Bioequivalence Requirements for Highly Variable and Narrow Therapeutic Index Drugs

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Bioequivalence Regulations Have a Remarkable Record

No prospective study has ever found that a generic product approved by the FDA based on a bioequivalence study in healthy volunteers does not show the same clinical efficacy and safety as the innovator product, even when special populations (e.g., elderly, women, severely sick patients) are studied.

WE DON'T HAVE A CLINICAL PROBLEM

- **The +25%/-20% Average Bioequivalence criteria are very tight**
- **Lack of a problem is not just verified by minimal Phase 4 problems that can be documented, also**
- **Many, many studies in special population subsets have been carried out to attempt to demonstrate lack of equivalence for approved generics (and of course efficacy and safety differences), but you don't see any of these results**

Yet for Many Years I Categorized the U.S. Bioequivalence Guidelines as Procrustean

The manufacturer of the test product must show using two one-sided tests that a 90% confidence interval for the ratio of the mean response (usually AUC and C_{max}) of its product to that of the reference product is within the limits of 0.8 and 1.25 using log transformed data.

(Procrustean ≡ marked by an arbitrary, often ruthless disregard for individual differences or special circumstances.)

Note: This began to change in 2000 with the introduction of the BCS Guidance

Highly Variable (HV) Drugs ($CV_{within} \geq 30\%$)

One problem with the Procrustean Regulations was that the safest drugs, those exhibiting high within subject variability, were the hardest to prove that a generic was bioequivalent to the innovator.

Highly variable drugs are the safest, since by definition, HV approved drugs must have a wide therapeutic index, otherwise there would have been significant safety issues and lack of efficacy during Phase 3.

Highly variable narrow therapeutic index drugs are dropped in Phase 2 since it is not possible to prove either efficacy or safety.

From 1998-2001 I served as the Chair of the FDA Expert Panel on Individual Bioequivalence

The following slides review the recommendations of the Panel and subsequent developments with respect to variability issues with respect to bioequivalence in the previous decade.

Individual Bioequivalence (IBE)

$$\frac{(\mu_{Test} - \mu_{Ref})^2 + \sigma_D^2 + (\sigma_{WithinT}^2 - \sigma_{WithinR}^2)}{\sigma_{WithinR}^2} \leq \theta$$

Initial Promises for IBE

- Addresses the correct question (switchability)
- Considers subject by formulation interaction (σ_D)
- Incentive for less variable test product
- Scaling based on variability of the reference product both for highly variable drugs and for certain agency-defined narrow therapeutic range drugs
- Encourages use of subjects more representative of the general population

Re-examination of the Initial Promises for IBE

- Addresses the correct question (switchability)—**Necessity questionable**
- Considers subject by formulation interaction—**Unintelligible parameter**
- Incentive for less variable test product—**ABE with scaling could also solve this issue**
- Scaling based on variability of the reference product both for highly variable drugs and for certain agency-defined narrow therapeutic range drugs– **ABE with scaling could also solve this issue**
- Encourages use of subjects more representative of the general population—**Failed**

At this time, individual bioequivalence still remains a theoretical solution to solve a theoretical clinical problem. We have no evidence that we have a clinical problem, either a safety or an efficacy issue, and we have no evidence that if we have the problem that individual bioequivalence will solve the problem and, in essence, it had been abandoned, until recently resurrected for NTI drugs.

Progesterone

The Poster Drug for High Variability

A repeat measures study of Prometrium® 2x200 mg capsules in 12 healthy post-menopausal females yielded:

Intrasubject CV for AUC of 61%

Intrasubject CV for Cmax of 98%

A generic company calculated that a 2 period crossover BE study for Progesterone Capsules, 200 mg would require dosing in **300** postmenopausal women to achieve adequate statistical power.

The FDA draft guidance on Progesterone (revised Feb 2011) details the methodology recommended.

