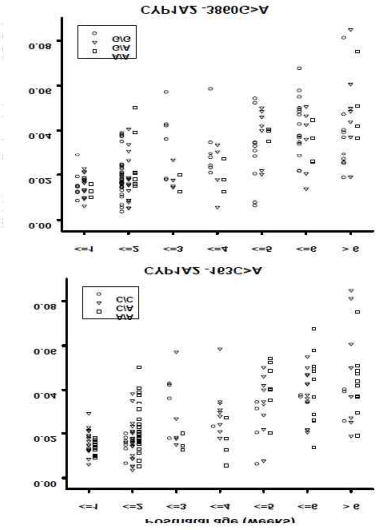
Final model

One Compartment IV bolus Model
No significant effect of Genotypes
Vd (ml)=3590×(BWT/4)$^{0.766}$×(AGE/2)$^{0.283}$ (CV=31.1%);
CL (ml/h)=32.6×(BWT/4)$^{1.21}$ (CV=27.0%).

Lee and Chung et al. Arch Dis Child 2012;97:569–572

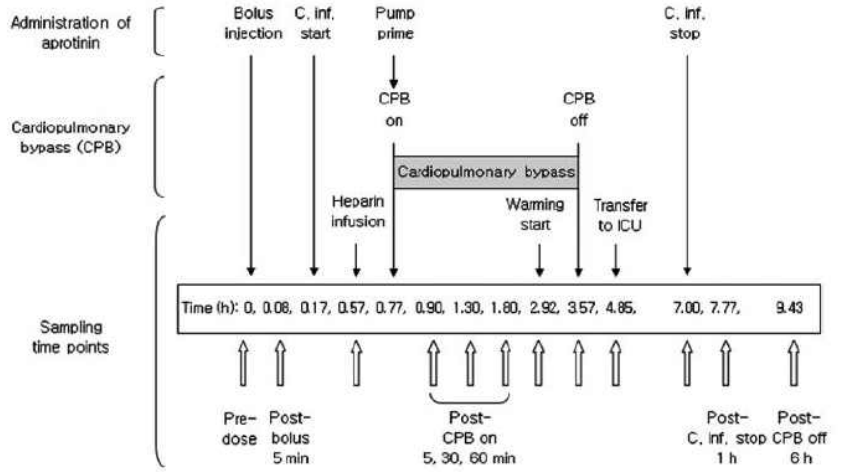
Theophylline PK & CYP1A2

- **Patients**
  - 100 premature infants in NICU
  - <37 weeks in gestational age
- **Covariates**
  - oxygen support, sex, delivery mode, CYP1A2 genotypes, GA, postnatal age (PNA), postconceptional age (GA+PNA), weight (BW), height, BUN, creatinine, AST, and ALT
- **Final Model**
  - One-compartment model with rapid absorption and first-order elimination
  - No effect of CYP1A2 genotypes
  - **CL (L•h^{-1}) = 0.00492 * (BW)$^{3.53}$ + 0.00646 * (PNA)**
  - **Vd (L) = 1.53 * (BW)**



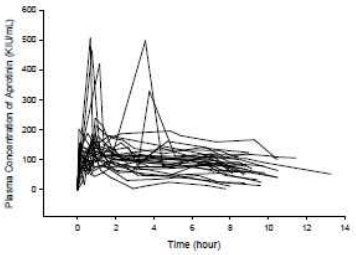
Slide Courtesy of Bo-Hyung Kim, Ther Drug Monitor in 2nd Revision

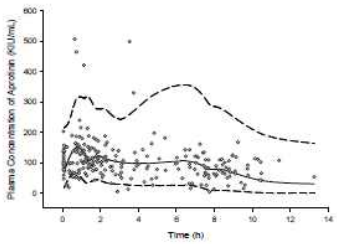
Aprotinin Pop PK Study



Slide Courtesy of Bo-Hyung Kim,
Tae et al. J Clin Pharmacol. 2011;51(8):1163-76

Aprotinin Pop PK Study





Visual predictive check for the final model with a full data set of the 27 patients

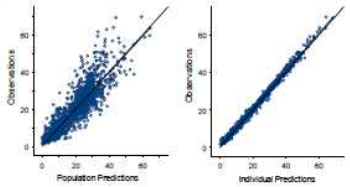
Final Model

- Two compartment model + CPB effect on CL/Vc + inter-occasion variability on CL/Vc
- Pre- & post-CPB; CL (mL/h) = **350**×exp(ηIIV+ηIOV)
- During CPB; CL (mL/h) = **687**×exp(ηIIV)

Slide Courtesy of Bo-Hyung Kim,
Tae et al. J Clin Pharmacol. 2011;51(8):1163-76

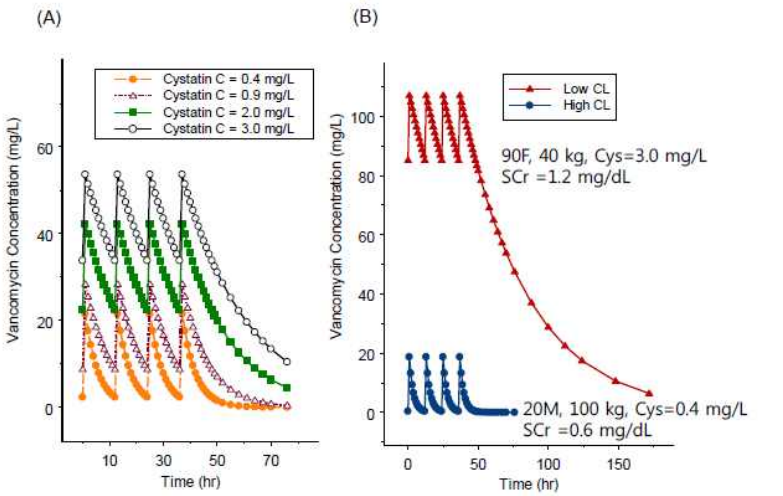
Vancomycin and Cystatin C

- 678 patients with normal serum Cr (<1.2 mg/dL): 1,373 concentrations (Peak & Trough)
- Final POP PK Model
  - One Compartment
  - $CL=4.9*(1+\theta_{CLage}*(age-57))*(1+\theta_{CLTBW}*(TBW-60.8))*(1+\theta_{CLSCr}*(SCr-0.8))*(Cystatin\ C/0.91)^{-0.78}$, (if female, apply 0.85)
  - $V=46.2*(1+\theta_{Vage}*(age-57))*(1+\theta_{VTBW}*(TBW-60.8))$, (if female, apply 0.88)



