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Prediction of within-subject variability using population approaches and its application to demonstrate highly variable drug

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PAGK Trainee session

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Contents

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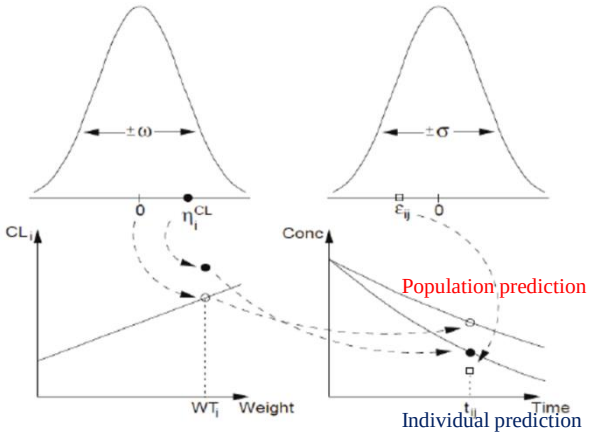
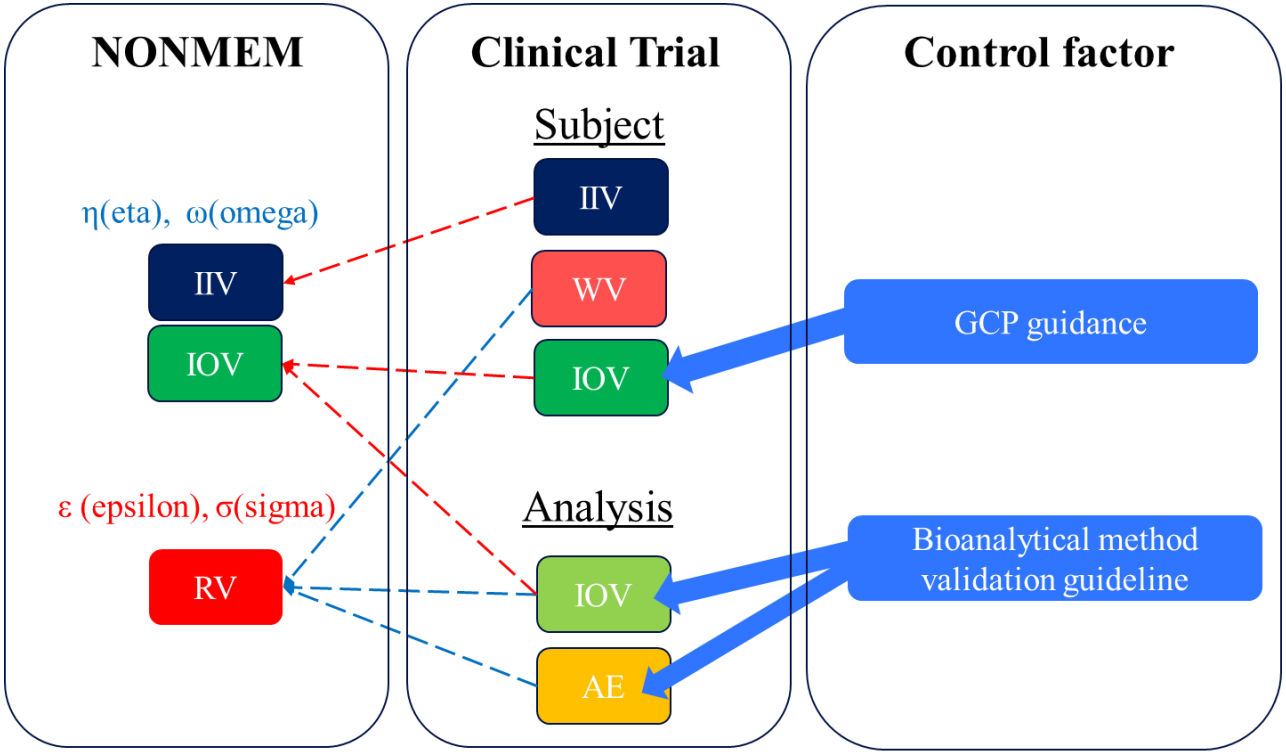
I. Background and Objective

