



## WORKED EXAMPLE

Bioequivalence study of a  
new sildenafil 100 mg  
orodispersible film  
compared to the  
conventional film-coated  
100 mg tablet administered  
to healthy male volunteers



**Title:** Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers.

**Objective:** The aim of this study was to assess the bioequivalence between the new sildenafil 100 mg orodispersible film and the conventional marketed 100 mg film-coated tablet after single-dose administration to healthy male volunteers.

**Year:** 2012

**Source:** Drug Design, Development and Therapy

**Link:** <https://doi.org/10.2147/DDDT.S124034>

**Protocol:** N/A

**Clinical Area:** Sexual Health



### Sample Size Section in Paper/Protocol:

“Sildenafil and N-desmethyl-sildenafil rate (Cmax) and extent (AUC) of absorption were compared between test and reference using analysis of variance for a crossover design on log-transformed data”

“The highest **coefficient of variance for the pharmacokinetic parameters Cmax and AUC was estimated to be 0.383** ... Fixing the **significance level  $\alpha$  at 5%** and the **hypothesized test/reference mean ratio to 1**, 50 subjects were considered sufficient to attain a **power of 80%** to correctly conclude the **bioequivalence between the two formulations within the range 80.00%–125.00%** for all parameters (Cmax and AUC)”

### Summary of Necessary Parameter Estimates for Sample Size Calculation

Parameter	Value
Significance Level	0.05
Lower Equivalence Limit	0.8
Upper Equivalence Limit	1.25
Expected Ratio	1
Coefficient of Variation	0.383
Power	80%



**Step 1:**

Select the **MTE2co Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design** table from the Study Design Pane.

This can be done **using the radio buttons** or alternatively, you can **use the search bar** at the end of the Select Test Design & Goal window.

The 'Select Test' dialog box is shown with the following settings:

- Design:**  Fixed,  Bayesian,  Adaptive
- Goals:**  Means,  Proportions,  Survival,  Counts,  Agreement,  Regression
- No. of Groups:**  One Group,  Paired,  Cross-over,  Two,  > 2,  Hierarchical
- Analysis Methods:**  Inequality,  Equivalence,  Non-inferiority,  Intervals

Search results for 'Two One-Sided Equivalence Tests (TOST) for Two Group or Crossover Design':

- ▶ Two One-Sided Equivalence Tests (TOST) for Two Group or Crossover Design (Double-click for options)
- ▲ TOST for ratio of means (logscale) for two-group or crossover design (Double-click for options)
  - MTE2t... Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means
  - MTE2c... Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design**
  - MTE4 Two One-Sided Equivalence Tests for Ratio of Two Normal Means for Crossover Design
  - MTE5 Equivalence Higher-Order Crossover Design for Two Means using Differences
  - MTE8 Equivalence Higher-Order Crossover Design for Two Means using Ratios
  - MTE26 Equivalence Test for Pairwise Mean Differences in a Williams Crossover Design
  - MTE31 Two Poisson Cross-over Equivalence

Search bar: Type here to search all tests... Clear Search

Buttons: OK, Cancel



**Step 2:**

Enter the parameter values for sample size calculation taken from the study description.

The significance level, equivalence limits, expected ratio and power can be entered directly from the study design.

The screenshot shows the nQuery software interface. The title bar reads 'nQuery'. The menu bar includes 'File', 'Edit', 'View', 'Assistants', 'Plot', and 'Help'. The toolbar contains various icons for file operations and statistical functions. The active window title is 'Two One-Sided Equivalence Tests for Ratio of Two Log-Normal'. The main area displays a table with the following data:

	1	2	3
Test Significance Level, $\alpha$	0.050		
Lower Equivalence Limit for $\mu_0/\mu_1$ , $\Delta(L)$	0.800		
Upper Equivalence Limit for $\mu_0/\mu_1$ , $\Delta(U)$	1.250		
Expected Ratio, $\mu_0/\mu_1$	1.000		
Crossover ANOVA, sqrt(MSE) (In Scale)			
SD differences, $\sigma$ (In Scale)			
Power (%)			
Sample Size per Sequence, n			

The square root of the mean square error parameter is estimated from the coefficient of variation. A table for this conversion can be accessed from the **Assistants** menu. Go to the menu and select **Assistants > Standard Deviation > From Coefficient of Variation**.