Chung JY and Song YG, JKMS Accepted

Predicted Vancomycin Concentrations

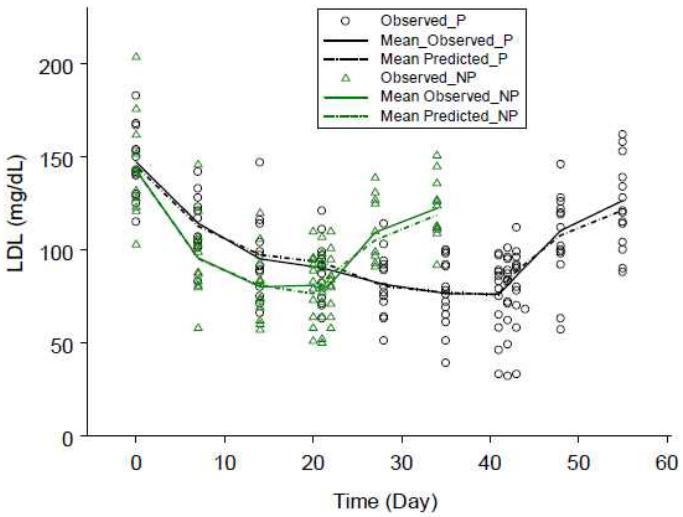


Chung JY and Song YG, JKMS Accepted

Prospectively Designed Clinical Study

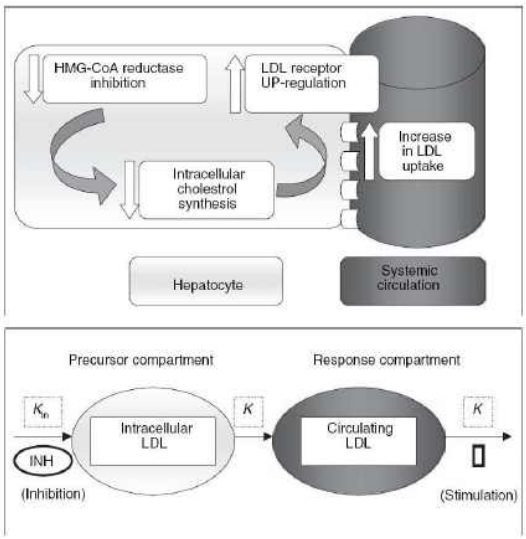
Modeling of LDL-C lowering effect of atorvastatin in Korean dyslipidemic patients and non-patients

LDL-C Profiles after Atorvastatin Tx in Korean dyslipidemic patients and non-patients



Oh ES et al. IJCPT. 2012;50(9):647-56

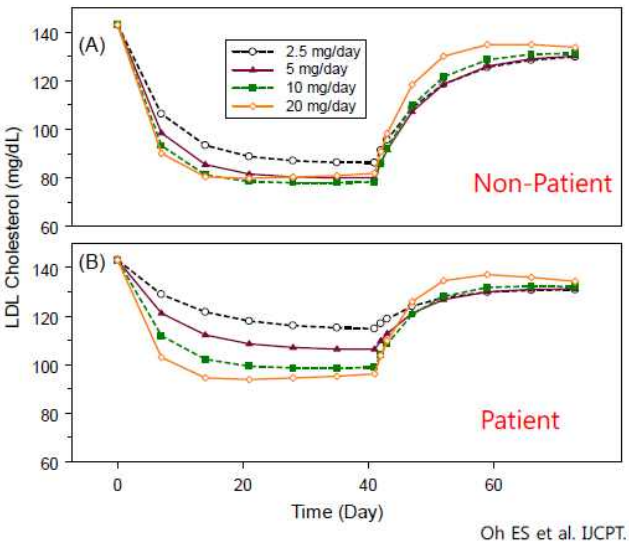
Model for Statin action



Parameters	Estimate
K_{in} (g/L/day)	0.15
K_{out} (day^{-1})	0.105
INH	0.09
SD50 patient (mg)	11.9
SD50 non-pat.(mg)	2.0
ISV (K_{in})	0.016
ISV (SD50)	0.98

