



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 (C_{max}) 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 C_{max} and AUC was estimated to be 0.383** ... Fixing the **significance level α 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 (C_{max} 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 contains the following options:

- 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

The search results list is as follows:

- ▶ 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 with a spreadsheet titled "MTE2co-1 / Two One-Sided Equivalence Tests for Ratio of Two Log-Normal". The spreadsheet has columns for parameters and three test scenarios (1, 2, 3). The "Expected Ratio, μ_0/μ_1 " row is highlighted in light blue and contains the value 1.000 in column 1. The "Power (%)" and "Sample Size per Sequence, n" rows are highlighted in light yellow.

	1	2	3
Test Significance Level, α	0.050		
Lower Equivalence Limit for μ_0/μ_1 , $\Delta(L)$	0.800		
Upper Equivalence Limit for μ_0/μ_1 , $\Delta(U)$	1.250		
Expected Ratio, μ_0/μ_1	1.000		
Crossover ANOVA, sqrt(MSE) (In Scale)			
SD differences, σ (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, listing various statistical tools. The 'Standard Deviation' option is highlighted. In the background, a spreadsheet is visible with a table titled 'ce Tests for Ratio of Two Log-'. The table has three columns labeled 1, 2, and 3, and several rows of numerical data.

	1	2	3
0.050			
0.800			
1.250			
1.000			

The 'Estimate Standard Deviation' dialog box is shown. It contains a list of radio button options for different methods of estimating standard deviation. The 'From Coefficient of Variation' option is selected.

- 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 for 'OK' and 'Cancel' are located at the bottom of the dialog.

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

nQuery

File Edit View Assistants Plot Help

Home Two One-Sided Equivalen Standard Deviation fro x +

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 σ in log scale	0.36997116			
Observed mean, \bar{x}				
Estimated mean, μ , 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, α	0.050					
Lower Equivalence Limit for μ_0/μ_1 , $\Delta(L)$	0.800					
Upper Equivalence Limit for μ_0/μ_1 , $\Delta(U)$	1.250					
Expected Ratio, μ_0/μ_1	1.000					
Crossover ANOVA, \sqrt{MSE} (ln Scale)	0.370					
SD differences, σ (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, α	0.050					
Lower Equivalence Limit for μ_0/μ_1 , $\Delta(L)$	0.800					
Upper Equivalence Limit for μ_0/μ_1 , $\Delta(U)$	1.250					
Expected Ratio, μ_0/μ_1	1.000					
Crossover ANOVA, \sqrt{MSE} (ln Scale)	0.370					
SD differences, σ (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, σ (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 expected geometric mean ratio varies. We will see the effect on power with a total sample size of 50 (25 per sequence) for true mean ratios between 0.9 to 1.1. We would expect the power to decrease as the mean difference approaches either equivalence margin and be maximised at a value of 1 (i.e. equidistant between the lower and upper equivalence limits).

The dialog box titled "Select X-axis, Y-axis" contains the following settings:

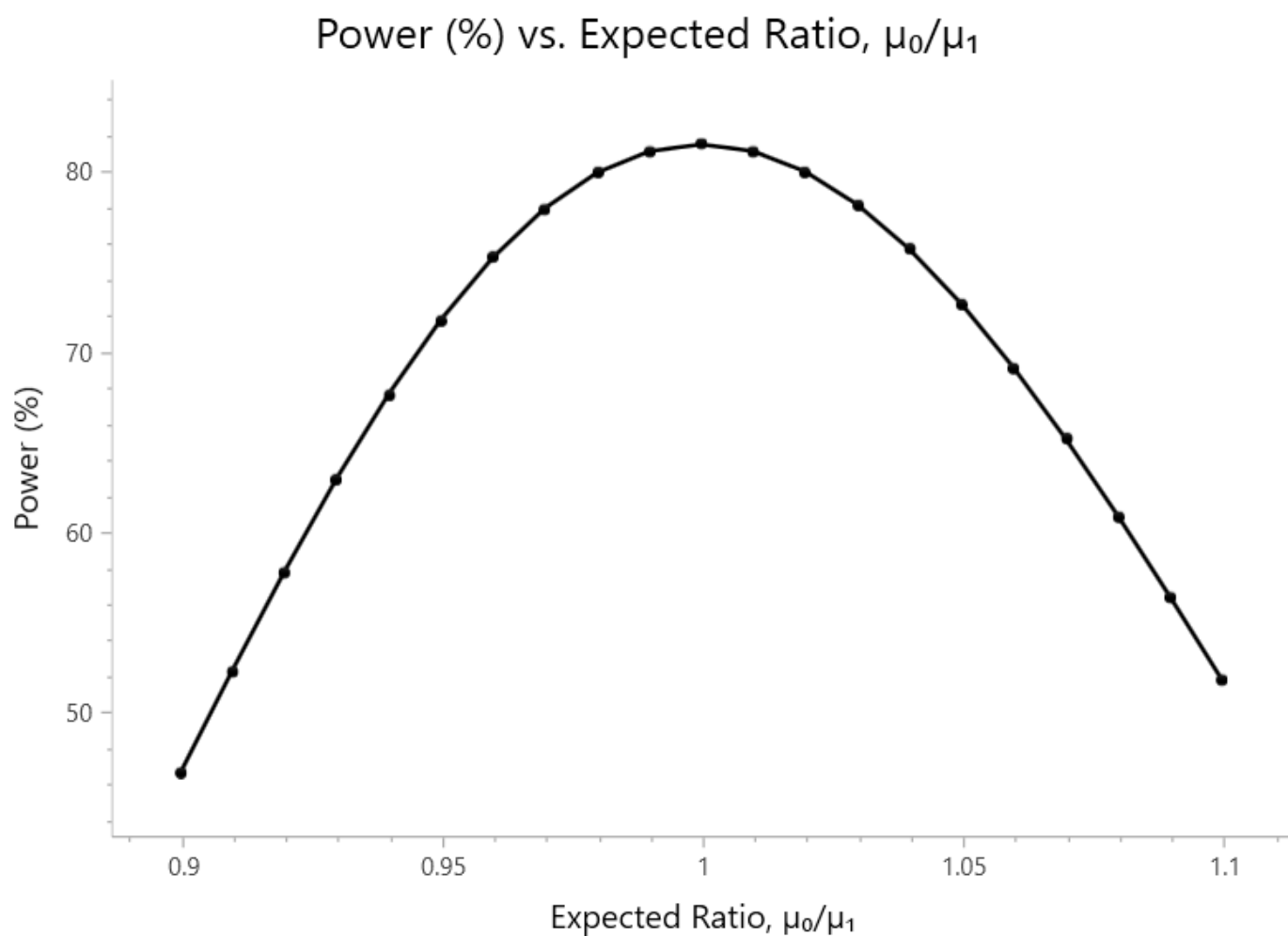
- X-axis and Y-axis variables:**
 - X-axis: Expected Ratio, μ_0/μ_1
 - Y-axis: Power (%)
- X-axis range and step size:**
 - Min value: 0.9
 - Max value: 1.1
 - Step size: 0.01

Buttons for "OK" and "Cancel" are located at the bottom right.

User-Selected Rows / Column 1

— □ ×

Edit... ▾



Note that the true equivalent ratio above and below one in this example is equal to the reciprocal (i.e. $1/\text{ratio}$) so the power for 0.9 and 1.1 would not be expected to be the same as can be seen above. However, a ratio of 1.11111111 (i.e. $1/0.9$) would give the same power as 0.9

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