CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761074Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.:	761074
SERIAL NO.:	0000
DATE RECEIVED BY THE CENTER:	November 2, 2016
DRUG NAME:	MYL-1401O (proposed biosimilar to HERCEPTIN® trastuzumab, Genentech Inc.)
DOSAGE FORM:	• an off-white to pale yellow lyophilized powder for concentrate for solution for infusion • one 50 mL clear, (b) (4) glass vial with (b) (4) injection stopper (b) (4) and sealed with 20 mm aluminum flip-off seal
INDICATIONS:	For the treatment of adjuvant breast cancer, metastatic breast cancer, and metastatic gastric cancer.
APPLICANT:	Mylan GmbH
REVIEW FINISHED:	June 20, 2017
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1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistics reviewer in the Office of Biostatistics analyzed the comparative results of 3 critical quality attributes: HER2 binding, relative potency, and relative ADCC activity, which were recommended for equivalence testing analysis by the Office of Biotechnology Products. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where σ_R represents US-licensed reference product variability or the comparator variability.

Nine lots of MYL-1401O, 22 lots of US-licensed Herceptin, and 22 lots of EU-approved Herceptin were used for equivalence testing of HER2 binding. The results are summarized in Table 1.

Table 1 Results of equivalence testing for HER2 binding

Comparison	# of lots	Mean difference%	90% confidence interval for the mean difference%	Equivalence margin%	Equivalent
MYL-1401O vs. US	(9, 22)*	0.8	(-6.5, 8.1)	(-18.4, 18.4)	Yes
MYL-1401O vs. EU	(9, 22)*	-2.1	(-8.4, 4.3)	(-14.1, 14.1)	Yes
EU vs. US	(22, 22)	2.9	(-2.7, 8.4)	(-18.4, 18.4)	Yes

*The 90% confidence interval for the mean difference between the test and comparator is adjusted by the sample size imbalance.

Nine lots of MYL-1401O, 22 lots of US-licensed Herceptin, and 22 lots of EU-approved Herceptin are included in the Relative potency dataset for the statistical equivalence testing. The results are shown in Table 2.

Table 2 Results of equivalence testing for relative potency

Comparison	# of lots	Mean difference%	90% confidence interval for the mean difference%	Equivalence margin%	Equivalent
MYL-1401O vs. US	(9, 22)*	-6.1	(-13.0, 0.7)	(-13.4, 13.4)	Yes
MYL-1401O vs. EU	(9, 22)*	-6.1	(-13.4, 1.2)	(-16.1, 16.1)	Yes
EU vs. US	(22, 22)	0.0	(-5.0, 5.0)	(-13.4, 13.4)	Yes

*The 90% confidence interval for the mean difference between the test and comparator is adjusted by the sample size imbalance.

Thirteen lots of MYL-1401O, 21 lots of US-licensed Herceptin, and 26 lots of EU-approved Herceptin are included in the relative ADCC activity dataset for the statistical equivalence testing. The results are shown in Table 3.

Table 3 Results of equivalence testing for relative ADCC activity

Comparison	# of lots	Mean difference%	90% confidence interval for the mean difference%	Equivalence margin%	Equivalent
MYL-1401O vs. US	(13, 21)*	3.5	(-4.3, 11.3)	(-17.3, 17.3)	Yes
MYL-1401O vs. EU	(13, 26)*	2.5	(-1.2, 9.0)	(-24.0, 24.0)	Yes
EU vs. US	(26, 21)	1.0	(-5.8, 7.8)	(-17.3, 17.3)	Yes

*The 90% confidence interval for the mean difference between the test and comparator is adjusted by the sample size imbalance.

As shown in Tables 1, 2 and 3, the results from the statistical equivalence testing of HER2 binding, relative potency, and relative ADCC activity support a demonstration that the proposed biosimilar MYL-1401O is highly similar to US-licensed Herceptin and also support the analytical bridge between US-licensed Herceptin and EU-approved Herceptin.

2 INTRODUCTION

On November 2, 2016, the applicant (Mylan) submitted to the US Food and Drug Administration (FDA) a 351(k) BLA, which included an analytical similarity assessment of comparing MYL-1401O and US-licensed Herceptin.

The applicant characterized multiple lots of US-licensed Herceptin and EU-approved Herceptin using a comprehensive set of analytical methods during the MYL-1401O development.