Fundamental & Clinical Pharmacology 20 (2006) 321–330

Simulation for LDL response: 6-week treatment

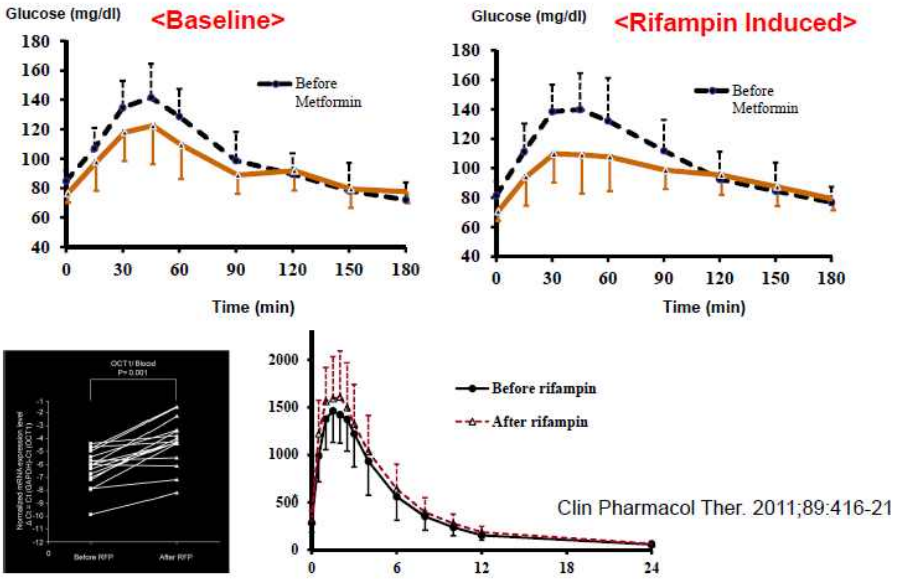


Oh ES et al. IJCPT. 2012;50(9):647-56

PK Modeling for the Exploration of
Drug Interaction Mechanism

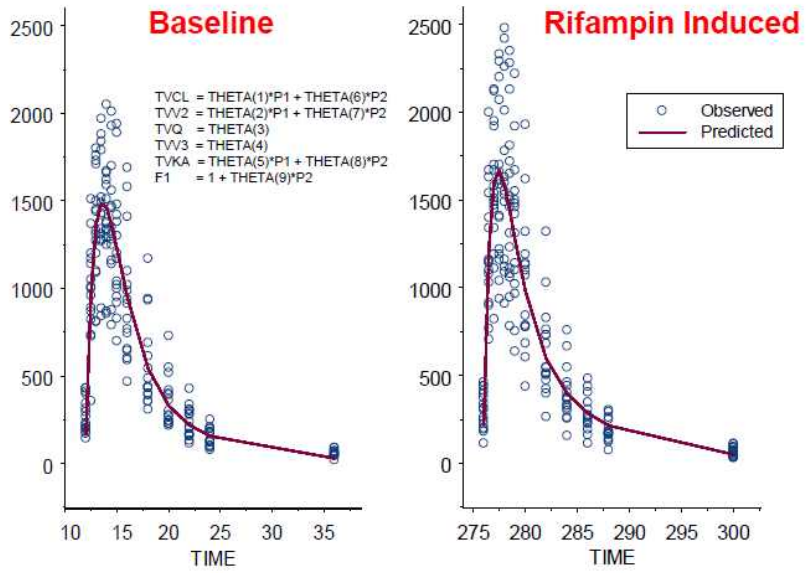
Metformin and Rifampin

Rifampin Enhanced Glucose Lowering of Metformin

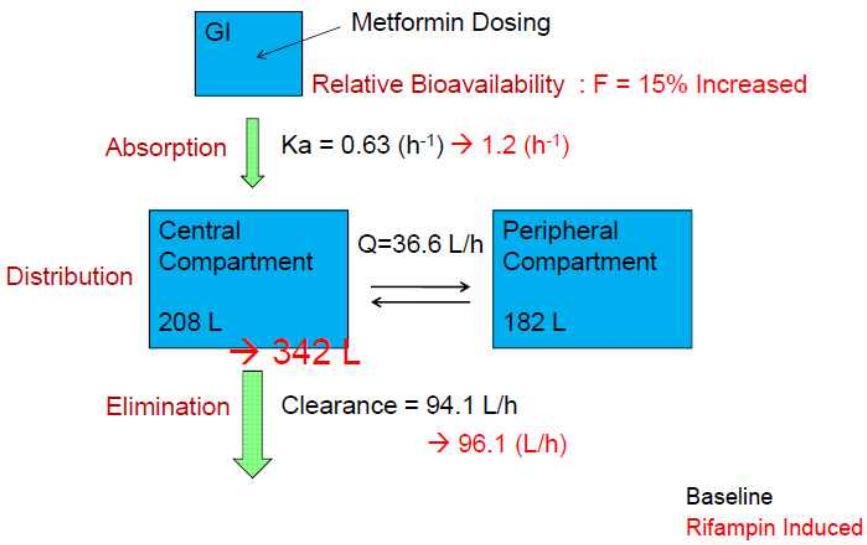


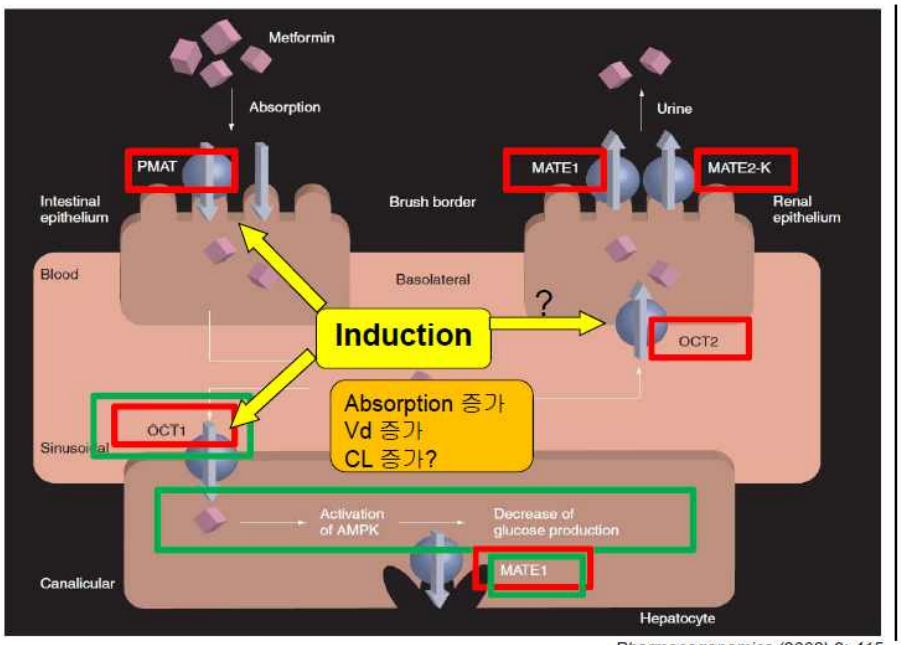
Clin Pharmacol Ther. 2011;89:416-21

Compartmental Modeling Analysis



Compartmental PK Modeling Analysis

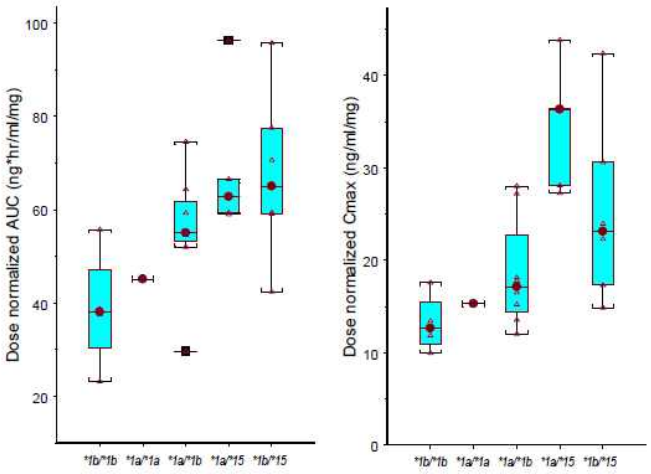




Pharmacogenomics (2008) 9: 415

Supplementary

Effect of *OATP1B1* (*SLCO1B1*) variant alleles on the pharmacokinetics of pitavastatin



Chung et al. Clin Pharmacol Ther 2005;78:342–50.

Supplementary

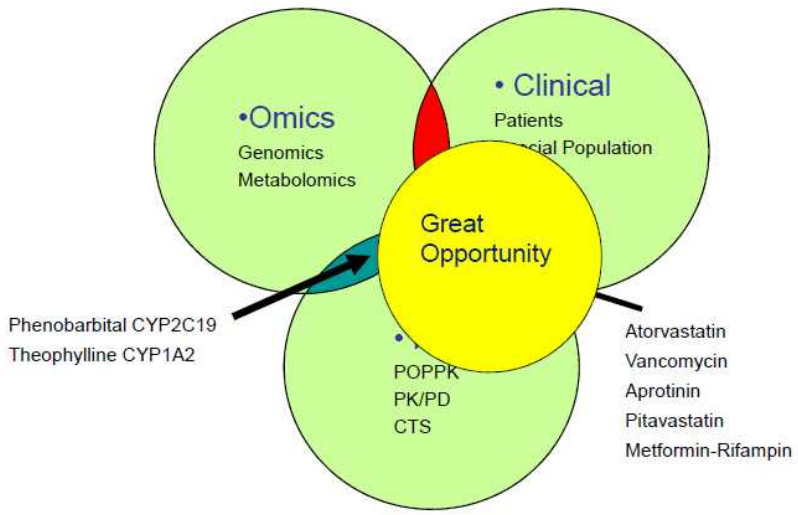
PK Parameter modeling

- $PKPAR = Q1 \cdot THETA_{*1a} + Q2 \cdot THETA_{*1b} + Q3 \cdot THETA_{*15}$
  - Sum of two partial THETA(CL) of the three alleles (THETA*1a, THETA*1b, and THETA*15)
  - Calculated the quantitative proportional contribution to pharmacokinetic parameter by each alleles using NONMEM

Supplementary

Estimated allele specific pharmacokinetic parameter

Allele specific Clearance	Mean CL/F estimate (ml/hr)	SE† of estimation
$THETA_{*1b}$	12.5	1.3
$THETA_{*1a}$	9.3	1.4
$THETA_{*15}$	4.3	1.5
Genotype specific Clearance		
*OATP-C*1b/*1b*	**25.0**	
*OATP-C*1a/*1b*	21.8	
*OATP-C*1a/*1a*	18.6	
*OATP-C*1b/*15*	16.8	
*OATP-C*1a/*15*	13.6	
*OATP-C*15/*15*	**8.6**	



Perspectives

- 임상자료 모델링&시뮬레이션 영역 지속적 확장
- Multidisciplinary Approach
  - Pharmacometrics Core Network with Clinical Departments
- Model based Individual Therapy : Therapeutic Drug Management

Acknowledgements

SNUH 서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

- Dept. of Clinical Pharmacology & Therapeutics
  - Bo Hyung Kim
  - Yoo Mi Tae
  - Sung Eun Kim
  - Pf. Kyoung Soo Lim
  - Pf. Kyung Sang Yu
  - Pf. In Jin Jang