Drugs with High Variability BE Measures: Approach Now Recommended by OGD

This approach is Mixed Scaled Average BE

Normal non-scaled average bioequivalence for CV < 30%

Reference-scaled average bioequivalence (ABE) for CV ≥ 30%

Protocol for Reference-Scaled ABE Approach

BE study uses a three-period, reference-replicated, crossover design with sequences of TRR, RTR, & RRT

A four-period design is also acceptable (sequences of TRTR and RTRT) T = test product; R = reference product

Usual pharmacokinetic sampling to determine Cmax, AUC(0-t), and AUC(0-inf)

At least 24 subjects should be enrolled

Protocol for Reference-Scaled ABE Approach

a. Reference replicate data analyzed for determination of σ_{wR}
b. If $\sigma_{wR} < \sigma_{w0}$ then data analyzed using unscaled average BE method
c. If $\sigma_{wR} \geq \sigma_{w0}$ then data analyzed using scaled average BE and point-estimate criteria

Drugs with HV BE Measures: Reference-Scaled ABE Approach

BE limits, upper, lower = EXP $\pm$ 0.223 $\sigma_{wR} / \sigma_{w0}$

- Where $\sigma_{w0} = 0.25$
- The point estimate (Test/Reference geometric mean ratio must fall within [0.80-1.25]
- <u>Both conditions must be passed by the test product to conclude BE to the reference product</u>
- If test variability is higher than reference variability then product is less likely to be declared BE to reference

Bioequivalence Example

Study run in 24 healthy individuals

AUC_T/AUC_R = 0.93 ± 0.30 C.I. 0.76 – 1.10

$C_{max,T}/C_{max,R}$ = 0.90 ± 0.42 C.I. 0.72 – 1.12

Under average BE FDA requirements, both AUC and C_{max} fail (as a result of studying too few subjects)

However, under referenced scaled BE:

For AUC σ_{wR} = 0.38 and σ_{wT} = 0.29, then calculated

Reference scaled C.I. 0.713 – 1.403 Pass

For C_{max} σ_{wR} = 0.40 and σ_{wT} = 0.31, then calculated

Reference scaled C.I. 0.700 – 1.428 Pass

Calculations of reference scaled C.I. from:

EXP ± 0.223 σ_{wR} / σ_{w0} (Note: EXP -0.223 = 0.8, EXP +0.223 =1.25)

It is important to note :

1. **There is no scientific basis or rationale for the point estimate recommendations (even though I was the initiator of this recommendation)**
2. **There is no belief that addition of the point estimate criteria will improve the safety of approved generic drugs**
3. **The point estimate recommendations are only "political" to give greater assurance to clinicians and patients who are not familiar (don't understand) the statistics of highly variable drugs**

Highly Variable Conclusions

- **Highly variable drugs on the market are the safest drugs because marked swings in systemic drug levels have been shown to not affect safety and efficacy in individual patients.**
- **High variability can result from a number of environmental and genetic factors, none of which appear to require any special considerations not already found in the labeling of the innovator drug.**
- **The HV drug guidance is a strong advance leading to significant cost and human subject exposure savings with no increased potential for safety and lack of efficacy issues related to the methodology.**

Narrow Therapeutic Index Drugs Are:

Defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. Serious events are those that are persistent, irreversible, slowly reversible, or life-threatening, possibly resulting in hospitalization, disability or even death. Example NTI drugs include warfarin, levothyroxine, carbamazepine, lithium carbonate, phenytoin and theophylline.

FDA, 2011

Those for which relatively small changes in systemic concentration lead to marked changes in pharmacodynamic response.

Benet and Goyan, 1995

Those for which a 20% or smaller change in dosage, with bioavailability remaining constant, produces clinically significant and undesirable pharmacodynamic alterations.

Levy, 1998

Why is meeting bioequivalence criteria a relatively minor concern for drugs with narrow therapeutic indices?