The screenshot shows the nQuery software interface. The 'Assistants' menu is open, with 'Standard Deviation' selected. The background spreadsheet displays data for a crossover ANOVA. The table below represents the data shown in the spreadsheet:

	1	2	3
0.050			
0.800			
1.250			
1.000			

The 'Estimate Standard Deviation' dialog box is shown with the following options:

- From Standard Error
- From SD1 and SD2 (pooled SD)
- From Range
- From Percentile
- From Coefficient of Variation
- From Upper Confidence Limit
- From SD1, SD2, Correlation
- For Cluster Sampling
- For specified x values
- Of residuals (errors)

Buttons: OK, Cancel



Enter the Coefficient of Variation into the conversion table and the estimate of the standard deviation will automatically be calculated.



MOT15-1 / Standard Deviation from Coefficient of Variation assuming Log-Normality

	1	2	3	4
Coefficient of variation, $CV = \sigma/\bar{x}$	0.383			
Estimated $\sigma$ in log scale	0.36997116			
Observed mean, $\bar{x}$				
Estimated mean, $\mu$ , in log scale				

Enter the estimate of standard deviation in the main table and the standard deviation of the differences will automatically be calculated.

MTE2co-1 / Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design

	1	2	3	4	5	
Test Significance Level, $\alpha$	0.050					
Lower Equivalence Limit for $\mu_0/\mu_1$ , $\Delta(L)$	0.800					
Upper Equivalence Limit for $\mu_0/\mu_1$ , $\Delta(U)$	1.250					
Expected Ratio, $\mu_0/\mu_1$	1.000					
Crossover ANOVA, $\sqrt{MSE}$ (ln Scale)	0.370					
SD differences, $\sigma$ (ln Scale)	0.523					
Power (%)						
Sample Size per Sequence, n						

Finally, enter the required power and the sample size per sequence will automatically be calculated.

MTE2co-1 / Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design

	1	2	3	4	5	6
Test Significance Level, $\alpha$	0.050					
Lower Equivalence Limit for $\mu_0/\mu_1$ , $\Delta(L)$	0.800					
Upper Equivalence Limit for $\mu_0/\mu_1$ , $\Delta(U)$	1.250					
Expected Ratio, $\mu_0/\mu_1$	1.000					
Crossover ANOVA, $\sqrt{MSE}$ (ln Scale)	0.370					
SD differences, $\sigma$ (ln Scale)	0.523					
Power (%)	80					
Sample Size per Sequence, n	25					



The analysis requires a sample size of 25 subjects per sequence (total sample size of 50) to achieve a power of 80% to reject the null hypothesis that the standard and experimental treatments are not equivalent. This is consistent with the sample size reported in the study design.

### Output Statement:

*"When the sample size in each sequence group is 25 (and the total sample size is 50), a crossover design will have 80% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 0.8 and the null hypothesis that the ratio of test mean to the standard mean is above 1.25; i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two treatments are equivalent, assuming that the expected ratio of means is 1, the Crossover ANOVA,  $\sqrt{MSE}$  (ln scale) is 0.37 (the SD differences,  $\sigma$  (ln scale) is 0.523), that data will be analyzed in the natural log scale using t-tests for differences in means, and that each t-test is made at the 5% level."*