The Agency carefully reviewed their submission and sent out the first information request (IR) to the applicant on Jan 27, 2017 regarding the data integrity, consistency and correctness in the Comparability and Analytical Similarity report. The applicant responded the IR and submitted the second version of data to the Agency on Feb 10, 2017. On Feb 16th, 2017, the Agency sent out another IR to obtain the data in a different format such as .csv or SAS so that the reviewers can easily read in computer using statistical software. On Feb 21st, 2017 the applicant provided the requested data. On Mar 27, 2017 the Agent sent out the third IR regarding the reference standard used for the lots. On April 11, 2017, the applicant responded back with updated data with the reference standard information added. They used the same reference standard for all of the samples in the analytical similarity studies.

Our comments regarding Mylan's statistical equivalence testing (Tier 1 approach) is provided in Section 4 based on the most updated data and analysis submission, and our independent statistical equivalence testing analyses are present in Section 5.

3 DATA ANALYZED

Mylan submitted the updated analytical data on April 11th, 2017. Note that in Table 4, the HER2 binding data of 22 US-licensed Herceptin lots, 22 EU-approved Herceptin lots, 9 MYL-1401O lots were submitted by Mylan.

Mylan also provided and analyzed the relative potency for 22 lot values of EU-approved Herceptin, 9 lot values of MYL-1401O, and 22 lot values of US-licensed Herceptin.

And the relative ADCC activity data were submitted by Mylan with 26 lot values of EU-approved Herceptin, 13 lot values of MYL-1401O, and 21 lot values of US-licensed Herceptin.

Table 4 Number of lots from each product

Product	Number of lots		
	HER2 binding	Relative potency	Relative ADCC activity
US-licensed Herceptin	22	22	21
MYL-1401O	9	9	13
EU-approved Herceptin	22	22	26

4 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Mylan conducted Tier 1 statistical equivalence testing with the margin defined as $1.5\hat{\sigma}_R$ for HER2 binding, relative potency, and relative ADCC activity. Mylan followed the analysis guidelines provided by FDA.

5 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommended that Mylan apply a tiered approach in the Agency's responses to IND meetings with Mylan. That is, product quality attributes amendable to statistical evaluation are assigned to three tiers based on their criticality. The quality attributes with potential highest risk in product quality, efficiency, safety and PK/PD are generally assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. Quality attributes with lower impact are generally assigned to Tier 2 and their analytical similarity is evaluated by Quality Range approach. That is, a high percentage of the biosimilar data should be covered by (Mean – X*SD, Mean + X*SD) defined by the reference product. Here, the multiplier X typically ranges from 2 to 4. The quality attributes with the lowest risk are generally assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display.

This review focuses on the equivalence test in Tier 1.

5.1 Statistical method

Let μ_T and μ_R be respectively the population means of the quality attribute for the test product and the population mean of the quality attribute for the US-licensed Herceptin product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Herceptin. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Herceptin product, we aim to reject the null hypothesis of the following null and alternative hypotheses:

$$H_0 : \mu_T - \mu_R \le \theta_1 \text{ or } \mu_T - \mu_R \ge \theta_2$$

$$H_1 : \theta_1 < \mu_T - \mu_R < \theta_2$$

Here $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$, θ_1 and θ_2 are equivalence margins.

We reject H_0 if the 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Herceptin product if the 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. This specific equivalence margin was set as 1.5 times the standard deviation of the quality attribute for the US-licensed Herceptin product to ensure an adequate power for the case in which a small but sufficient number of lots are available for testing. For example, the probability of rejecting H_0 in the above two one-sided tests procedure with the equivalence margin being $\pm(-1.5\sigma_R, 1.5\sigma_R)$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 biosimilar lots and 10 US-licensed Herceptin lots. First we estimate σ_R by the sample variability of the US-licensed Herceptin product (or by the sample variability of EU-approved Herceptin in the comparison between MYL-1401O and EU-approved Herceptin) and then in the statistical analysis, θ_1 and θ_2 are treated as a constant, not a random variable.

Let X_{Tj} be the observed value of the quality attribute of interest for Batch *j* of the test product (the proposed biosimilar product) and X_{Rj} be the observed value of the quality attribute of interest for Batch *j* of the US-licensed Herceptin product. Since the two products are manufactured by two manufacturers, two groups are independent. $\overline{X}_i = \sum_{j=1}^{n_i} X_{ij} \Big/ n_i$, and $S_i^2 = \sum_{j=1}^{n_i} (X_{ij} - \overline{X}_i) \Big/ (n_i - 1)$, where n_i is the number of lots in the i^{th} product, $i = T, R$.

Under the unequal variance of the test product and the US-licensed Herceptin product, the (1-2α)*100% confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\overline{X}_T - \overline{X}_R - t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}, \overline{X}_T - \overline{X}_R + t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}} \right). \quad (1)$$

Here $t_\alpha(\nu)$ is the 1-α quantile and ν is the degrees of freedom calculated by

Satterthwaite's approximation.

