

Bioequivalence Testing for Highly Variable Drug Products (HVDP)

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Background, Statement of the Problem

- Bioequivalence (BE) studies investigate and compare the pharmacologic characteristics of different formulations of a drug product with respect to the rate and extent of exposure to a new formulation (Test) and a reference listed formulation (RLD).
- This assumes that the reference and test products have similar variability.
- Also generally assumes that the properties of Absorption, Distribution, Metabolism, and Excretion (ADME) behave in a similar manner (little variability) within a subject (and population).
- What happens when a drug product does not have a consistent ADME profile, with small amounts of variability within or between subjects?

Background, Statement of the Problem

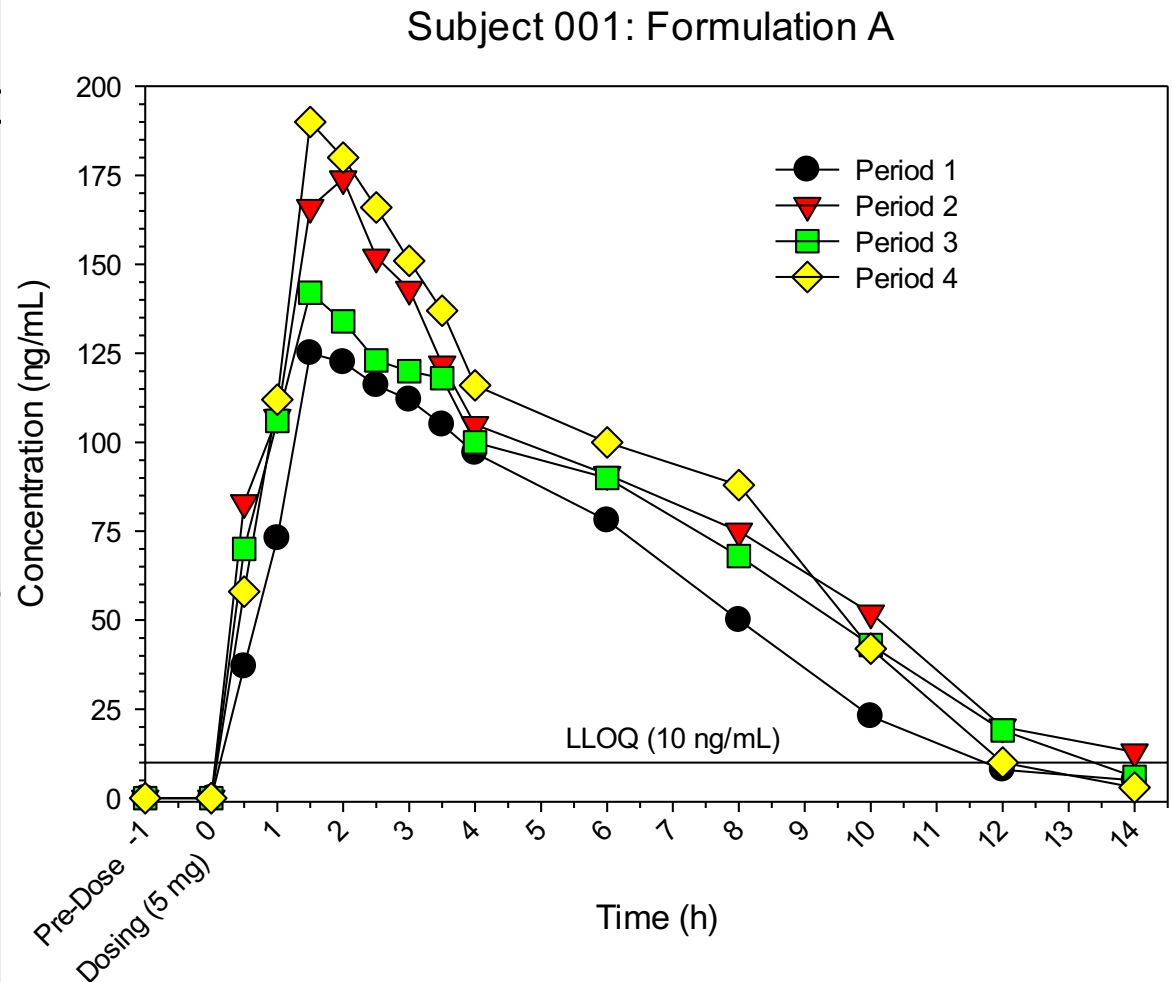
- Highly variable drug products (HVDP) are drugs whose rate and extent of absorption shows large dose-to-dose variability within the same subject.
- HVDP's are generally defined as those drugs whose intra-patient coefficient of variation (C_{max} and/or AUC) is approximately 30% or greater.
- How does one design a bioequivalence study with such a large amount of intra-subject variability?