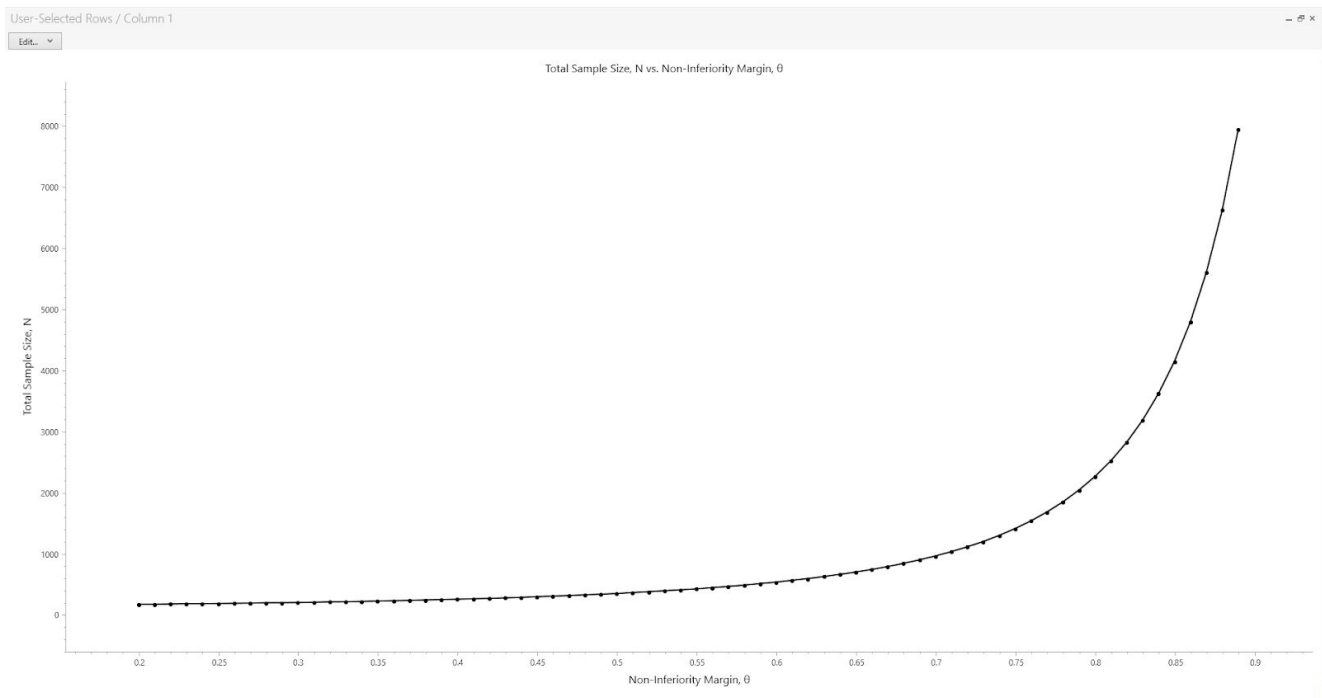
### Step 3:

nQuery also provides plotting options. To access the plotting tools, highlight the completed columns that you wish to work with, go to the menu and select: **Plot > User-Selected Rows**.

In this case, we will demonstrate how the sample size per sequence is affected when the lower equivalence limit varies between , keeping all other parameters constant. A non inferiority margin of 0.2 would require that the experimental treatment achieves at least 20% of the reference treatment, each in comparison to placebo. A non inferiority margin of 0.9 would require that the experimental treatment achieves at least 90% of the reference treatment, each in comparison to placebo. With this in mind, we expect the sample size to increase as the non-inferiority margin increases.

The dialog box titled "Select X-axis, Y-axis" has a red close button in the top right corner. It is divided into two sections. The first section, "X-axis and Y-axis variables", contains two dropdown menus: "X-axis:" is set to "Non-Inferiority Margin,  $\theta$ " and "Y-axis:" is set to "Total Sample Size, N". The second section, "X-axis range and step size", contains three input fields with spinners: "Min value:" is 0.2, "Max value:" is 0.9, and "Step size:" is 0.01. At the bottom of the dialog are "OK" and "Cancel" buttons.





The **Edit** button at the top of the output allows users to customise the appearance of the plot.