Why Do Bioequivalence Studies in Healthy Volunteers?

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Why Do Bioequivalence Studies?

1. Most visible reason—Therapeutically equivalent generic drug products can save money for consumers, patient care organizations and governments.

2. Major use of BE studies–-Changes in formulation components, manufacturing process, manufacturing site and other preapproval and SUPAC changes.

3. Most critical innovator use---Showing that the formulation to go on the market is therapeutically equivalent to the formulation used to prove safety and efficacy in the Phase III studies.

Therapeutic Equivalents

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Bioequivalent Drug Products

This term describes **pharmaceutical equivalent products** that display comparable bioavailability when studied under similar experimental conditions.

- the **rate and extent of absorption** of the test drug do not show **a significant difference** from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a **single dose** or multiple doses

Federal Register Definition

Bioavailability describes the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action.

U.S. Federal Register, January, 1977

Ambiguities: "absorbed", "site of drug action"

Calculations of Extent of Bioavailability

You well know the measure of extent of availability as Area Under the systemic concentration Curve (AUC) over all time :

$$AUC = \frac{F \cdot D}{CL}$$ (Eq. 1)

If one assumes that clearance is constant for both the intravenous (iv) dose and the extravascular (ev, usually po) dose, and that the bioavailability (F) of the iv dose is 1, then the absolute F for the ev dose will be given by Eq. 2.

$$F = \frac{AUC_{ev} \cdot D_{iv}}{AUC_{iv} \cdot D_{ev}}$$ (Eq. 2)

When unchanged drug in urine (Ae) data is used to calculate F, the fraction of the available dose excreted in the urine (fe) is assumed to be constant for both doses and as shown below:

$$F \cdot D = Ae_{\infty} / fe \qquad \text{(Eq. 3)}$$

$$\text{Systemic } F = \frac{Ae_{ev} \cdot D_{iv}}{Ae_{iv} \cdot D_{ev}} \qquad \text{(Eq. 4)}$$

Rate of Availability: Although all agree on Eqs. 2 and 4 as a measure of extent of availability, the method for measuring rate of availability is more controversial. The FDA previously felt that none of the more difficult to calculate methods provide more reliability than the simple comparison of concentrations, C_{max}. Therefore, although not required, FDA always asks for a comparison of C_{max} between the two products. But today serious consideration is being given to alternatives such as AUC up to T_{max}.

A panel of 12 healthy volunteers received in a randomized study a 50 mg i.v. bolus dose, a 50 mg oral solution and 50 mg oral tablet of a drug. Individual blood concentration parameters for each subject following each of the three doses are given in Table 1 (AUC0 $\rightarrow \infty$ for all three doses and Cmax and Tmax for the oral doses).

Table 1. AUC, C_{max} and T_{max} Following 50mg IV and PO Dosing of Drug Y in 12 Healthy Volunteers

	IV	Oral Solution			Oral Tablet		
Subject	AUC	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}
	(ng-hr/ml)	(ng-hr/ml)	(ng/ml)	(hr)	(ng-hr/ml)	(ng/ml)	(hr)
1	234	152	54.6	0.5	164	48.2	1.5
2	300	240	47.3	0.5	244	49.6	2.0
3	326	217	84.0	1.0	228	97.2	1.0
4	318	207	68.7	1.0	210	75.6	1.5
5	212	141	37.6	1.5	155	52.2	2.0
6	275	196	63.4	1.0	187	65.5	1.5
7	301	192	51.9	1.5	211	65.1	1.5
8	235	188	57.5	1.0	193	48.3	1.5
9	325	223	43.6	1.0	224	53.3	1.5
10	280	205	55.9	1.5	217	53.6	1.5
11	272	179	28.1	1.0	190	32.7	2.0
12	272	162	36.2	1.5	189	34.0	2.0
Mean	279	192	52.4	1.1	201	56.3	1.6
S.D.	37	30	15.4	0.4	26	17.8	0.3
%CV	13.3	15.6	29.4	36.4	12.9	31.6	18.8