Random effect in Pop PK data

- **Unexplained differences between individuals**
  - **Inter-individual variability, Between-subject variability, eta (η)**
  - **Intra-individual variability, Residual variability, epsilon (ε)**
  - **Inter-occasion variability**





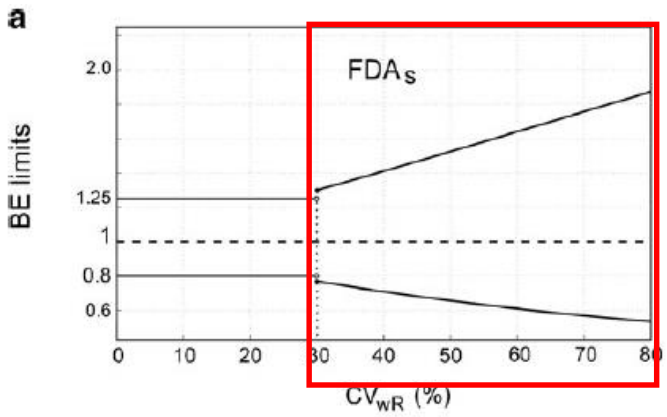
IIV : Inter-individual variability, IOV : Inter occasional variability, RV : Residual variability, WV : Within-subject variability, AE : Analytical error

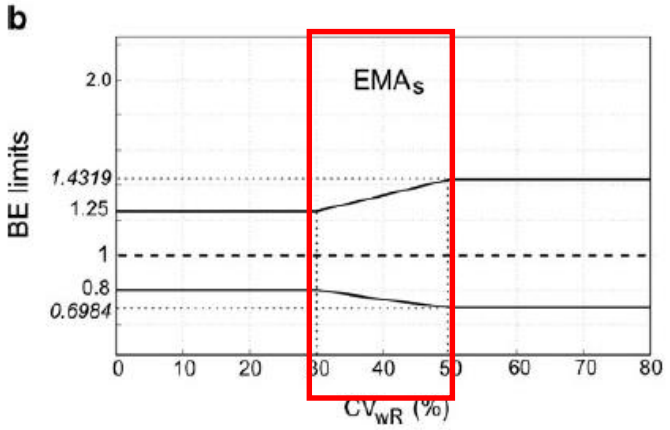
Background for highly variable drug

Definition of highly variable drug(HVD)

HVDs : drug products exhibiting within-subject variability of 30% (CV_W, coefficient of variation) or greater in the pharmacokinetic measures AUC and/or Cmax

Widening of BE limited based on reference variability _ FDA vs EMA





$$Upper/Lower\ limits = \exp\left(\pm\ln(1.25)\cdot\frac{s_{wR}}{s_{w0}}\right)$$

$$Upper/Lower\ BE\ limits = \exp\left(\pm k\cdot s_{wR}\right)$$

Vangelis Karalis et al. Bioequivalence of Highly Variable Drugs: A Comparison of the Newly Proposed Regulatory Approaches by FDA and EMA, Pharm Res (2012) 29:1066–1077

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Objectives

1. **Verification how well NONMEM can estimated residual variability through simulated population pharmacokinetic dataset under various condition**

2. **Confirmation that this population approach can be applied to the real highly variable drug case.**

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II. Method

Overall experiment scheme

A. Experiment 1 (5 different levels of WV(10%, 20%, 30%, 40%, and 50%) without IIV's change(0%)

Generating of simulation data sets using by R

1000 simulation data sets
- CL=10 L/hr, V=50 L
- AMT = 100 mg
- 12 sampling point
  = 0, 0.083, 0.167, 0.333, 0.5, 1, 2, 4, 6, 8, 12 & 24 hr
- Subject No. = 6, 12, 18, 24 & 30
- WV = 10, 20, 30, 40 & 50%
- IIV = 0%

PK Modeling execution using by NONMEM

I.V. PK model
- 1 compartment I.V. modeling
- Proportional error model
- FOCE with interaction estimation

Comparison RV with WV

Comparison two values
- WV established in R code
- RV estimated by NONMEM
- Success data for approximation of RV to WV