If $n_R > 1.5n_T$, the (1-2α)*100% confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(\nu^*)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}},\ \bar{X}_T - \bar{X}_R + t_\alpha(\nu^*)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}} \right). \quad (2)$$

Here $n_R^* = \min(n_R, 1.5n_T)$ and $\nu^* = \dfrac{\left(\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}\right)^2}{\frac{1}{n_T - 1}\left(\frac{S_T^2}{n_T}\right)^2 + \frac{1}{n_R - 1}\left(\frac{S_R^2}{n_R^*}\right)^2}$.

If the number of biosimilar lots, n_T, is 50% more than the number of reference lots, n_R, we can apply a similar approach as above with $n_T^* = \min(1.5 \times n_R, n_T)$ for the confidence interval calculation. In the following analyses, we use α=0.05.

5.2 FDA statistical equivalence testing for HER2 binding

The HER2 binding data points of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin are displayed in Figure 1. There appears a small mean difference among the 3 products. The variability of MYL-1401O is smallest among 3 products.

Nine lots of MYL-1401O, 22 lots of US-licensed Herceptin, and 22 lots of EU-approved Herceptin are included for the statistical equivalence testing for the HER2 binding. Descriptive statistics for the HER2 binding data are listed in Table 5.

Figure 1 Scatter plot of HER2 binding for US-licensed Herceptin, MYL-1401O, and EU-approved Herceptin

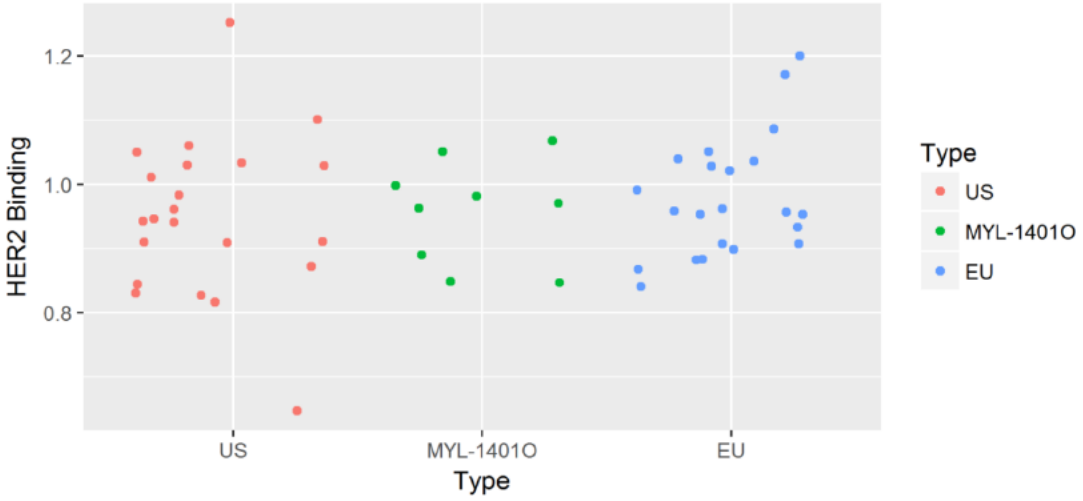

Table 5 Descriptive statistics for the HER2 binding data

Product	Number of lots	Sample mean%	Sample standard deviation%	Minimum %	Maximum %
US-licensed Herceptin	22	95	12	65	125
MYL-1401O	9	96	8	85	107
EU-approved Herceptin	22	98	9	84	120

Since we don't assume equal variance of test and reference products, we use Satterthwaite approximation for obtaining 90% confidence interval for the mean difference between US-licensed Herceptin and MYL-1401O. From Table 6, it is seen that the HER2 binding of MYL-1401O is equivalent to the HER2 binding of US-licensed Herceptin. Similarly, the HER2 binding of MYL-1401O is equivalent to the HER2 binding of EU-approved Herceptin, and the HER2 binding of EU-approved Herceptin is equivalent to the HER2 binding of US-licensed Herceptin.

Table 6 Equivalence testing results for the HER2 binding

Comparison	# of lots	Mean difference%	90% confidence interval for mean difference	Equivalence margin	Equivalent
MYL-1401O vs. US	(9, 22)*	0.8	(-6.5, 8.1)	(-18.4, 18.4)	Yes
MYL-1401O vs. EU	(9, 22)*	-2.1	(-8.4, 4.3)	(-14.1, 14.1)	Yes
EU vs. US	(22, 22)	2.9	(-2.7, 8.4)	(-18.4, 18.4)	Yes

*The 90% confidence interval for the mean difference between the test and comparator is adjusted by the sample size imbalance.