Table 2. Tablet and Oral Solution Bioavailability for Drug Y

Subject	% Bioavailability (Absolute F)		AUC Ratio (Relative F)	C_{max} Ratio
	Solution	Tablet	Tablet/Solution	Tablet/Solution
1	65.0	70.1	1.079	0.883
2	80.0	81.3	1.017	1.049
3	66.6	69.9	1.051	1.157
4	65.1	66.0	1.014	1.100
5	66.5	73.1	1.099	1.388
6	71.3	68.0	0.954	1.033
7	63.8	70.1	1.099	1.254
8	80.0	82.1	1.027	0.840
9	68.6	68.9	1.004	1.222
10	73.2	77.5	1.059	0.959
11	65.8	69.9	1.061	1.164
12	59.6	69.5	1.167	0.939
Mean	68.8	72.2	1.053	1.082
S.D.	6.3	5.3	0.055	0.163
% CV	9.2	7.3	5.2	15.1

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Standard Bioequivalence Study

- Cross-over

- Small number of healthy normal adults

  (usually 24 to 36)

- Single doses of test and reference products

- Measures of area under the curve (AUC) and the peak blood or plasma concentration (C_{max}) examined by statistical procedures

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What is the justification for studying bioequivalence in healthy volunteers?

"Variability is the enemy of therapeutics" and is also the enemy of bioequivalence. We are trying to determine if two dosage forms of the same drug behave similarly. Therefore we want to keep any other variability not due to the dosage forms at a minimum. We choose the least variable "test tube", that is, a healthy volunteer.

Disease states can definitely change bioavailability, but we are testing for bioequivalence, not bioavailability.

No drug products that has been shown to be bioequivalent in healthy volunteers has then been demonstrated not to be bioequivalent in patient populations, even a specific subset.

Personal example:
Furosemide (Lasix®) in small elderly women with congestive heart failure.

"Two formulations whose rate and extent of absorption differ by –20% / +25% or less are generally considered bioequivalent.

The use of the –20% / +25% rule is based on a medical decision that, for most drugs, a –20% / +25% difference in concentration of the active ingredient in blood will not be clinically significant."

Statistical Criteria

Two one-sided statistical tests are carried out using log-transformed data from the bioequivalence study to show that the 90% confidence interval for the ratio of AUC and C_{max} of the generic to the innovator is within the limits of 0.8 to 1.25

Definition of Bioequivalence in the Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations") Prior to 2002

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Orange Book Text from 2002

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products. Numerically this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

Orange Book Text from 2002(Continued)

For statistical reasons, all data is log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (Cmax and AUC). The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test /reference ratio of 1). Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials, pharmacodynamic studies, or comparative in-vitro methodology.

Example 1.

Low Variability Drug

See data in Tables 1 and 2. Drug Y exhibits low variability across the population. Test whether the solution and tablet are bioequivalent in these 12 healthy subjects.

Tablet/Solution Ratio

Parameter	Mean	Lower 90% CIL	Upper 90% CIL
$AUC_{0 \to \infty}$	1.051	1.025	1.079
C_{max}	1.071	0.987	1.163

Note: The analysis was performed on log transformed data so the means here are slightly different than those in Table 2.

(CIL – confidence interval limit)

Example 2: Test vs. Reference in 36 Subjects for a Highly Variable Drug (within subject C.V. >30%)

	AUC	C_{max}
Test	224 ± 146	80 ± 62
Reference	212 ± 129	79 ± 48
Ratio of Means (Test/Reference)	1.05	1.01
90% Confidence Interval		
Lower Limit	0.83	0.87
Upper Limit	1.33	1.21

Note: The 0.80 – 1.25 criteria is applied to the 90% confidence interval, not the ratio of means.