Overall experiment scheme _ Cont'd

B. Experiment 2 (5 different levels of WV(10%, 20%, 30%, 40%, and 50%) with IIV's change(10→50%)

Generating of simulation data sets using by R

1000 simulation data sets
- CL=10 L/hr, V=50 L
- AMT = 100 mg
- 12 sampling point
  = 0, 0.083, 0.167, 0.333, 0.5, 1, 2, 4, 6, 8, 12 & 24 hr
- Subject No. = 6, 12, 18, 24 & 30
- WV = 10, 20, 30, 40 & 50%
- IIV = 10, 20, 30, 40 & 50%

PK Modeling execution using by NONMEM

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Application for real case(e.g. eperisone)

Pharmacokinetic and bioequivalence study of sugar-coated and film-coated eperisone tablets in healthy subjects, Hyun-Ju Lee et al., International Journal of clinical pharmacology and therapeutics, Vol. 57, No1(55-62), 2019

R scaled approach

G/P	P1	P2	P3
A (N=12)	R	R	T
B (N=10)	R	T	R
C (N=11)	T	R	R

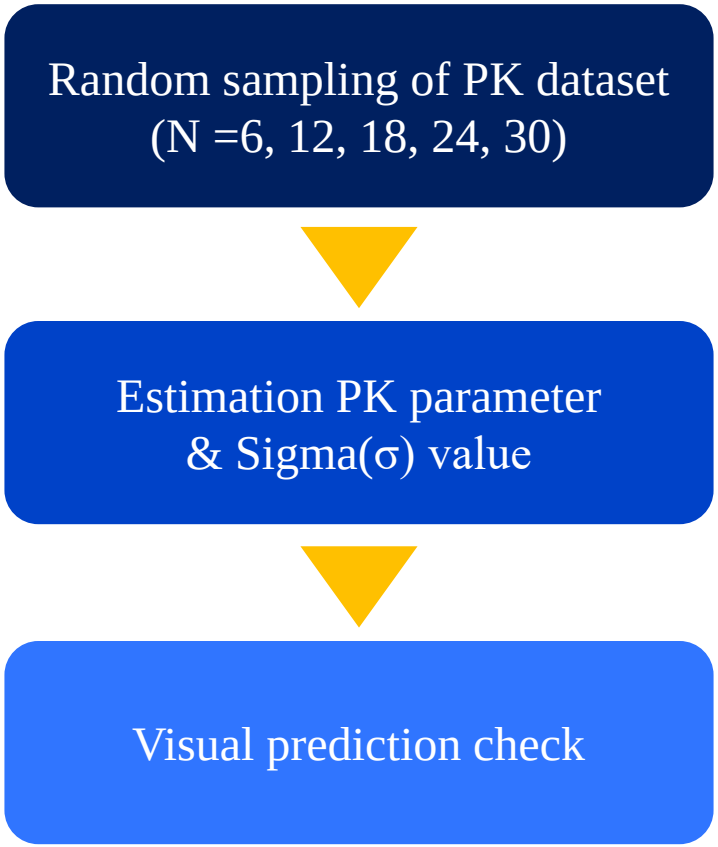
R : Murex® 50 mg, Cho Dang Pharm Co., Ltd
T : Eperex® 50 mg, Korea United Pharmaceutical Co., Ltd

Result : Geometric mean ratio, 90% confidential intervals and within subject variability for AUC_t and C_{max} using the EMA method

Parameters	GMR	90% CI	SwR	CVwR(%)	BE limit
AUCt	0.9836	0.8275 ~ 1.1692	0.332	33.17	0.8 ~ 1.25
Cmax	0.9402	0.7587 ~ 1.1652	0.474	50.21	0.6984 ~ 1.4319