5.3 FDA statistical equivalence testing for relative potency using an SK-BR3 cell-based inhibition of proliferation assay

The relative potency data points of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin are displayed in Figure 2. Clearly the mean of MYL-1401O is smaller than both the US-licensed Herceptin and EU-approved Herceptin.

Nine lots of MYL-1401O, 22 lots of US-licensed Herceptin, and 22 lots of EU-approved Herceptin are included in the relative potency dataset for the statistical equivalence testing.

Descriptive statistics for the relative potency data of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin are listed in Table 7.

From Table 8, it is seen that the equivalence of relative potency between MYL-1401O and US-licensed Herceptin is supported. The equivalence of relative potency between MYL-1401O and EU-approved Herceptin is supported. The equivalence of relative potency between US-licensed Herceptin and EU-approved Herceptin is supported.

Figure 2 Scatter plot of relative potency for US-licensed Herceptin, MYL-1401O, and EU-approved Herceptin

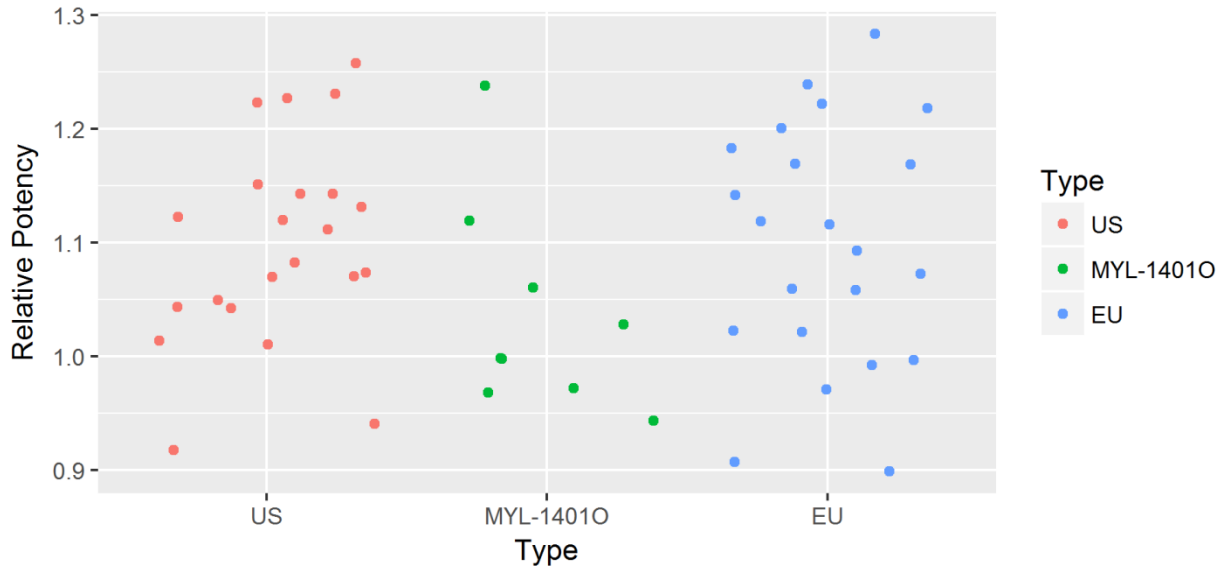

Table 7 Descriptive statistics for the relative potency data

Product	Number of lots	Sample mean%	Sample standard deviation%	Minimum%	Maximum %
US-licensed Herceptin	22	110	9	92	126
MYL-1401O	9	104	9	94	124
EU-approved Herceptin	22	110	11	90	128

Table 8 Equivalence testing results for the relative potency

Comparison	# of lots	Mean difference%	90% confidence interval for mean difference%	Equivalence margin%	Equivalent
MYL-1401O vs. US	(9, 22)*	-6.1	(-13.0, 0.7)	(-13.4, 13.4)	Yes
MYL-1401O vs. EU	(9, 22)*	-6.1	(-13.4, 1.2)	(-16.1, 16.1)	Yes
EU vs. US	(22, 22)	0.0	(-5.0, 5.0)	(-13.4, 13.4)	Yes

*The 90% confidence interval for the mean difference between the test and comparator is adjusted by the sample size imbalance.

5.4 FDA statistical equivalence testing for relative ADCC activity measured using SK-BR3 and human PBMC-based assay

The relative ADCC activity data points of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin are displayed in Figure 3.