- **By definition, approved drugs with narrow therapeutic indices exhibit small intrasubject variability.**
- **If this were not true, patients would routinely experience cycles of toxicity and lack of efficacy, and therapeutic monitoring would be useless.**

NTI Drugs Frequently Listed in Legislative Bills Proposed in Various States to Limit Generic Substitution of NTI Drugs

	CV%		
	Inter Subject AUC (mean)	Intra Subject AUC (range)	Intra Subject C_{max} (range)
Carbamazepine (n=15)	**38**	**4-19**	**5-18**
Digoxin (n=5)	**52**	**13-32**	**14-26**
Levothyroxine sodium (n=9)	**20**	**4-16**	**5-19**
Phenytoin sodium (n=12)	**51**	**4-19**	**7-20**
Theophylline sustained release	**31**	**13-24**	**12-26**
Warfarin sodium (n=29)	**53**	**3-11**	**7-20**

(LZ Benet, Transplant. Proc. 31: 1642-44. 1999;
LX Yu, GPhA Fall Technical Workshop, 2011, from FDA website)

Narrow Therapeutic Index Drugs BE Measures: Approach Now Recommended by OGD

Protocol for Reference-Scaled ABE Approach

BE study uses a four-way crossover fully replicated design i.e., Test product given twice. Reference product given twice

This design will provide the ability to:

--Scale a criterion to the within-subject variability of the reference product, and

--Compare test and reference within-subject variance to confirm that they do not differ significantly

Usual pharmacokinetic sampling to determine Cmax, AUC(0-t), and AUC(0-inf)

At least 24 subjects should be enrolled

The FDA draft guidance on Warfarin (recommended Dec 2012) details the methodology recommended.

Recommended BE Limits for Generic NTI Drugs

- **BE limits will change as a function of the within-subject variability of the reference product (reference scaled average bioequivalence as for HV drugs)**
- **If reference variability is ≤ 10%, then BE limits are reference-scaled and are narrower than 90.0-111.11%. (Lamotrigine example of Prof. Polli yesterday, but the USP potency limits for lamotrigine tablets is 90-110%)**
- **If reference variability is > 10%, then BE limits are reference-scaled and wider than 90.0-111.11%, but are capped at 80-125% limits.**
- **The Agency believes that this recommendation encourages development of low-variability formulations.**

However, the Warfarin draft recommended guidance for NTI drugs contains a new requirement

Sponsors must calculate the 90 % confidence interval of the ratio of the within subject standard deviation of test product to reference product σ_{WT}/σ_{WR}. The upper limit of the 90% confidence interval for σ_{WT}/σ_{WR} will be evaluated to determine if σ_{WT} and σ_{WR} are comparable. The proposed requirement for the upper limit of the 90% equal-tails confidence interval for σ_{WT}/σ_{WR} is less than or equal to 2.5.

What Will be the Consequence of Decreasing the Bioequivalence Interval for NTI Drugs?

Primary Consequence:

Increase the number of subjects required to meet bioequivalence requirements.

Secondary Consequence:

Dissuade innovator and generic manufacturers from modifying dosage form and manufacturing processes.

Third Consequence:

Satisfy those who call for a decreased bioequivalence interval for NTI drugs.

I View the New NTI Bioequivalence Recommended Requirements as Revisiting Individual Bioequivalence and the Point Estimate Criteria for HV Drugs

I believe that tightening the bioequivalence interval for most NTI drugs will yield little real benefit to patients, but correspondingly the negative consequences to manufacturers would also be relatively minor in terms of increased costs. However, the placebo effect related to publicizing such individualization of bioequivalence intervals may yield positive psychological benefits for patients and clinicians. And the new ratio of variances requirement is quite similar to the subject-by-formulation parameter from IBE that was instituted with no relevant experience as to its deficiencies or benefits.

Bioequivalence Regulations Have a Remarkable Record

No prospective study has ever found that a generic product approved by the FDA (based on a bioequivalence study in healthy volunteers using the 80-125% criteria) does not show the same clinical efficacy and safety as the innovator product, even when special populations (e.g., elderly, women, severely sick patients) are studied.

Conclusions

The recommended HV drug bioequivalence criteria will allow quite safe drugs to be approved on a more realistic cost basis, with no or little change in safety outcomes.

The recommended NTI drug bioequivalence criteria will make the US position much more similar to the rest of the world (and even more onerous), with no or little change in safety outcomes.