Application for real case(e.g. eperisone) _ Cont'd

Work flow



Random sampling from reference drug's PK data

PK modeling : 1 compartment, oral absorption, first-order elimination

Model diagnostic

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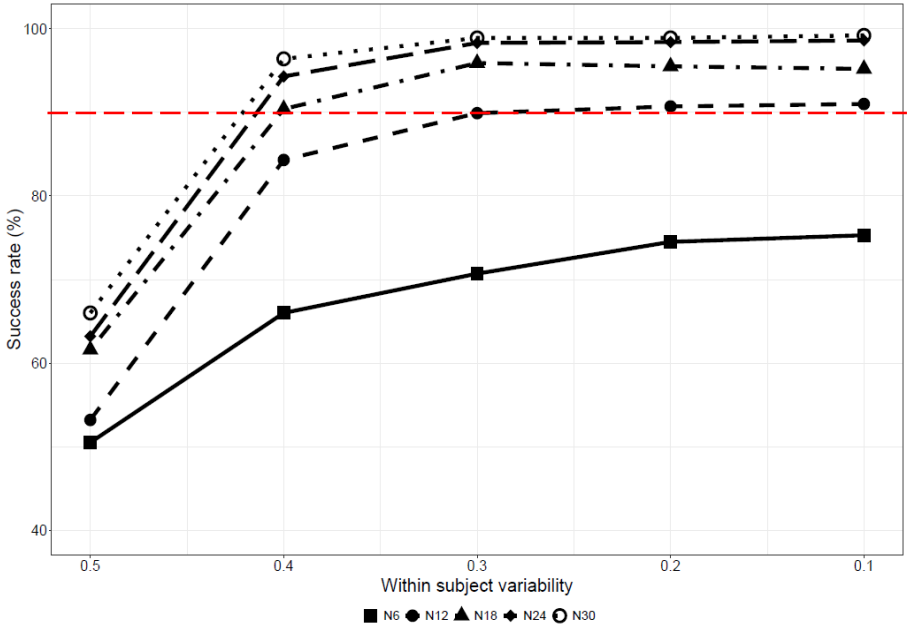
III. Results

Result for Experiment 1

(5 different levels of WV(10%, 20%, 30%, 40%, and 50%) without IIV's change(0%)

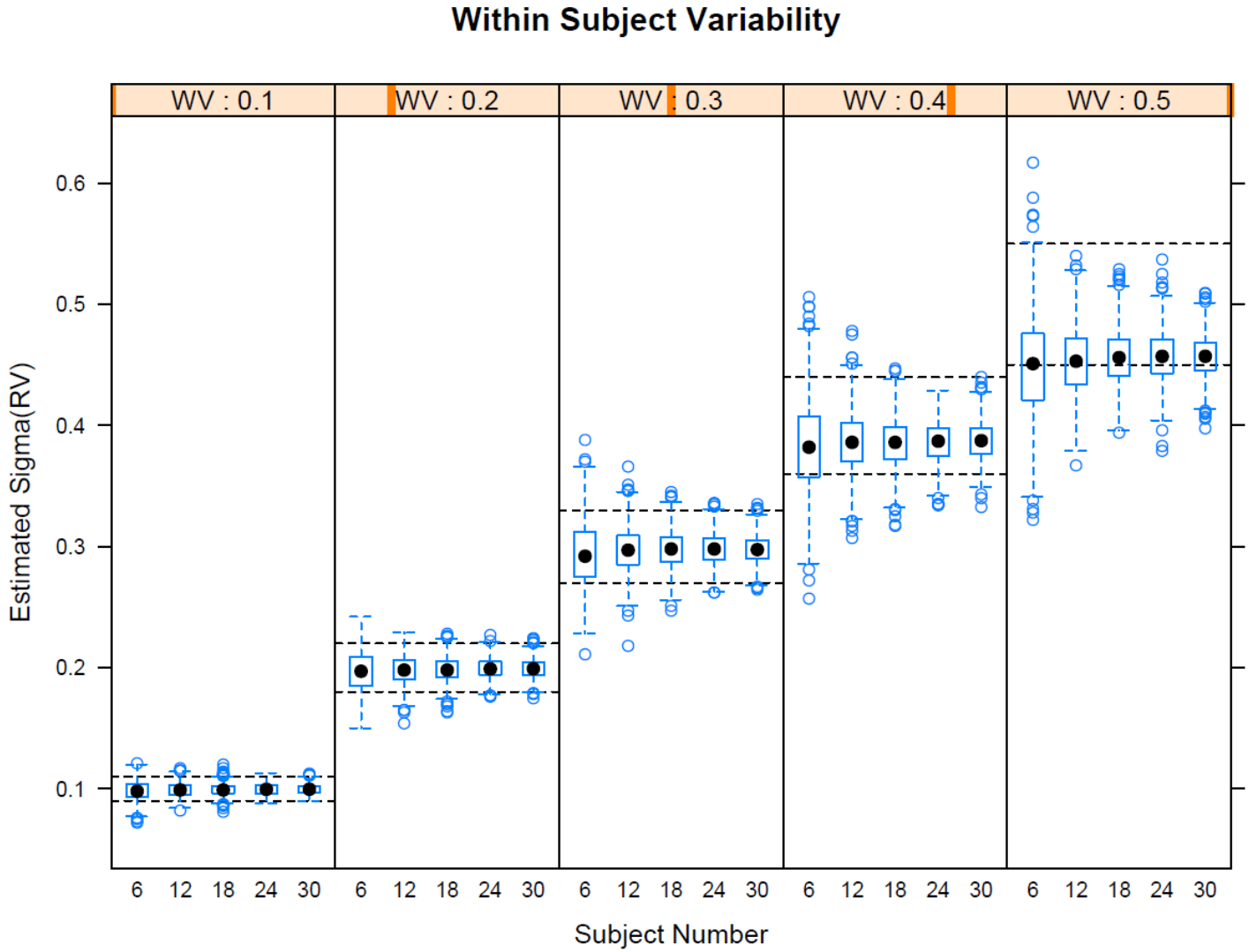
Setting WV(%)	Success rate(%)* for each subject number				
	N=6	N=12	N=18	N=24	N=30
10	75	**91**	**95**	**99**	**99**
20	75	**91**	**96**	**98**	**99**
30	71	**90**	**96**	**98**	**99**
40	66	84	**90**	**94**	**96**
50	51	53	62	63	66

