



Establishing statistical similarity for an insulin biosimilar based on equivalence and interval approaches

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Statistical approaches

- Analysis of covariance

Fixed factor compound (eg. Insulin lispro Sanofi, EU sourced Humalog and US-sourced Humalog); Covariate batch age

One data point per batch -> common intercept (release value) and slope (change over time) assumed for all batches of one compound

- Equivalence approach

Functional assays

$$\text{Ratio} = \frac{\text{Mean}_{\text{Testsample}}}{\text{Mean}_{\text{Reference}}} \quad \text{with 90\% Confidence Interval}$$

Physico-chemical assays

$$\text{Bias}_{\text{Abs}} = |\text{Mean}_{\text{Testsample}} - \text{Mean}_{\text{Reference}}| \quad \text{Bias}_{\text{Rel}} = \frac{(\text{Mean}_{\text{Testsample}} - \text{Mean}_{\text{Reference}})}{\text{Mean}_{\text{Reference}}} * 100$$

with 90% Confidence Interval

- Interval approach

90%-confidence/ 98%-coverage
Tolerance Intervals from Reference

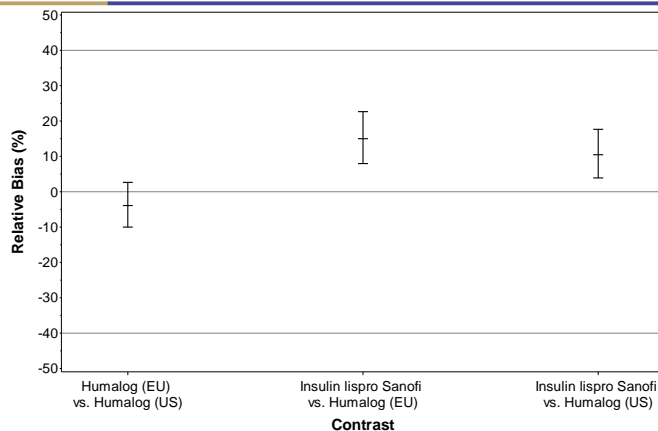
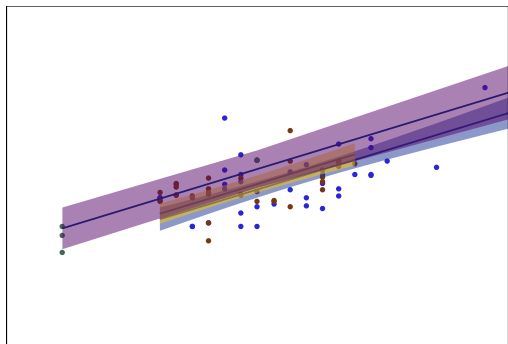
$$z_{(1+p)/2} \sqrt{1 + \frac{1}{n}} \sqrt{\frac{\sigma_E^2}{F_{\alpha, df, \infty}}}$$

90% Prediction Interval for single future batch from Biosimilar

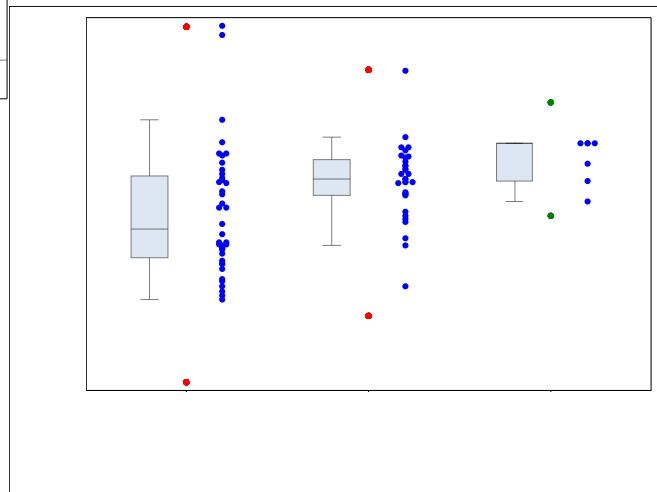
$$t_{(1-\alpha/2k), df} \sqrt{\sigma_E^2} \sqrt{1 + \frac{1}{n}}$$

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Results - Insulin-related substances (IRS) by HPLC



Contrast	Months	Relative bias	90% CI of rel. bias
Humalog (EU) vs. Humalog (US)	12	-3.87	[-10.06; 2.73]
Insulin lispro Sanofi vs. Humalog (EU)	12	15.03	[7.93; 22.66]
Insulin lispro Sanofi vs. Humalog (US)	12	10.58	[3.86; 17.77]

