Bioequivalence model examples

Knowledge of how to do basic tasks using the Phoenix interface, such as creating a project and importing data, is assumed.

Analyzing average bioequivalence of 2x2 crossover study example

The objective of this study is to compare a newly developed tablet formulation to the capsule formulation that was being used in Phase II studies. Both had a label claim of 25 mg per dosing unit.

A 2x2 crossover design was chosen for this study. Twenty subjects were randomly assigned to one of two sequence groups. Within each sequence group, each subject took both formulations, with a washout period between. Drug concentrations in plasma were measured, and the AUClast (area under a curve computed to the last observation) was calculated.

Data for this example are provided in `…\Examples\WinNonlin\Supporting files`. The dataset used is `Data 2x2.CSV`.

The completed project (`Bioequivalence_2x2.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the object

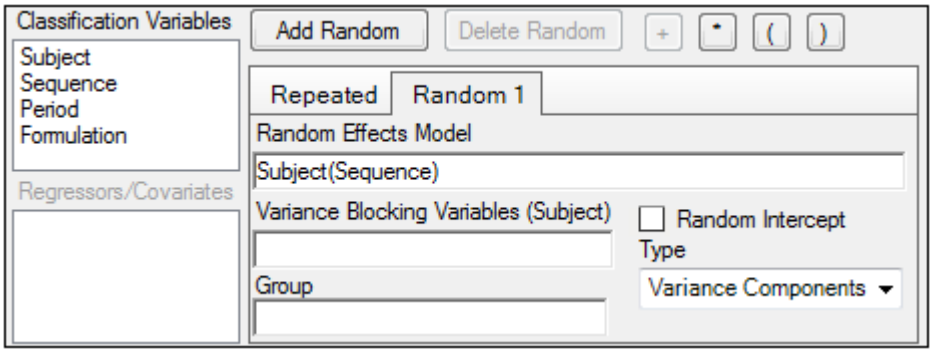
1. Create a new project named `Bioequivalence_2x2`.
2. Import the file `…\Examples\WinNonlin\Supporting files\Data 2x2.CSV`.
3. Right-click **Data 2x2** in the Data folder and then select **Send To > Computation Tools > Bioequivalence**.
4. In the Main Mappings panel:
   Leave **Sequence** mapped to the **Sequence** context.
   Leave **Subject** mapped to the **Subject** context.
   Leave **Period** mapped to the **Period** context.
   Leave **Formulation** mapped to the **Formulation** context.
   Map **AUClast** to the **Dependent** context.

Average is selected as the **Type of Bioequivalence**, and **Capsule** is selected as the **Reference Formulation**.

6. Select the **Fixed Effects** tab, make sure that: `Sequence+Formulation+Period` appears in the **Model Specification** field. **Ln(x)** is selected in the **Dependent Variables Transformation** menu.

7. Select the **Variance Structure** tab.

   The random effects are already specified in the Variance Structure tab. If they are not, type `Subject(Sequence)` in the Random Effects Model field.



Execute and view the results

1. Click (**Execute** icon) to execute the object.

   The Average Bioequivalence worksheet indicates that the difference in ln(AUClast) between formulations is 0.046±0.073 (Difference±Diff_SE). The 90% confidence interval for the ratio is 92.216 (CI_90_Lower) to 118.780 (CI_90_Upper).

   Since the interval is completely contained between 80 and 125, one can conclude that the formulations are bioequivalent.

2. Select the **Partial Tests** worksheet and compare with the **Sequential Tests** worksheet.

   Because the data are balanced, the sequential and partial tests are identical. Note that, in the tests, Sequence is statistically significant, but no other factor is.

   Select any cell with a numerical value in the Bioequivalence worksheet output and look in the value display bar above to see the full precision of 15 decimal places.

2	Ln(AUClast)		Sequence	1	18	9.1791447	0.0072041006
3	Ln(AUClast)		Formulation	1	18	0.38918061	0.54055657
4	Ln(AUClast)		Period	1	18	0.38553091	0.54244126

Sequential Tests worksheet for 2x2 crossover study

This concludes the Bioequivalence example of analyzing a 2x2 crossover study.

Analyzing average bioequivalence of a replicated crossover design example

The objective of this study is to compare a newly developed tablet formulation to a capsule formulation that was used in Phase II studies. Both formulations have the same label claim per dosing unit.