연세대학교 의료원 YONSEI UNIVERSITY HEALTH SYSTEM

- Dept. of Clinical Pharmacology
  - Pf. Eun Sil Oh
  - Pf. Kyungsoo Park
  - Sung Kweon Cho
- Dept. of Internal Medicine Gangnam Hospital
  - Pf. Yong Goo Song
- Dept. of Pediatrics
  - Pf. Min Soo Park
  - Pf. Soon Min Lee

CURRICULUM VITAE

성 명 : 김 용 호

소 속 : G S K

Dr. Joseph (Yong Ho) Kim is a director of Clinical Pharmacology Modeling Simulation Group in Quantitative Sciences at GlaxoSmithKline Research & Development Center in Research Triangle Park, NC from 2002 by joining Clinical Pharmacokinetic Modeling and Simulations Group. Before joining the company, he was a consulting scientist and support specialist at Pharsight Inc. in Cary, North Carolina. He got his PhD in Pharmaceutical Science from the University of the Pacific in Stockton, California on Population PK of HIV drugs in children and adolescents with advanced HIV disease. He holds a B.S. degree in Pharmacy from Kyung Hee University and an M.S. degree in Clinical Pharmacy from the same university.

Dr. Kim holds pharmacist licenses from Korea and California and had practiced as a clinical pharmacist in both countries. He is a contributor of two chapters of a book titled Pharmacometrics: the Science of Quantitative Pharmacology, E. Ette and P. Williams (eds.), John Wiley & Sons, 2007. The book explains the science of pharmacometrics and its application to drug development, evaluation, and patient pharmacotherapy, providing a comprehensive set of tools for the training and development of pharmacometricians. Since 2006, Dr. Kim has served as an adjunct professor at the School of Pharmacy, University of North Carolina at Chapel Hill and advised a PhD student and taught advanced pharmacokinetics. He is a frequently invited speaker for many international meetings. Currently, he is residing in Shanghai, China as a global assignee to establish a Clinical Pharmacology Modeling Simulation Group in GSK China R&D and will return to USA in February 2013.