Background Example of HVDP Concentration Profile Assay

PK parameter C_{max} ranges between 125 ng/mL and 190 ng/mL, with similar ranges for AUC.

The intrasubject variability for this subject is around 38%.

This drug product meets the definition of a Highly Variable Drug Product (HVDP)



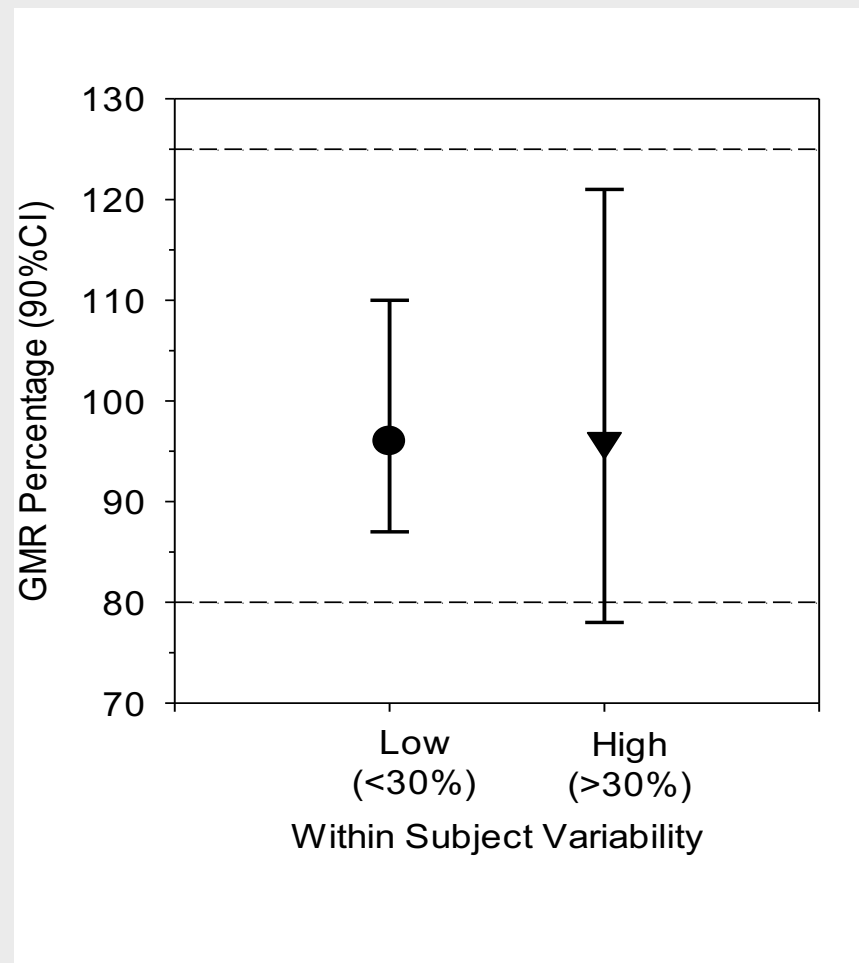
Background Example of HVDP Concentration Profile Assay

What happens in a traditional two-period bioequivalence study design to the 90% confidence intervals in the presence of subjects with high intrasubject variability?

