

Contains Nonbinding Recommendations

Draft Guidance on Warfarin Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Warfarin Sodium

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: 4-way, fully replicated crossover design *in-vivo*
Strength: 10 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Warfarin has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_{0-∞}, as described in the Guidance for Industry: "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations".

Applicants may consider using the reference-scaled average bioequivalence approach for warfarin described below.

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2. Type of study: Fed
Design: 4-way, fully replicated crossover design *in-vivo*
Strength: 10 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: See additional comments above. See Amantadine Hydrochloride Oral Tablet guidance for recommendation regarding fed studies.
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Analytes to measure (in appropriate biological fluid): Warfarin in plasma, using an achiral assay.

Bioequivalence based on (90% CI): Warfarin

Waiver request of in-vivo testing: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg and 7.5 mg are eligible for a waiver of in-vivo bioequivalence testing based on (i) acceptable bioequivalence studies on the 10 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Method Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each

of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Explanation: FDA has concluded that Warfarin sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- For warfarin there is a narrow range between therapeutic and toxic doses or the associated blood or plasma concentrations (i.e., exposures);
- Warfarin toxicities are serious and not symptomatic or reversible;
- Subtherapeutic warfarin concentrations may lead to serious and life-threatening complications;
- Warfarin is subject to therapeutic monitoring based on pharmacodynamic markers; and
- Warfarin has low within subject variability.

The study should be a fully replicated crossover design in order to

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference product within-subject variability.

Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs:

Step 1. Determine s_{WR} , the estimate of within-subject standard deviation (SD) of the reference product, for the pharmacokinetic (PK) parameters AUC and Cmax.

Calculation for s_{WR} can be conducted as follows:

$$s_{WR}^2 = \frac{\sum_{i=1}^m \sum_{j=1}^{n_j} (D_{ij} - \overline{D}_i)^2}{2(n-m)}$$

Where:

i = number of sequences m used in the study

[$m=2$ for fully replicated design: TRTR and RTRT]

j = number of subjects within each sequence

T = Test product

R = Reference product

$D_{ij} = R_{ij1} - R_{ij2}$ (where 1 and 2 represent replicate reference treatments)

$$\overline{D}_i = \frac{\sum_{j=1}^{n_i} D_{ij}}{n_i}$$

$n = \sum_{i=1}^m n_i$ (i.e. total number of subjects used in the study, while n_i is number of subjects used in sequence i)

Step 2. Use the referenced-scaled procedure to determine BE for individual PK parameter(s).

Determine the 95% upper confidence bound for:

$$\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta s_{WR}^2$$

Where:

- \overline{Y}_T and \overline{Y}_R are the means of the ln-transformed PK endpoint (AUC and/or Cmax) obtained from the BE study for the test and reference products, respectively
- $\theta = \left(\frac{\ln(\Delta)}{\sigma_{w0}}\right)^2$ (scaled average BE limit)
- and $\sigma_{w0} = 0.10$ (regulatory constant), $\Delta = 1.11111 (=1/0.9)$, the upper BE limit

The method of obtaining the upper confidence bound is based on Howe's Approximation I, which is described in the following paper:

W.G. Howe (1974), Approximate Confidence Limits on the Mean of X+Y Where X and Y are Two Tabled Independent Random Variables, Journal of the American Statistical Association, 69 (347): 789-794.

Step 3. Use the unscaled average bioequivalence procedure to determine BE for individual PK parameter(s). Every study should pass the scaled average bioequivalence limits and also regular unscaled bioequivalence limits of 80.00-125.00%.

Step 4. 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.

The $(1-\alpha)100\%$ CI for $\frac{\sigma_{WT}}{\sigma_{WR}}$ is given by

$$\left(\frac{s_{WT}/s_{WR}}{\sqrt{F_{\alpha/2}(v_1, v_2)}}, \frac{s_{WT}/s_{WR}}{\sqrt{F_{1-\alpha/2}(v_1, v_2)}} \right)$$

where

- s_{WT} is the estimate of σ_{WT} with v_1 as the degree of freedom
- s_{WR} is the estimate of σ_{WR} with v_2 as the degree of freedom
- $F_{\alpha/2, v_1, v_2}$ is the value of the F-distribution with v_1 (numerator) and v_2 (denominator) degrees of freedom that has probability of $\alpha/2$ to its right.
- $F_{1-\alpha/2, v_1, v_2}$ is the value of the F-distribution with v_1 (numerator) and v_2 (denominator) degrees of freedom that has probability of $1-\alpha/2$ to its right.
- here $\alpha = 0.1$.