Working as a Pharmacometrician in US/UK/EU – what are they looking for? Hiring manager's perspective

Joseph Kim, PhD, RPh

Director, Clinical Pharmacology Modeling and Simulation, R&D GlaxoSmithKline, Research Triangle Park, USA

Pharmacometrics can be defined as the study of mathematical models of biology, pharmacology, disease and physiology used to describe and quantify interactions between xenobiotics and patients including beneficial effects and side-effects resultant from such interfaces1. Since the publication of FDA Guidance of Population PK in 1999, the demand for pharmacometrician has increased dramatically. This semina will first overview the current status of pharmacometrician in academia, industry and regulatory environments. The focus will be on industry pharmacometrician in US/UK/EU for their roles/functions, qualifications, salaries and experiences. In addition, the recruiting processes of drug industry for pharmacometrian will be discussed in detail so that the audience can understand the interview processes and prepare job interview if they need one. In additon, the prospects of the field will also be discussed.

1. http://www.med.upenn.edu/kmas/

Working as a Pharmacometrician in US/UK/EU – what are they looking for? Hiring manager's perspective

Joseph Kim, PhD,RPh
Director
Clinical Pharmcology Modeling & Simulation
R&D China

Agenda

- Current situation
- Future
- What do I need do/know?

Current Situation

Distribution of Pharmacometrician

	Response Percent	Response Count
Small PhRMA	6.3%	13
Medium PhRMA	16.9%	35
Big PhRMA	**31.4%**	**65**
Generics	0.0%	0
Regulatory Agency	1.0%	2
CRO	9.2%	19
Consultant	7.3%	15
Academic Institution	23.7%	49
Research Hospital	4.4%	9
	Name of Company / Institution	78
	answered question	**207**
	skipped question	**2**

Based on survey completed in 2007 from NMUsers listserve
(http://www.med.upenn.edu/kmas/). Also found in Barrett et.al. *J Clin Pharmacol 2008 48: 632*

Role of Pharmacometrician

	Response Percent	Response Count
Pharmacometrics	58.2%	114
Drug Metabolism & Pharmacokinetics	13.3%	26
Clinical Pharmacology	25.5%	50
Biostatistics	3.1%	6
Other (please specify)		20
answered question		196
skipped question		13

Based on survey completed in 2007 from NMUsers listserve (http://www.med.upenn.edu/kmas/). Also found in Barrett et.al. *J Clin Pharmacol 2008 48: 632*

Background of Pharmacometrician

	Response Percent	Response Count
Pharmaceutics	41.8%	84
Statistics / Biostatistics	21.4%	43
Pharmacy	42.8%	86
Engineering	11.4%	23
Medicine	6.0%	12
Pharmacology	31.8%	64
Business (Marketing/Operations)	0.5%	1
Other (please specify)		20
answered question		201
skipped question		8

Based on survey completed in 2007 from NMUsers listserve (http://www.med.upenn.edu/kmas/). Also found in Barrett et.al. *J Clin Pharmacol 2008 48: 632*

Highest Degree of Pharmacometrician

	Response Percent	Response Count
BS	1.0%	2
MS	17.2%	36
MD	3.8%	8
MBA	0.5%	1
PharmD	9.1%	19
PhD	68.4%	143
answered question		209
skipped question		0

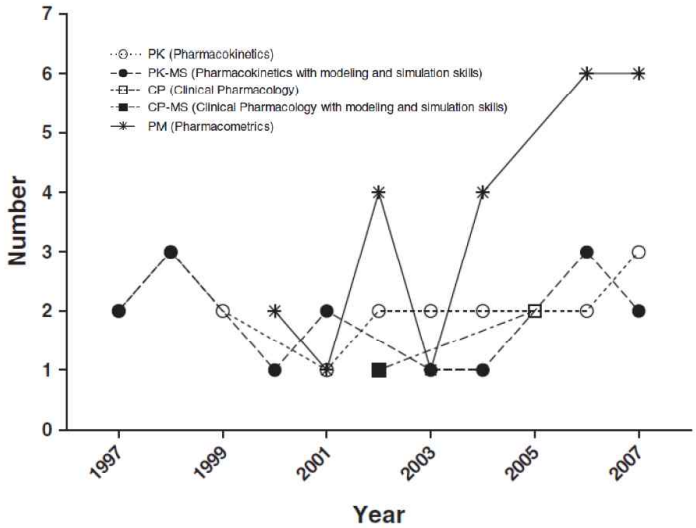
Based on survey completed in 2007 from NMUsers listserve (http://www.med.upenn.edu/kmas/). Also found in Barrett et.al. *J Clin Pharmacol 2008 48: 632*

Source of Pharmacometrics Training

	Response Percent	Response Count
Self-taught	28.0%	58
On the job experience	43.5%	90
Some level of relevant training in school plus experience	56.0%	116
Trained at institution with reputation for pharmacometrics	32.4%	67
answered question		207
skipped question		2

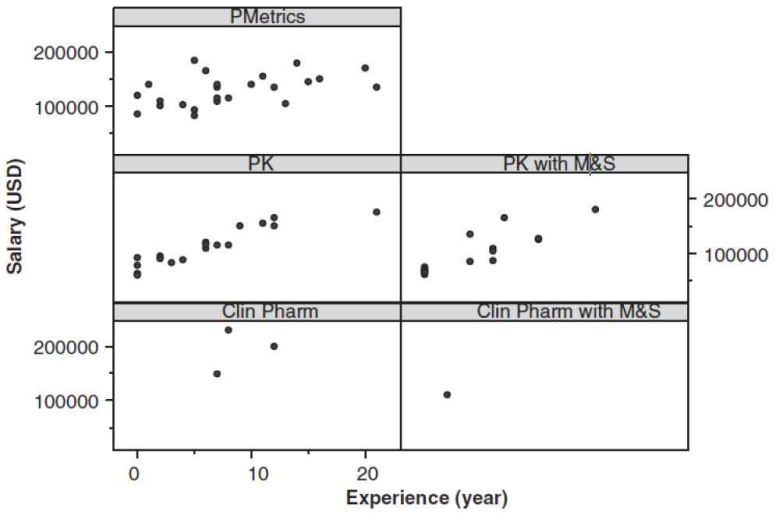
Based on survey completed in 2007 from NMUsers listserve (http://www.med.upenn.edu/kmas/). Also found in Barrett et.al. *J Clin Pharmacol 2008 48: 632*