Thirteen lots of MYL-1401O, 21 lots of US-licensed Herceptin, and 26 lots of EU-approved Herceptin are included in the relative ADCC activity dataset for the statistical equivalence testing. Descriptive statistics for the relative ADCC activity data of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin are listed in Table 9.

From Table 10, it is seen that the equivalence of relative ADCC activity between MYL-1401O and US-licensed Herceptin is supported. The equivalence of relative ADCC activity between MYL-1401O and EU-approved Herceptin is supported. The equivalence of relative ADCC activity between US-licensed Herceptin and EU-approved Herceptin is supported.

Figure 3 Scatter plot of relative ADCC activity for US-licensed Herceptin, MYL-1401O, and EU-approved Herceptin

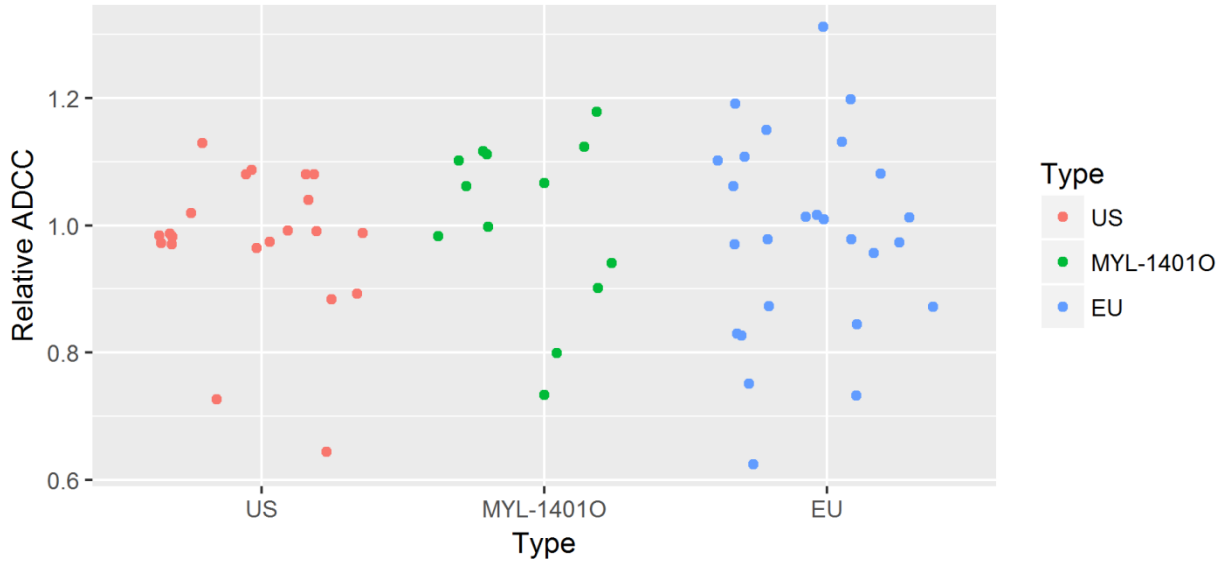

Table 9 Descriptive statistics for the relative ADCC activity data

Product	Number of lots	Sample mean%	Sample standard deviation%	Minimum%	Maximum %
US-licensed Herceptin	21	97	12	64	113
MYL-1401O	13	101	13	73	118
EU-approved Herceptin	26	98	16	62	131

Table 10 Equivalence testing results for the relative ADCC activity

Comparison	# of lots	Mean difference	90% confidence interval for mean difference	Equivalence margin	Equivalent
MYL-1401O vs. US	(13, 21)*	3.5	(-4.3, 11.3)	(-17.3, 17.3)	Yes
MYL-1401O vs. EU	(13, 26)*	2.5	(-1.2, 9.0)	(-24.0, 24.0)	Yes
EU vs. US	(26, 21)	1.0	(-5.8, 7.8)	(-17.3, 17.3)	Yes

*The 90% confidence interval for the mean difference between the test and comparator is adjusted by the sample size imbalance.

6 CONCLUSION AND RECOMMENDATION

The results from the statistical equivalence testing of the HER2 binding, the relative potency, and the relative ADCC activity support a demonstration that the proposed biosimilar MYL-1401O is highly similar to US-licensed Herceptin. The statistical analyses of the HER2 binding, the relative potency and the relative ADCC activity in the three pair-wise comparisons (MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin) also support the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Herceptin and the MYL-1401O product to support a demonstration of biosimilarity to US-licensed Herceptin.

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