If SAS[®] is used for statistical analysis*

PROC MIXED should be used for fully replicated (4-period, 2-sequence replicated crossover_4-way) BE studies

*not necessary to use SAS[®] if other software accomplishes same objectives

Example SAS Codes: 4-period, 2-sequence replicated crossover study

For a bioequivalence study with the following sequence assignments in a fully replicated 4-way crossover design:

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

The following codes are an example of the determination of reference-scaled average bioequivalence for LAUCT. Assume that the datasets TEST and REF, have already been created, with TEST having all of the test observations and REF having all of the reference observations.

Dataset containing TEST 1 observations:

```
data test1;
  set test;
  if (seq=1 and per=1) or (seq=2 and per=2);
  lat1t=lauct;
run;
```

Dataset containing TEST 2 observations:

```
data test2;
  set test;if (seq=1 and per=3) or (seq=2 and per=4);
  lat2t=lauct;
run;
```

Dataset containing REFERENCE 1 observations:

```
data ref1;
  set ref;if (seq=1 and per=2) or (seq=2 and per=1);
  lat1r=lauct;
run;
```

Dataset containing REFERENCE 2 observations:

```
data ref2;
  set ref;
  if (seq=1 and per=4) or (seq=2 and per=3);
  lat2r=lauct;
run;
```

The number of subjects in each sequence is n_1 and n_2 for sequences 1 and 2, respectively.

Define the following quantities:

$T_{ijk} = k^{th}$ observation ($k = 1$ or 2) on T for subject j within sequence i

$R_{ijk} = k^{th}$ observation ($k = 1$ or 2) on R for subject j within sequence i

$$I_{ij} = \frac{T_{ij1} + T_{ij2}}{2} - \frac{R_{ij1} + R_{ij2}}{2}$$

and

$$D_{ij} = R_{ij1} - R_{ij2}$$

I_{ij} is the difference between the mean of a subject's (specifically subject j within sequence i) two observations on T and the mean of the subject's two observations on R , while D_{ij} is the difference between a subject's two observations on R .

Determine I_{ij} and D_{ij}

```
data scavbe;
  merge test1 test2 ref1 ref2;
  by seq subj;
  ilat=0.5*(lat1t+lat2t-lat1r-lat2r);
  dlat=lat1r-lat2r;
run;
```

Intermediate analysis - ilat

```
proc mixed data=scavbe;
  class seq;
  model ilat =seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=iout1;
  ods output Estimates=iout2;
  ods output NObs=iout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - ilat, mixed';
run;
```

From the dataset IOU2, calculate the following:

IOU2:

```
pointest=exp(estimate);
x=estimate**2-stderr**2;
boundx=(max((abs(lower)),(abs(upper))))**2;
```

Intermediate analysis - dlat

```
proc mixed data=scavbe;
  class seq;
  model dlat=seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=dout1;
  ods output Estimates=dout2;
  ods output NObs=dout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - dlat, mixed';
run;
```

From the dataset DOUT1, calculate the following:

DOUT1: $s2wr=estimate/2$;

From the dataset DOUT2, calculate the following:

DOUT2: $dfd=df$;

From the above parameters, calculate the final 95% upper confidence bound:

```
theta=((log(1.1111))/0.1)**2;
y=-theta*s2wr;
```

```
boundy=y*dfd/cinv(0.95,dfd);  
swr=sqrt(s2wr);  
critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
```

Calculate the unscaled average bioequivalence limits:

Calculation of unscaled 90% bioequivalence confidence intervals:

```
PROC MIXED  
data=pk;  
CLASSES SEQ SUBJ PER TRT;  
MODEL LAUCT = SEQ PER TRT/ DDFM=SATTERTH;  
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;  
REPEATED/GRP=TRT SUB=SUBJ;ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;ods output  
Estimates=unscl;  
title1 'unscaled BE 90% CI - guidance version';title2 'AUCT';  
run;  
  
data unscl;  
set unscl;  
unscabe_lower=exp(lower);  
unscabe_upper=exp(upper);  
run;
```