Hiring trends for CPMS candidates placed between 1997 and 2007



Based on 61 new hires from a recruiting company. Barrett et.al. *J Clin Pharmacol 2008 48: 632*

Starting salary versus years of experience for CPMS candidates placed between 1997 and 2007

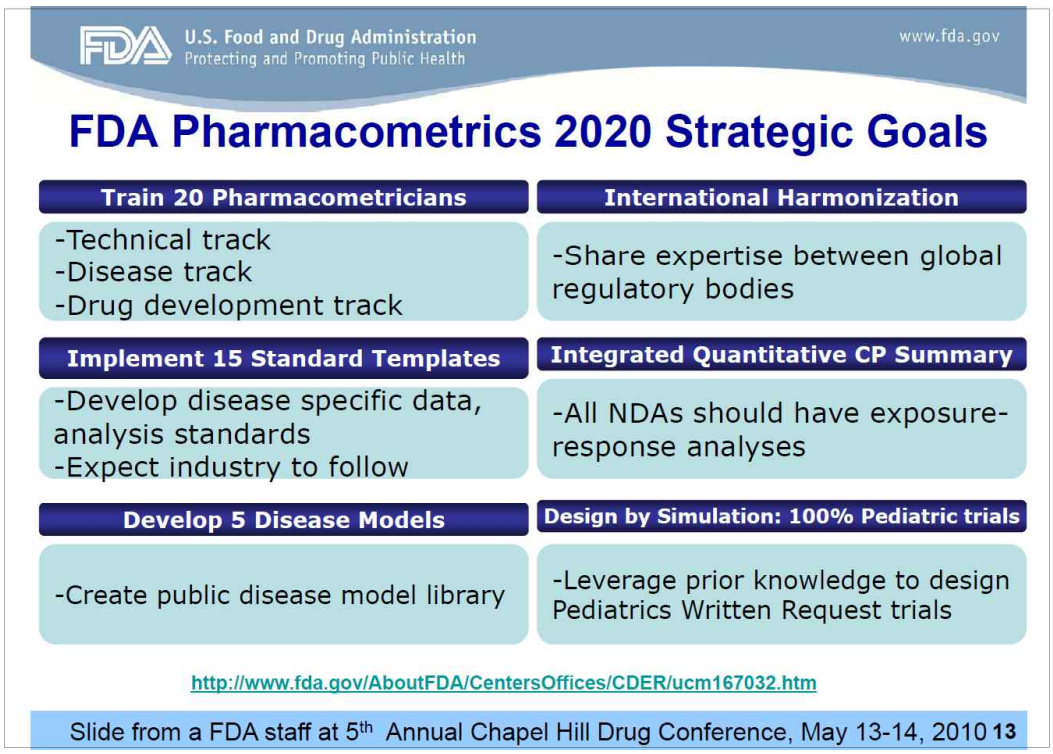


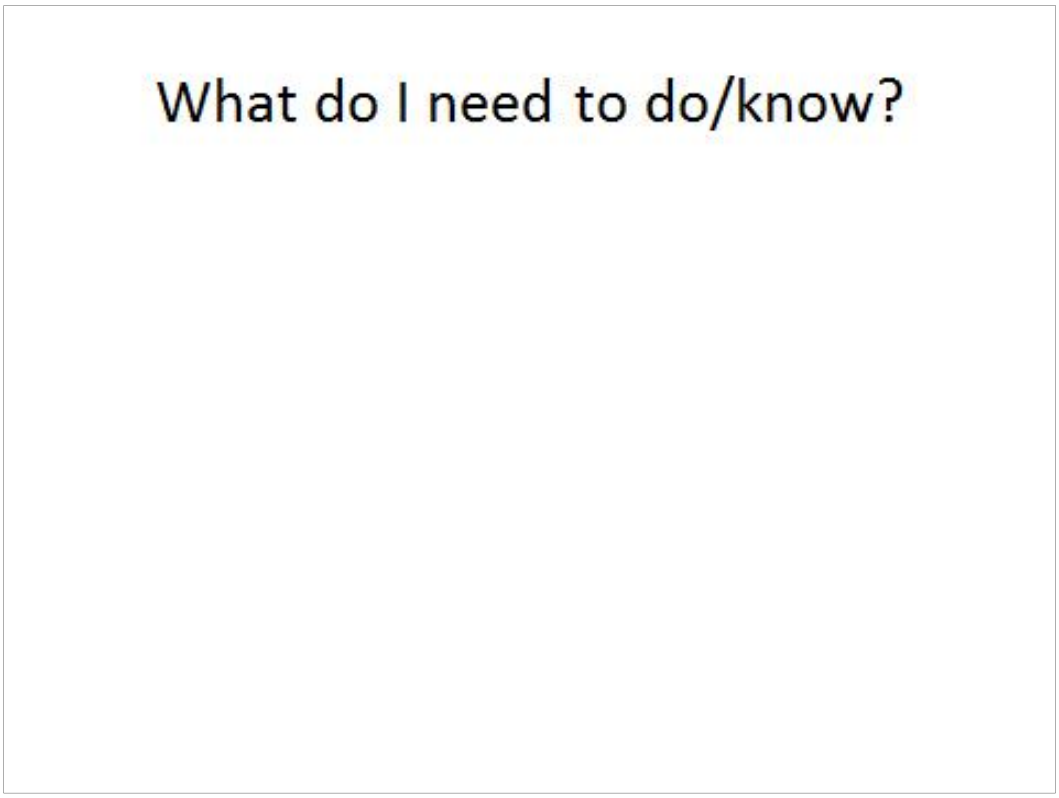
Based on 61 new hires from a recruiting company. Barrett et.al. *J Clin Pharmacol 2008 48: 632*