Tabulated summary for results of first experiment
*Success rate at which to estimated sigma values are included in True value(Setting WV values) ± 10%



Result for Experiment 1 _ Cont'd

(5 different levels of WV(10%, 20%, 30%, 40%, and 50%) without IIV's change(0%)



Result for Experiment 2

(5 different levels of WV(10%, 20%, 30%, 40%, and 50%) with IIV's change(10→50%)

Setting Condition		Success rate(%)* for each subject number				
WV(%)	IIV(%)	N=6	N=12	N=18	N=24	N=30
10	10	72	85	94	97	99
	20	68	87	94	98	99
	30	73	86	94	96	97
	40	69	87	90	92	93
	50	70	82	88	88	85
20	10	70	86	93	96	98
	20	74	87	94	97	99
	30	71	87	94	96	98
	40	70	88	95	95	99
	50	72	86	87	97	98
30	10	73	88	93	98	99
	20	70	86	92	96	98
	30	68	88	92	96	98
	40	69	84	94	96	98
	50	71	72	91	96	97
40	10	71	82	89	94	98
	20	66	83	90	95	96
	30	70	84	92	94	96
	40	70	87	91	94	97
	50	71	85	90	94	97
50	10	50	56	62	62	63
	20	54	62	59	66	65
	30	55	58	61	64	68
	40	56	59	65	65	67
	50	54	60	62	66	68

*Success rate at which to estimated sigma values are included in True value(Setting WV values) ± 10%

