Examining Intra-individual and Inter-individual Variability of Plasma Nicotine PK Parameters in e-Vapor Use by Adult Cigarette Smokers in Three Studies

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Introduction & Objective

Pharmacokinetic studies are often used to assess the rate and amount of nicotine delivery into the bloodstream during tobacco product use. Knowledge about intra-individual and inter-individual variability of pharmacokinetic (PK) parameters is important in the design of PK studies for e-Vapor products (EVPs). The objective of this work was to estimate the intra-individual and inter-individual variability of plasma nicotine PK parameters Cmax and AUC in EVP use by adult cigarette smokers in three clinical studies.

Methods

Study Products

Study	Product	Product Note
1	A	A MarkTen® product prototype
	B	A MarkTen® product prototype
	C	A MarkTen® product prototype
	D	A MarkTen® product prototype
	E	A market e-Vapor product
	F	A market e-Vapor product
2	A	A MarkTen® product prototype
	B	A MarkTen® product prototype
	C	A MarkTen® product prototype
	D	A MarkTen® product prototype
	E	Subject's Own Brand Cigarette
3	A	A MarkTen® product prototype
	B	A MarkTen® product prototype
	C	A MarkTen® product prototype
	D	A MarkTen® product prototype
	E	Subject's Own Brand Cigarette

Randomization Sequences

Study 1

1	A	B	F	C	E	D
2	B	C	A	D	F	E
3	C	D	B	E	A	F
4	D	E	C	F	B	A
5	E	F	D	A	C	B
6	F	A	E	B	D	C

Study 2 & 3

1	C	E	B	A	D
2	D	B	C	E	A
3	A	C	D	B	E
4	E	D	A	C	B
5	B	A	E	D	C

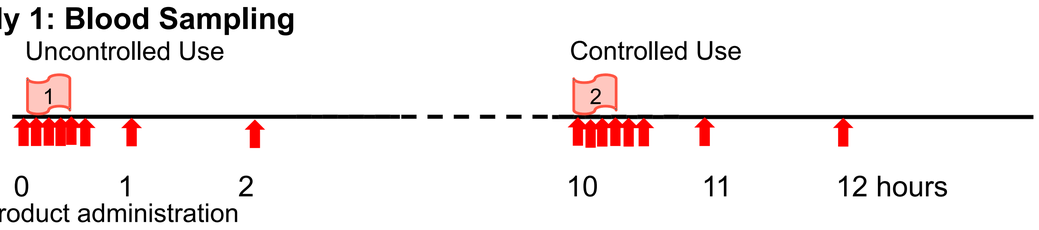
Randomization:
Study 1 (n = 25)
Study 2 (n = 30)
Study 3 (n = 30)

Product Use Conditions & PK Blood Draw

Study 1: Product Use

	Product use condition	
Parameter	Uncontrolled (UCC)	Controlled (CC)
Duration of product use	10 min	
Number of puffs	No restriction	10
Puff duration (sec)	No restriction	4
Inter-puff interval (sec)	No restriction	30

Study 1: Blood Sampling



Product administration

Blood sampling at -5, 2, 5, 10, 12, 15, 20, 25, 60 and 120 min following each product use condition

Study 2 & 3: Product Use

	Product use condition	
Parameter	Controlled (CC)	Uncontrolled (UCC)
Duration of product use		10 min
Number of puffs	10	No restriction
Puff duration (sec)	4	No restriction
Inter-puff interval (sec)	30	No restriction

Study 2 & 3: Blood Sampling

Product administration

Blood sampling at -5, 2, 5, 10, 12, 15, 20, 30, 60, 120 and 180 min following each product use condition

Statistical Methods

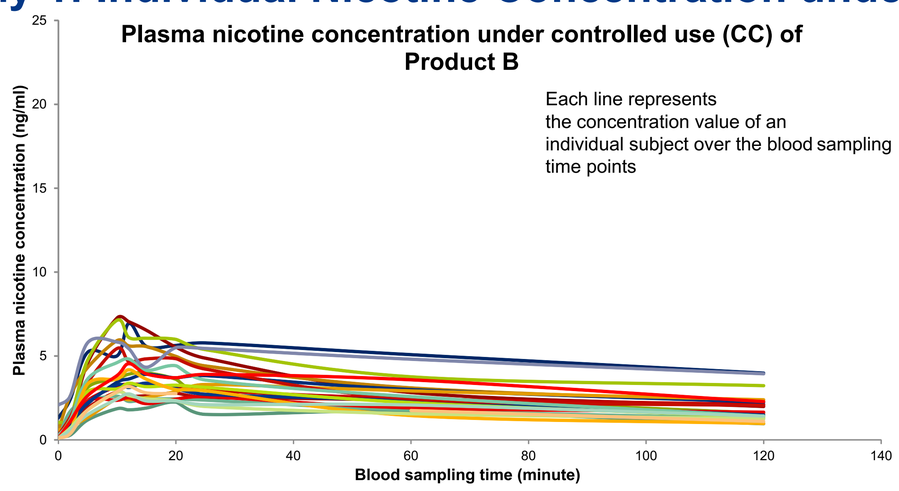
A linear mixed model for analysis of variance was performed on the log transformed PK parameters Cmax and AUC. The model included sequence, study product, and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. Compound symmetry was used as the covariance structure. The model generated covariance parameter estimates for subject (sequence) and residual, with the former as a measure for inter-subject variability and the latter for intra-subject variability. The estimates were converted to coefficient of variation (CV%). The modeling was conducted for each study condition for each study separately.