A RTRT/TRTR replicated crossover design was chosen for this study. Twenty subjects were randomly assigned to one of two sequence groups. Concentrations of the drug were measured in plasma, and the AUClast (area under the time-concentration curve, computed to the last observation) was calculated.

Note: The completed project (`Bioequivalence_replicated.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the object

1. Create a project called `Bioequivalence_replicated`.

2. Import the file `…\Examples\WinNonlin\Supporting files\Data 2x4.CSV`.

1. Right-click **Data 2x4** in the Data folder and select **Send To > Computation Tools > Bioequivalence**.

2. In the Mappings panel:
   Leave **Sequence** mapped to the **Sequence** context.
   Leave **Subject** mapped to the **Subject** context.
   Leave **Period** mapped to the **Period** context.
   Leave **Formulation** mapped to the **Formulation** context.
   Map **AUClast** to the **Dependent** context.

3. In the Model tab below the Setup panel, make sure that:
   Crossover is selected as the **Type of study**,
   Average is selected as the **Type of Bioequivalence**, and
   Capsule is selected as the **Reference Formulation**.

4. Select the **Fixed Effects** tab and make sure that:
   `Sequence+Formulation+Period` appears in the **Model Specification** field.
   Ln(x) is selected in the **Dependent Variables Transformation** menu.

   Note: Phoenix has automatically selected a model specification and classification variables based on the model for replicated crossovers.

Notice that the default variance structure for a replicated crossover design is substantially different from and more complex than that for the 2x2 crossover design. As a result, the model fitting is more difficult as well.

In the **Random 1** sub-tab, make sure that:
`Formulation` appears in the Random Effects Model field.
`Subject` appears in the Variance Blocking Variables field.
Banded No-Diagonal Factor Analytic(f) is selected in the **Type** menu.
`2` is specified as the **Number of factors**.

In the **Repeated** sub-tab, make sure that:
`Period` appears in the Repeated Specification field.
`Subject` appears in the Variance Blocking Variables field.
`Formulation` appears in the Group field.
Variance Components is selected in the **Type** menu.

Execute and view the results

A user can expect that about 50% of datasets analyzed will produce a non-positive definite G matrix. This does not imply that the model-fitting is invalid, but only that a user must be careful not to over-interpret the variance estimates. The interval on the formulation difference will still have the expected statistical properties.

1. Execute the object.

   The Average Bioequivalence worksheet indicates that the analysis just failed to show bioequivalence since the 90% confidence interval=91.612 (CI_90_Lower) and 125.772 (CI_90_Upper).

2. Select the **Partial Tests** worksheet and compare with the **Sequential Tests** worksheet.

   Because the data are balanced, the sequential and partial tests are identical.

	Dependent	Units	Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
1	Ln(AUClast)		int	1	18.002928	1.0179746	0.3263692
2	Ln(AUClast)		Sequence	1	18.002928	1.3287236	0.26410896
3	Ln(AUClast)		Formulation	1	55.5831	0.55936476	0.4576691
4	Ln(AUClast)		Period	3	55.740133	0.071944219	0.97474377

Partial Tests worksheet for replicated crossover study

2	Ln(AUClast)		Sequence	1	18.002928	1.3287236	0.26410896
3	Ln(AUClast)		Formulation	1	55.5831	0.55936476	0.4576691
4	Ln(AUClast)		Period	3	55.740133	0.071944219	0.97474377

Sequential Tests worksheet for replicated crossover study

This concludes the Bioequivalence example of analyzing a replicated crossover study.

Evaluating individual and population bioequivalence example

Phoenix can handle a wide variety of model designs suitable for assessing individual and population bioequivalence, including:

TRTR/RTRT/TRRT/RTTR
TT/RR/TR/RT
TRT/RTR/TRR/RTT
TRRTT/RTTRR
TRR/RTR/RRT
RTR/TRT
TRR/RTT/TRT/RTR/TTR/RRT
TRRR/RTTT
TTRR/RRTT/TRRT/RTTR/TRRR/RTTT

where T=Test formulation and R=Reference formulation.

Note: Each sequence must contain the same number of periods. For each period, each subject must have one measurement.

A bioequivalence example, included as part of "Testing the Phoenix installation", shows results for a RTR/TRT design. This example demonstrates an analysis of a TT/RR/TR/RT design.