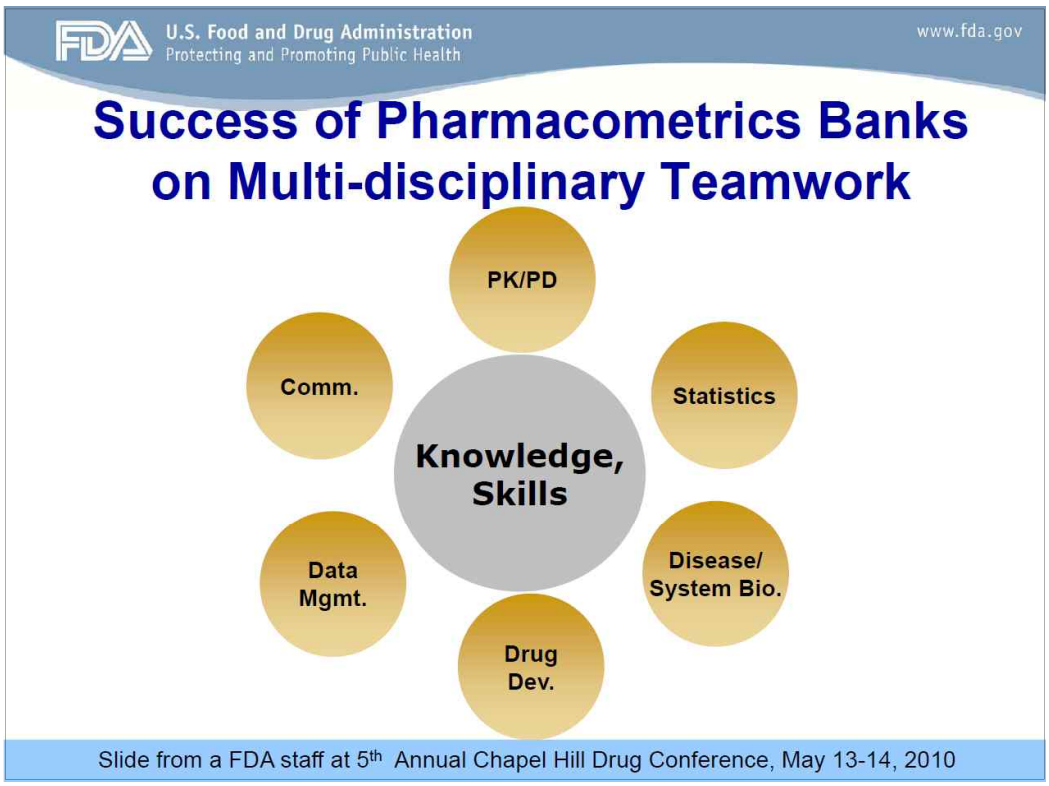
Future

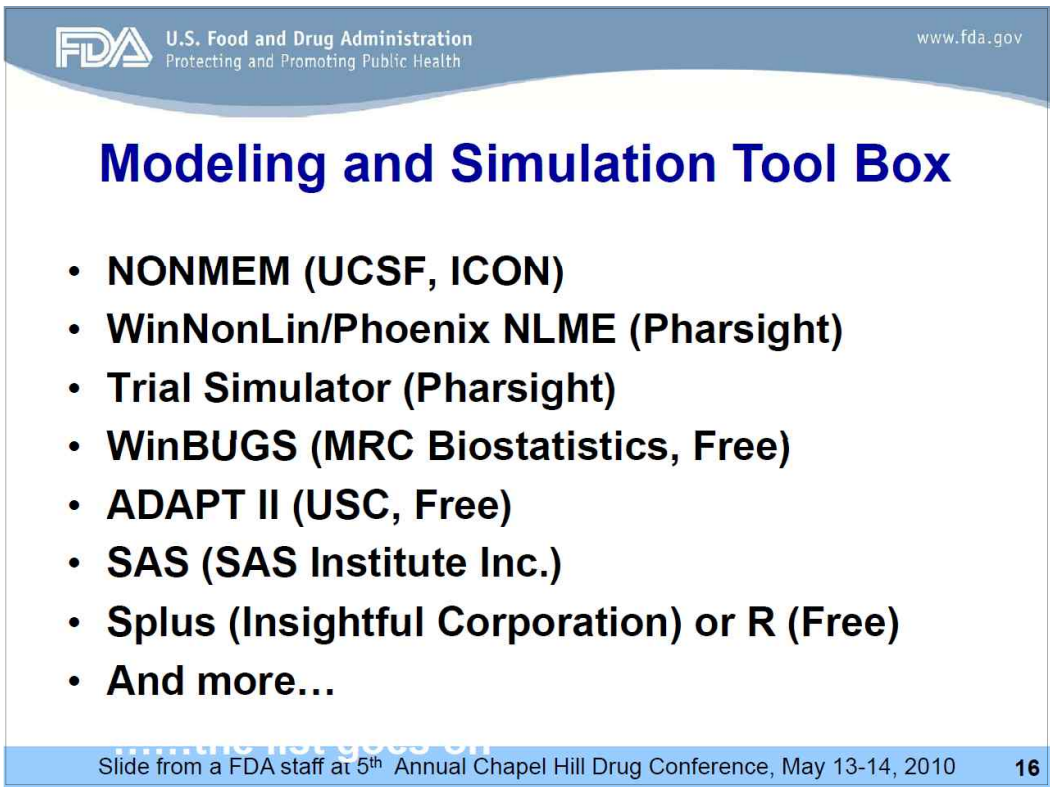
Markets

- Demand will be high
- Supply of pharmacometrician is increasing
- Employers are expecting more from candidates
  - Skills
  - experience


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
FDA Pharmacometrics 2020 Strategic Goals
Train 20 Pharmacometricians
-Technical track
-Disease track
-Drug development track
International Harmonization
-Share expertise between global regulatory bodies
Implement 15 Standard Templates
-Develop disease specific data, analysis standards
-Expect industry to follow
Integrated Quantitative CP Summary
-All NDAs should have exposure-response analyses
Develop 5 Disease Models
-Create public disease model library
Design by Simulation: 100% Pediatric trials
-Leverage prior knowledge to design Pediatrics Written Request trials
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm167032.htm
Slide from a FDA staff at 5th Annual Chapel Hill Drug Conference, May 13-14, 2010
13


What do I need to do/know?