The Geometric Mean ratio (GMR) is the same for low WSV and high WSV.

In the presence of high WSV (intrasubject variability > 30%) the 90% confidence intervals exceeds the lower bound (<80%) and the drug product does not pass for bioequivalence. Failed Study!

Expensive !



Study Failure Rate with Increasing Intra-subject Variability

Tanguay et al (2002) noted the following failure rates from 800 published studies with increasing intrasubject %CV

Intra-Subject CV%z	Studies Failing Bioequivalence (%)
<10%	6%
10-20%	10%
20-30%	26%
>30%	62%
Abstracted from M. Tanguay et al., AAPS Abstract, November 2002	

Study failure rates demonstrate that drug products with large amounts of intrasubject variability (>30%) will fail traditional bioequivalence testing.

More importantly: Data suggest that drug-products not previously thought to have a large WSV coefficient may in fact be classified as HVDP upon further study.

Estimated Sample Sizes for HDVP with Traditional 2x2 Crossover Study Design

Sample sizes for a traditional BE study Design (2x2 Crossover) increases to the point that the study cannot be completed (to many subjects, not ethical !, and they mostly fail)

Intra-Subject CV%z	Studies Failing Bioequivalence (%)	Estimated Sample Size with Traditional 2x2 Crossover
<10%	6%	18 – 72
10-20%	10%	36 – 112
20-30%	26%	96 - >250
>30%	62%	>300

Tothfalusi and Endrenyi (2012) Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs. Pharm Pharmaceut Sci15(1) 73 - 84, 2012

Regulatory Problem with HVDP Bioequivalence Studies

Traditional limits for GMR for C_{max}, AUC Parameters is 80%-125% with the 90% CI included within these boundaries.

- Generally Accepted by EMA, FDA, Health Canada, PMDA.

At present, there are no set specific acceptance criteria for HVD/Ps

Lets apply 90%CI to both C_{max} and AUC in this presentation for acceptance in order to stimulate discussion of the issue surrounding HVDP BE Studies

ABE1: Non-replicated study design

- Using two or more period data
- ANOVA 1

ABE3: Partially replicated study design

- Using three period Data
- Reference product is replicated
- ANOVA 2

ABE4: Fully replicated study design

- Using four period data
- Both test and reference products are replicated
- ANOVA 3

ANOVA 1:

- Contains several variance components
- WSV in ADME, plus a component of analytical variability
- Within formulation variability (WFV)
- Subject by formulation interaction ($S \times F$)
- Unexplained random variability

ANOVA-2:

- Formulation
- Period
- Subject
- Subject by Formulation Interaction

- Residual Variance (approx = WSV)
 - Can separate test and reference variances

Product A: Three Studies: All Failed due to ANOVA-CV%

	Study 1 ^a	Study 2 ^b	Study 3 ^c
In Cmax	42.3	39.9	37.2
In AUClast	34.8	36.6	33.0

^aBioequivalence study, n=37 (3-period study)

^bPharmacokinetic study n=11 (solution, 3-period study)

^cPharmacokinetic study, n=9, CPZ with & without quinidine (2-period study)

Product A (ABE3): Replicated Study: 3 x 37 Subjects

Measure	GMR%	CV%	90%CI
In Cmax	115	42.3	99-133
In AUClast	110	34.8	97-124

ANOVA-2 (GLM)

Measure	T v R ₁	T v R ₂	R ₁ v R ₂
In Cmax	103 - 146	89 - 126	72 - 102
In AUClast	97 - 128	94 - 125	85 - 112

ANOVA-1 (GLM)

Product B (ABE4)

22 healthy volunteers

2-Formulation, 4-Period, 4-Sequence Cross-Over design

Washout period, 2 weeks

17 plasma samples collected over 96 hours

Product B (ABE4):Test versus Reference

Measure	GMR%	CV%	90%CI
In Cmax	112	36.7	95-131
In AUClast	113	28.0	101-126

ANOVA-3: (MIXED)

