Equivalence Margins

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Calculation

Calculation performed:	02.06.2014 13:22:02, Matthias Schmitt (PLA 3.0.0 Build 623, nbmsc03, 10014)
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Signatures

Responsibility	Approval	Review

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Overview

Setup

Confidence Level (Defining for which kind of confidence intervals the equivalence margins will be calculated):	0.95
Tolerance Level (Defining the amount of data to be used for margin calculation):	0.9

Documentation

Date	17.03.2014 13:21:31

Result

	Basic Statistics				Equivalence Margins		
	n	mean	stderr	CV	upper	lower	reference mean
Difference of parameter (Test - Standard)							
Difference of slopes (Parameter B)	24	-0.13229	0.20130	152.2%	0.96561	-0.96561	
Difference of upper asymptotes (Parameter A)	24	-792.28332	1103.56323	139.3%	4964.69383	-4964.69383	
Difference of lower asymptotes (Parameter D)	24	260.92462	426.90967	163.6%	2720.34909	-2720.34909	
Ratio of parameter (Test / Standard)							
Ratio of slopes (B Test/B Standard)	24	1.07044	0.10617	9.9%	1.59227	0.81101	
Ratio of upper asymptotes (A Test/A Standard)	24	0.98314	0.02312	2.4%	1.03921	0.89938	
Ratio of lower aysmptotes (D Test/D Standard)	24	1.08759	0.14050	12.9%	3.18653	0.58134	
Scaled Parameter Range (Test - Standard)/reference mean (Standard)							
Scaled slope range (Parameter B)	24	0.06745	0.10263	152.2%	0.49232	-0.49232	-1.96134
Scaled upper asymptote rage	24	-0.01685	0.02346	139.3%	0.10556	-0.10556	47032.36497
Scaled lower asymptote range (Parameter D)	24	0.07584	0.12409	163.6%	0.79071	-0.79071	3440.39983
Curve Shape Tests							
Slope (B Standard)	24	-1.96134	0.12803	6.5%	-1.57826	-2.42667	
Upper asymptote (A Standard)	24	47032.36497	1829.90156	3.9%	51123.78808	43527.47735	
Lower asymptote (D Standard)	24	3440.39983	550.92765	16.0%	5319.09662	1297.80360	
EC 50 (C Standard)	24	-1.10989	0.09703	8.7%	-0.90674	-1.32496	
Difference of asymptotes (|A Standard - D Standard|)	24	43591.96513	1647.42849	3.8%	47581.28664	40375.57146	
Ratio of Asymptotes (A Standard / D Standard)	24	13.95889	1.99980	14.3%	37.38322	9.00925	
Scaled asymptote range ((A Standard - D Standard)/reference mean (Std))	24	0.92685	0.03503	3.8%	1.01167	0.85846	47032.36497
Additional Tests							
Nonlinearity sum of squares	24	8374504.52307	4214413.19346	50.3%	14881050.45452	0.00000	

Literature

Callahan, J. D.; Sajjadi, N. C. Testing the null hypothesis for a specified difference - The right way to test for parallelism. Bioprocessing Journal. 2003, 2, 71 - 78
Hauck, W. W.; Carpen, R. C.; Callahan, J. D.; De Muth, J. E.; Hsu, H.; Lansky, D.; Sajjadi, N. C.; Seaver, S. S.; Singer, R. R.; Weisman, D. Assessing parallelism prior to determining relative potency. PDA Journal of Pharmaceutical Science and Technology. 2005, 59, 127 - 137.
The United States Pharmacopeia Convention. <1032> Design and development of biological assays. 2010.
The United States Pharmacopeia Convention. <1034> Analysis of biological assays. 2010.

Remarks on the calculation routines of the sheet

The lower margin for the parameter difference is calculated as a quantile of the empirical distribution of the difference of the parameter estimates minus the quantile of the empirical distribution function of the standard errors. Which quantile is used is given by the tolerance level. The upper margin is calculated in the same way as the quantile of the empirical distribution of the defferences plus the quantile of the empirical distribution function of the standard errors. This is based on the method described in Callahan and Sajjadi (2003). The use of the empirical distribution function makes the method a little bit more robust.

The method for calculating the margins for ratios of parameters is based on the method described in Hauck et. al. (2006). Instead of removing the biggest and smallest value, we choose the number of values that will be removed by use of quantiles of the empirical distribution function of the ratios. The used quantile is given by the tolerance level. The confidence interval for a single ratio is computed by the Fieller formula (the basic statistic is computed for the complete data set). This implies that values where the Fieller formula delivers no result will be removed from the calculation.

Analogously the equivalence margins for the standard alone are computed. But here the application of the Fieller formula is only necessary in case of the ratio of asymptotes.

In case of the lack of fit, only an upper margin has to be computed. This is done by using the quantile of the empirical distribution function of the observed lack of fit values specified by the tolerance level. So the confidence level is ignored in this case.

The USP distinguishes between Sample Suitability and System Suitability. The tests comparing Test and Standard are usually used as sample suitability tests. The remaining tests are used for assessing system suitability.

To compute suitable equivalence margins, the number of observations has to be large enough. So far there is only very few experience with equivalence margins in context of biological assays. In Hauck et. al. (2005) the number of used values is 25.