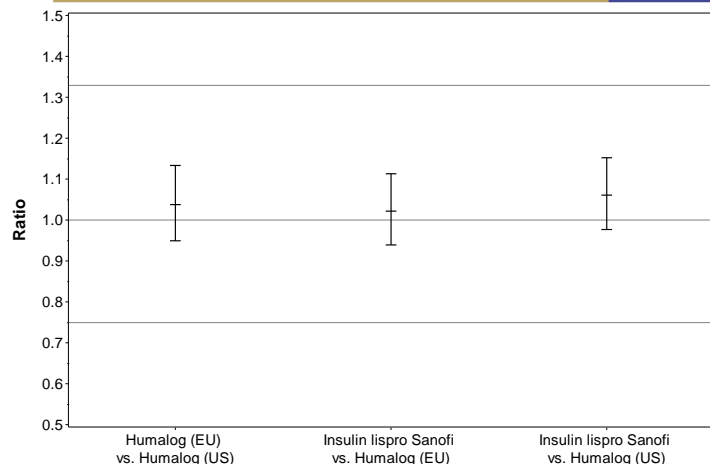


Compound	Months	Estimate	90% CI of Mean	Std. Err.	CV(%)
Humalog (EU)	12	1.0401	[0.979; 1.101]	0.0367	3.53
Humalog (US)	12	1.0819	[1.025; 1.139]	0.0342	3.16
Insulin lispro Sanofi	12	1.1963	[1.078; 1.315]	0.0710	5.93

Reference	Originator; 90% Tolerance Interval for p=0.98		SAR342434; 90% Prediction Intervals	
	Mean	Two-sided	Mean	Two-sided
Humalog (EU)	1.0401	[0.428; 1.653]	1.1963	[1.001; 1.392]
Humalog (US)	1.0819	[0.659; 1.505]		

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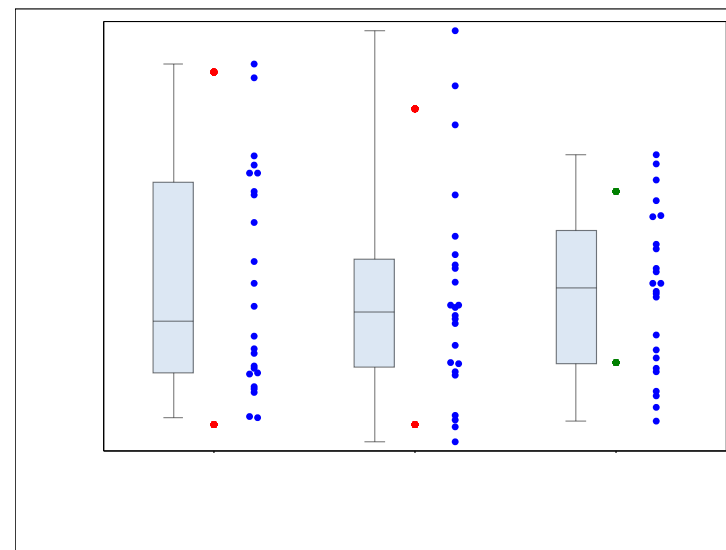
Results – Activity of human insulin receptor after stimulation



Reference	Originator; 90% Tolerance Interval for p=0.98		Insulin lispro Sanofi; 90% Prediction Intervals	
	Mean	Two-sided	Mean	Two-sided
HUMALOG EU	2.90E-08	[1.66E-08;5.06E-08]	2.97E-08	[2.25E-08;3.91E-08]
HUMALOG US	2.80E-08	[1.66E-08;4.71E-08]		

Compound	Mean	CV [%]	95% CI
HUMALOG EU	2.90E-08	3.85	[2.68E-08;3.14E-08]
HUMALOG US	2.80E-08	3.61	[2.59E-08;3.01E-08]
Insulin lispro Sanofi	2.97E-08	3.29	[2.77E-08;3.18E-08]

Contrast	Ratio	90% CI
Humalog (EU) vs. Humalog (US)	1.038	[0.9499;1.1339]
Insulin lispro Sanofi vs. Humalog (US)	1.061	[0.9779;1.1520]
Insulin lispro Sanofi vs. Humalog (EU)	1.023	[0.9394;1.1134]





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