TRADITIONAL BIOEQUIVALENCE REQUIREMENT

2 x 2 Crossover design

Limits of –20/+25% difference with 80% power to detect a –20/+25% difference in treatment means at the 5% nominal level

INTRASUBJECT CV (% Difference betw.Products)	NUMBER OF SUBJECTS REQUIRED
15.7% (no difference)	14
40.0% (no difference)	70
15.7% (±10% difference)	44
40.0% (±10% difference)	90

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What criteria must be met for "Expected…same clinical effect and safety?"

- **Meet compendial standards**

- **Meet GMP (Good Manufacturing Practice) standards**

- **Meet appropriate bioequivalence standard**

I am Chairman of the State of California Bioequivalency Advisory Panel (BAP)

The BAP was formed in 1985 when the State of California believed that they could save money on MediCal products (drug products funded by the state for poor patients) if the California Department of Health would approve drug products that had not yet been approved as bioequivalent by the FDA. The BAP was formed as a result of a law suite brought by pharmacists in California, that led to an agreement that before the State approved any new MediCal generic product the BAP had to hold a public hearing evaluating the new drug product and making a public recommendation to the Department of Health. The BAP held a number of hearings and never recommended that the State approve drug products not approved by the FDA. Within five years, the State decided to abandon this approach, but the BAP still exists due to the law suite agreement, even though the BAP has not met for 20 years.

I was struck in the BAP hearings with the testimony of patients, clinicians and patient relatives who frequently said:

a) " I don't want my patient, my loved one, or me as the patient to have to take a generic drug product based only on blood level measurements, usually in healthy volunteers, that has not been tested in patients."

b) "Why can't generic products be approved based on clinical studies?"

Why bioequivalence, not clinical efficacy?

- Myocardial infarction, 10% mortality, detection of 20% improvement *vs* placebo needs 8600 patients *e.g.* Yusif *et al*; 1988 JAMA 260: 2259-63

- Congestive heart failure, 30% mortality. SOLVD enalapril study – 2600 patients showed 16% risk reduction. 1991 N. Engl. J. Med. 325: 293-302

- Active treatment comparisons need more power and the "n" for 2 formulations of the same drug becomes astronomical

- In essence, if clinical studies were required to prove bioequivalence of generic products there would be no generic drug products

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In the late 1980's in the US there was a generic scandal when it was discovered that after the passage of the Hatch-Waxman Act in 1984 a number of unscrupulous individuals entered the generic drug industry.

Congress held hearings on the issue and I was asked to testify. At the hearings, I made what was considered a very surprising statement that made headlines in the newspapers.

I said that I predicted that 60% of the new drug products that came onto the market in the US had never been tested in patients.

Bioequivalence studies for New Molecular Entities Approved by FDA 1/1/81 – 12/31/90

Total NMEs approved.	**220**
For oral dosage administration	**97**
Bioavailability requirements waived (non or minimal absorption).	**3**
Unavailable or insufficient data to judge.	**7**
Final marketed formulation same as clinical trial.	**34 (39.1%)**
Final marketed formulation differs from that in clinical trail. (50 bioequivalence tested in vivo)	**53 (60.9%)**

Brand Name Products

When a brand name manufacturer of a product on the market makes a change in manufacturing (e.g. a new source of the active ingredient, change of the manufacturing site, change in the manufacturing process), they must convince the FDA that the product manufactured under the new conditions will give the same clinical efficacy and safety profile as the originally approved product.

They prove this by a bioequivalence study; the same study used by the generic manufacturer.

What is the Pass/Fail Record for Bioequivalence Studies of Generic Drugs?

273 Generic Applications in 1997

(J.E. Henney, JAMA 282: 1995, 1999)

For 127 in vivo bioequivalence studies

AUC 0-t_{last}	$3.47 \pm 2.84\%$	**Measures of extent-- how much**
AUC 0-Infinity	$3.25 \pm 2.97\%$	
Cmax	$4.29 \pm 3.72\%$	**Measure of rate—how fast**

Note that the mean difference between generic and innovator products is less than the 5% minimum mean difference in content uniformity allowed by the USP for the innovator (and generic) product.

Bottom Line

No prospective study has ever found that an FDA approved generic product 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.