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Success of Pharmacometrics Banks on Multi-disciplinary Teamwork
PK/PD
Comm.
Statistics
Knowledge, Skills
Data Mgmt.
Disease/ System Bio.
Drug Dev.
Slide from a FDA staff at 5th Annual Chapel Hill Drug Conference, May 13-14, 2010


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Modeling and Simulation Tool Box
• NONMEM (UCSF, ICON)
• WinNonLin/Phoenix NLME (Pharsight)
• Trial Simulator (Pharsight)
• WinBUGS (MRC Biostatistics, Free)
• ADAPT II (USC, Free)
• SAS (SAS Institute Inc.)
• Splus (Insightful Corporation) or R (Free)
• And more…
……the list goes on
Slide from a FDA staff at 5th Annual Chapel Hill Drug Conference, May 13-14, 2010
16

Recruiting processes

- Job posting (internal)
- External Announcement
- Phone interview (selected candidates)
- Reference check
- Face to face interview
- Decision to offer
- Offer acceptance

Summary

- Korean Pharma and Regulatory agency need (more) pharmacometricians to be successful in drug R&D
- Academia trained pharmacometricians need industry experience
- Need to go out and get experience from outside of country or create an environment within country to have collaborative effort on gaining experience

집단 약동/약력학 연구회 PAGK 회칙

제정 2006년 3월 17일

개정 2011년 5월 20일

제 1조(명칭)

본회는 집단 약동/약력학 연구회 (Population Approach Group in Korea; PAGK) 라고 한다.

제 2조(목적)

본회는 집단 약동/약력학을 통해 최적의 맞춤 약물요법과 효율적이고 과학적인 신약개발의 방법론을 발전시킴을 목적으로 한다.

제 3조(소속)

본회는 대한임상약리학회 산하의 연구회로 한다.

제 4조(활동)

본회는 제2조의 목적을 달성하기 위하여 다음과 같은 활동을 수행한다.

1) 학술집회의 개최
2) 집단 약동/약력학 워크숍의 개최와 교재 발간
3) 정부, 산업계 및 공공단체와 협동연구 및 사업
4) 국내외 집단 연구자들간의 학술 정보교환 및 공동연구
5) 기타 본회의 목적달성에 필요한 사항

제 5조(자격 및 구분)

본회의 회원은 다음과 같이 구분한다.

1) 개인회원은 본회의 목적에 찬동하는 임상약리학 또는 밀접히 관련된 학문분야를 전공한 개인으로 한다
2) 단체회원은 본회의 목적에 찬동하는 단체의 대표로 한다.
3) 특별회원은 본회의 목적과 사업에 찬동하여 이를 지원하는 자로 한다.

제 6조(취득)

본회의 회원 자격 취득은 소정의 원서를 제출하고 운영위원회의 승인을 얻어야 한다.

제 7조(권리와 의무)

회원은 회칙에 정한 바에 따라 운영위원 선출권과 담임권을 가지며, 회칙 및 본회의 결정사항을 준수하여야 한다.

제 8조(자격상실)

본회의 회원은 본회에서 정한 의무를 이행치 않은 경우 운영위원회의 결의로 회원의 자격을 상실한다

제 9조(운영위원회의 구성)

본회의 운영위원회는 회장 1명, 학술간사, 총무간사를 포함한 10명 이하의 운영위원, 1인의 감사로 구성한다.

제10조(선임)

회장과 감사는 총회에서 선출하며 운영위원은 회장이 추천하여 총회에서 인준한다.

제11조(임기)

운영위원의 임기는 1년으로 하며 연임할 수 있다. 단, 전임자의 유고로 인해 보선된 운영위원의 임기는 전임자의 잔여 임기로 한다.

제12조(운영위원의 직무)

1) 회장은 본회를 대표하여 회무를 총괄하고 총회, 운영위원회의 의장이 된다.

2) 학술간사와 총무간사는 회장을 보좌하며, 학술간사는 학술적 정책과 대외 업무에 관여하며 회장의 유고시 그 직무를 대행한다. 총무간사는 운영, 재무, 회원관리 등 대내적 업무에 관여한다.

3) 운영위원은 회장이 부의하는 제반 회무에 대하여 심의한다.

4) 감사는 본회의 회계 및 사업과 관련된 사항을 감사하고, 그 결과를 총회에 보고한다.

제13조(구분)

본회에는 총회 및 운영위원회를 둔다.

제14조(총회)

1) 총회는 출석회원으로 성립하며 운영위원의 선출 및 인준, 회칙개정 등 본회 운영에 필요한 주요사항을 의결한다.

2) 정기총회는 매년 1회 개최하며 임시총회는 회장이 필요에 따라 소집한다.

제15조(운영위원회)

1) 운영위원회는 총회에 부의하여 인준 또는 의결할 사항 등에 대하여 심의•의결한다.

2) 운영위원회는 본회의 제반 업무를 수행한다.

제16조(의결)

의결은 출석회원의 과반수로 한다.

제17조(회계년도)

본회의 회계년도는 매년 정기총회일에서 다음해 정기총회 전일까지로 한다.

제18조(재원)

본회의 재원은 입회비, 연회비, 특별회비, 찬조금, 수수료 및 기타 등으로 한다.

부칙

1) 본 회칙은 2006년 3월 17 일 창립총회에서 인준 받은 즉시 발효한다.
2) 본 개정회칙은 2011년 5월 20일부터 발효한다.
3) 본 회칙에 규정되지 않은 세칙은 일반관례에 준한다.

[MEMO]