Subject Demographics

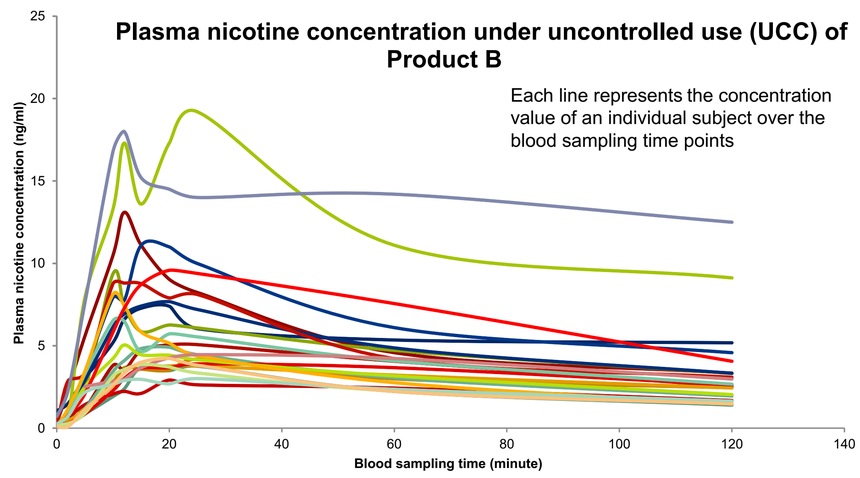
Characteristics	Study 1	Study 2	Study 3
All Subject (n)	25	30	30
Female (n)	10	16	12
Male (n)	15	14	18
Age (yrs) (mean, range)	35.6 (21, 58)	36.3 (22, 52)	38.5 (22, 64)
Black or African American (n)	4	9	7
White (n)	21	20	20
Others (n)	0	1	3
BMI (kg/m^2) (mean, SD)	27.55, 5.12	28.5, 4.11	28.2, 5.25
Height (in) (mean, SD)	67.4, 3.72	66.8, 3.49	67.0, 3.50
Weight (lb) (mean, SD)	175.25, 26.16	180.4, 28.39	179.4, 31.51

Results

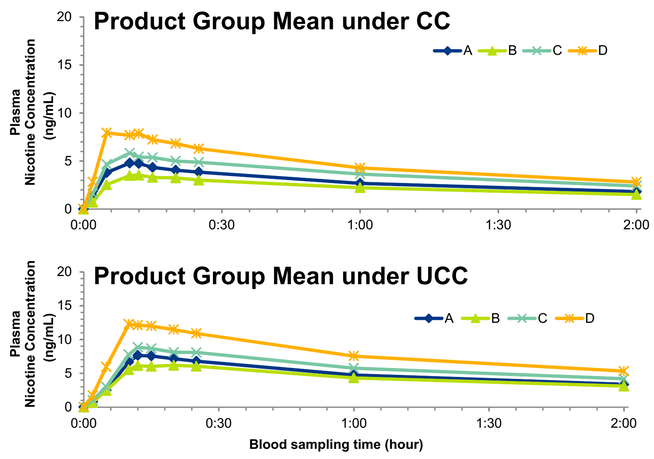
Study 1: Individual Nicotine Concentration under CC



Study 1: Individual Nicotine Concentration under UCC



Study 1: Group Average of Nicotine Concentration



A,B,C,D are MarkTen® e-Vapor prototypes

Statistical Model Estimates of PK Parameters

Product	Study 1				Study 2				Study 3			
	CC		UCC		CC		UCC		CC		UCC	
	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
A	4.70	5.13	7.25	8.35	3.42	4.95	5.83	9.62	3.62	5.21	6.08	9.61
B	3.41	4.12	5.84	6.70	3.78	5.45	6.06	9.66	3.70	5.43	6.87	10.69
C	3.48	4.34	5.86	7.37	3.74	5.41	5.13	8.36	3.15	4.92	5.33	9.02
D	5.90	6.95	8.06	9.74	3.51	5.28	5.36	8.95	3.37	4.89	5.68	8.63

Values are geometric means, the unit is ng/ml for Cmax and mn*ng/ml for AUC, for MarkTen® prototypes only.

Statistical Significance of Fixed Model Effects*

	Study 1				Study 2				Study 3			
	CC		UCC		CC		UCC		CC		UCC	
Fixed Effect	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
Sequence	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Period	<0.05	NS	<0.01	<0.01	NS	NS	<0.05	NS	NS	<0.05	NS	NS
Product	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

*Include all study products in a study.

Inter- and Intra-subject Variability (CV%)

Study	Variability	Cmax		AUC	
		CC	UCC	CC	UCC
1	Inter-subject	28	53	28	54
1	Intra-subject	26	28	21	22
2	Inter-subject	46	54	40	53
2	Intra-subject	39	26	25	33
3	Inter-subject	42	52	40	54
3	Intra-subject	29	35	22	30

Summary & Conclusion

- The intra-individual and inter-individual variability was larger under the uncontrolled product use than under the controlled use.
- The intra-individual and inter-individual variability was similar for the two PK parameters under the same product use condition.
- In all studies, the intra-individual variability for both parameters was smaller than the inter-individual variability.
- The variability estimates can aid in the design of future EVP PK studies (e.g. sample size estimation).

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