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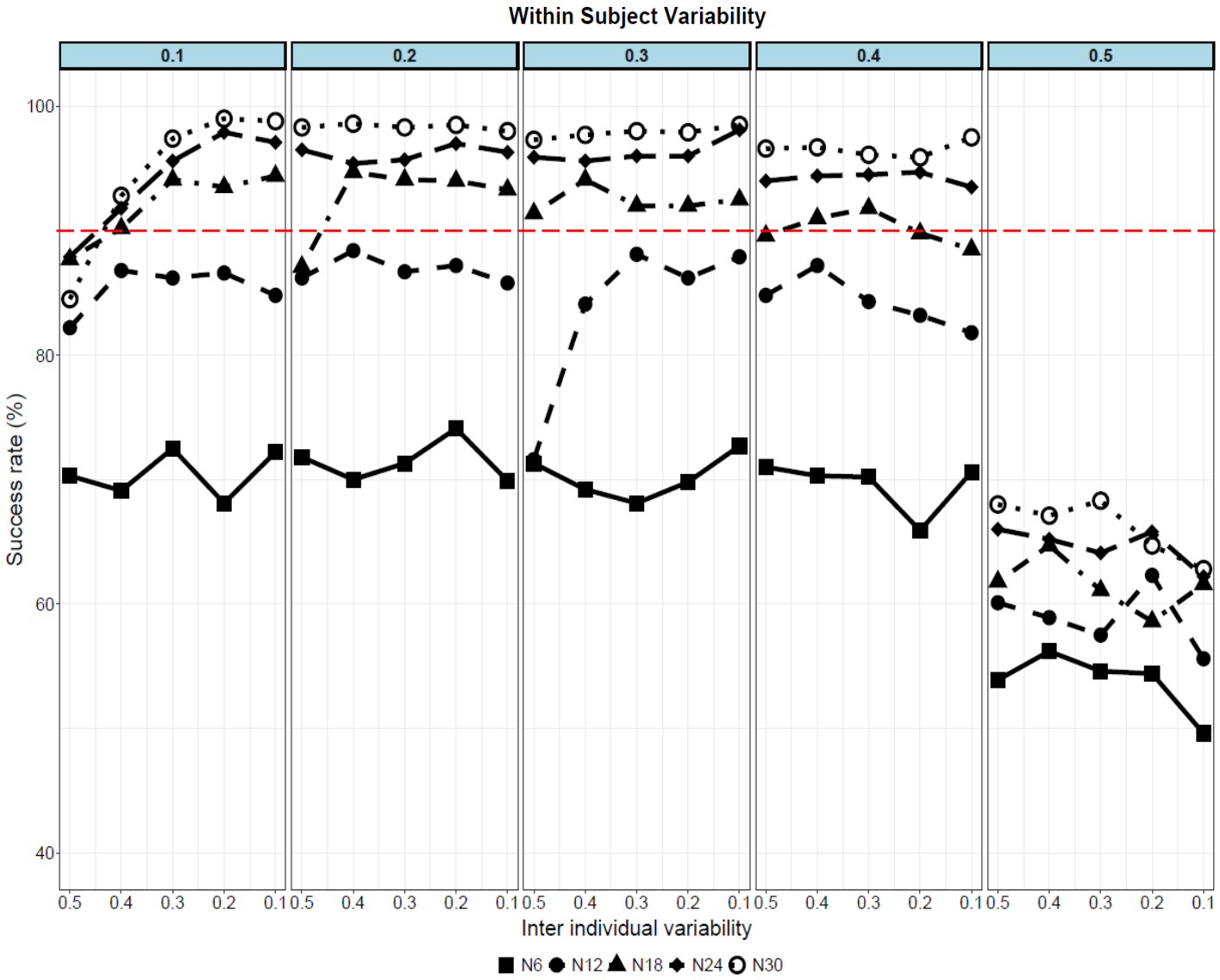
Result for Experiment 2 _ Cont'd

(5 different levels of WV(10%, 20%, 30%, 40%, and 50%) with IIV's change(10→50%)



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Result for Experiment 2 _ Cont'd