Note: The completed project (`Bioequivalence_IndPop.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the population/individual model

1. Create a project called `Bioequivalence_IndPop`.
2. Import the file `…\Examples\WinNonlin\Supporting files\TT RR RT TR.DAT`.

   Notice that the number of subjects is not the same in each sequence group. TT, RR, TR, and RT each have 4 subjects, whereas RT has 5.
3. Right-click **TT RR RT TR** in the Data folder and select **Send To > Computation Tools > Bioequivalence**.
4. In the Model tab below the Setup panel, select the **Population/Individual** option button in the **Type of Bioequivalence**

5. Map the data types to the following contexts:
   Leave **Sequence** mapped to the **Sequence** context.
   Leave **Subject** mapped to the **Subject** context.
   Leave **Period** mapped to the **Period** context.
   Leave **Formulation** mapped to the **Formulation** context.
   Map **AUC** to the **Dependent** context.

6. In the Model tab, make sure that:
   Crossover is selected in the **Type of study** area. Crossover studies are the only permitted type for Population/Individual bioequivalence analysis.
   Population/Individual is set as the **Type of Bioequivalence**.
   R is selected in the **Reference Value** menu.

7. Select the **Fixed Effects** tab and make sure that **Ln(x)** is set as the **Dependent Variables Transformation**. The values will be log-transformed before the analysis.

8. Select the **Options** tab and enter 95 as the **Confidence Level**.

Execute and view the Population/Individual model results

1. Execute the object.

2. Select the **Population Individual** worksheet in the Results list.

	Dependent	Units	Statistic	Value	Upper_CI	Conclusion
1	Ln(AUC)		Difference(Delta	-0.012731099		
2	Ln(AUC)		Ratio(%Ref)	98.73496		BE shown for ra
3	Ln(AUC)		SigmaR	0.34459595		
4	Ln(AUC)		SigmaWR	0.050238748		
5	Ln(AUC)		Ref_Pop_eta	-0.22871866	0.013887295	Pop. BE not sho
6	Ln(AUC)		Const_Pop_eta	-0.090659369	0.10146367	Pop. BE not sho
7	Ln(AUC)		Mixed_Pop_eta	-0.22871866	0.013887295	Pop. BE not sho
8	Ln(AUC)		Ref_Indiv_eta	0.00090975147	0.043498602	Indiv. BE not sh
9	Ln(AUC)		Const_Indiv_eta	-0.092586522	-0.050460177	Indiv. BE shown
10	Ln(AUC)		Mixed_Indiv_eta	-0.092586522	-0.050460177	Indiv. BE shown

Inspect the results for mixed scaling. For population bioequivalence, the upper limit is 0.014 > 0, and therefore population BE has not been shown. For individual bioequivalence, the upper limit is –0.05 < 0, and so individual BE has been shown.

Compare average bioequivalence

1. Right-click the **Bioequivalence** object in the Object Browser and select **Copy**

2. Right-click **Workflow** in the Object Browser and select **Paste**.

Crossover is selected as the **Type of study**, and **R** is selected as the **Reference Formulation**.

4. Select the **Fixed Effects** tab and make sure that:
`Sequence+Formulation+Period` appears in the **Model Specification** field.
Ln(x) is selected in the **Dependent Variables Transformation** menu.

5. Select the **Variance Structure** tab.

   In the **Random 1** sub-tab, make sure that:
   `Formulation` appears in the Random Effects Model field.
   `Subject` appears in the Variance Blocking Variables field.
   Banded No-Diagonal Factor Analytic(f) is selected in the **Type** menu.
   `2` is in the **Number of factors** field.

   Select the Variance Structure's **Repeated** tab and make sure that:
   `Period` appears in the **Repeated Specification** field.
   `Subject` appears in the **Variance Blocking Variables** field.
   `Formulation` appears in the **Group** field.

Execute and view the average bioequivalence results

1. Execute the object.

   Using the model for average bioequivalence on replicated crossover designs resulted in a 90% lower interval of 87.277% (CI_90_Lower) and a 99.715% upper interval (CI_90_Upper) for the ratio of average AUC. Therefore a user can also conclude average bioequivalence is achieved. This is not always the case. Data can pass individual BE and fail average BE, and data can also pass average BE and fail individual BE.

This concludes the Bioequivalence individual/population evaluation example.

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