Product B (ABE4): Test-1 versus Test-2

Measure	GMR%	CV%	90%CI
In Cmax	97	26.0	84-111
In AUClast	97	18.7	87-107

ANOVA-1: (GLM)

Product B (ABE4): Ref-1 versus Ref-2

Measure	GMR%	CV%	90%CI
In Cmax	87	49.9	66-113
In AUClast	87	39.2	71-108

ANOVA-1: (GLM)

Product C (ABE4)

37 healthy volunteers

2-Formulation, 4-Period, 4-Sequence Cross-Over design

Washout period, 1 week

15 plasma samples collected over 13.5 hr

Product C (ABE4) Test versus Reference

Measure	GMR%	CV%	90%CI
In Cmax	104	41.7	92-117
In AUClast	103	35.8	93-114

ANOVA-3: (MIXED)

Product C (ABE4): Test-1 versus Test-2

Measure	GMR%	CV%	90%CI
In Cmax	99	29.6	87-111
In AUClast	92	32.5	81-106

ANOVA-1: (GLM)

Product C (ABE4): Ref-1 versus Ref-2

Measure	GMR%	CV%	90%CI
In Cmax	107	33.7	94-123
In AUClast	109	27.1	97-122

ANOVA-1: (GLM)

How to Deal with HVDPs

HVDs are generally safe drugs

High WSV of C_{max} is often the problem

A 90%CI is not required for C_{max} in the case of “uncomplicated drugs”

BE Study

- Multiple dose study
- BE on the basis of metabolite
- Area correction method to reduce intra-subject variability
- Application of stable isotope technique

* From Published Literature

Statistical Considerations

- Scaled ABE criteria
- GMR-dependent scale ABE limits
- Individual Bioequivalence (IBE)

BE Study Design

- Replicate Design
- Group sequential design

*From Published Literature

Replicated Bioequivalence Study Designs

Design	Sequence	Study Period			
		I	II	III	IV
Partially-Replicated, 3-period, 3-sequence, Reference product is replicated	TRR	T	R	R	N/A
	RTR	R	T	R	
	RRT	R	R	T	
Partially-Replicated, 3-period, 3-sequence, Test product is replicated	RTT	R	T	T	N/A
	TRT	T	R	T	
	TTR	T	T	R	
Fully-Replicated, 4-period, 6-sequence	RTTR	R	T	T	R
	TRTR	T	R	T	R
	TTRR	T	T	R	R
	RTRT	R	T	R	T
	RRTT	R	R	T	T
	TRRT	T	R	R	T
Fully-Replicated, 4-period, 2-sequence	RTRT	R	T	R	T
	TRTR	T	R	T	R

T = Test Product, R = Reference Product

Possible Approaches: Relaxing Criteria

Widening the BE limits from $\pm 20\%$ (80-125% on the log scale) to $\pm 30\%$ (70-143% on the log scale)?

- CPMP Guidelines permit a sponsor to justify prospectively widening the BE Limits to, say, 75-133%, for $C_{\max}$

Lowering the confidence level, e.g., from 90% to 80%

Widen the BE Limits for HVDs

The BE Limits can be scaled to Within Subject Variability

2-Period design: scale to the residual SD

Replicate design: scale to the within-subject SD of the reference formulation

Conclusion

- If Ref scaled ABE is to be considered, we suggest that $\sigma_{w0} = 0.25$ seems reasonable
- Scaling can lead the GMR to rise to unacceptably high levels
 - Therefore one can consider a constrain on the GMR
- More work needs to be completed with simulations on the impact of increasing numbers of BLOQ samples over extended sampling schemas, with various constraints on GMR and ABE.
- Regulatory Authorities are aware of the issues with HVDP and will discuss with Sponsors practical and scientifically sound ideas for BE study Designs for a HVDP.

QUESTIONS