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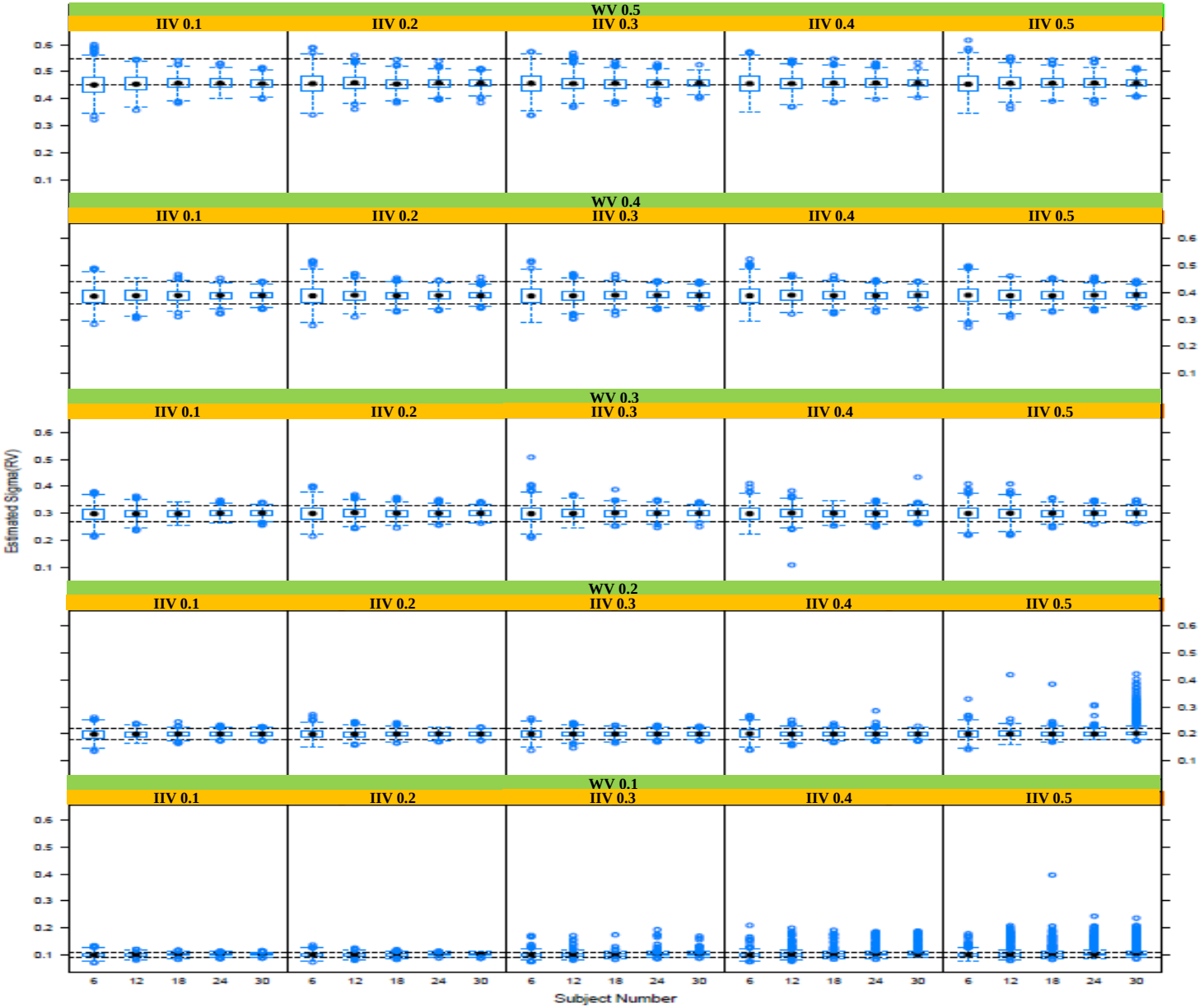

Result for real case application

The result for real application

Subject No.	6	12	18	24	30
Sigma, σ (%)	44.9	47.7	44.5	43.8	47.2

Cf. Result from original reference

Parameters	GMR	90% CI	SwR	CVwR(%)	BE limit
AUCt	0.9836	0.8275 ~ 1.1692	0.332	33.17	0.8 ~ 1.25
Cmax	0.9402	0.7587 ~ 1.1652	0.474	50.21	0.6984 ~ 1.4319

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IV. Summary and Conclusion

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Summary and Conclusion

- **When the IIV was no change(0%)**
  → **WV 10~30%** : 90% or more prediction success rate with **12 or more** subjects
  → **WV 40%** : 90% or more prediction success rate with **18 or more** subjects
  → **WV 50%** : **Underestimation** at 6~30 subjects

- **When the IIV was change(10~50%)**
  → **WV 10~40%** : 90% or more prediction success rate with **18 or more** subjects
  → **WV 50%** : **Underestimation** at 6~30 subjects

- **Real HVD case(eperisone)**
  → **Our Pop. approach** result : **44 ~47%** for RV at which **6~30 subject** number
  cf. BE result : 33.17% as a CV_{wR} for AUC and 50.21% as CV_{wR} for Cmax

In conclusion, we have confirmed that our methodology is relatively accurate in well-estimating within subject variability from population PK data. Also, we have confirmed that it can be used as a tool to judge the highly variable drug.

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Thank you