

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761081Orig1s000

STATISTICAL REVIEW(S)



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA No.:	761081
DATE RECEIVED BY OB:	June 30, 2017
DRUG NAME:	PF-05280014; Trazimera (trastuzumab-qyyp) (proposed biosimilar to Herceptin)
DOSAGE FORM:	lyophilized powder in a strength of 420 mg/vial
INDICATION:	HER2 overexpressing breast cancer
APPLICANT:	Pfizer
REVIEW FINISHED:	March 8, 2018
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PROJECT MANAGER:	Clara Lee

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1 Executive summary and recommendation

The CMC statistical reviewer in the Office of Biostatistics analyzed the comparative results of two critical Quality Attributes (QAs): inhibition of cell growth bioassay, and primary NK ADCC which were recommended for equivalence testing analysis by the Office of Biotechnology Products (OBP). Tier 1 statistical equivalence testing was conducted using equivalence margins of ± 1.5 times of the standard deviation of the comparator product, estimated by $\hat{\sigma}_R$, where the subscript R represents the comparator product. Samples from 11 batches of PF-05280014 (Pfizer), 64 batches of US-licensed Herceptin (US), and 74 batches of Herceptin sourced from EU (EU) were used for evaluating the similarity of inhibition of cell growth bioassay using the equivalence testing. The results are summarized in Table 1.

Table 1 Results of Equivalence Testing for the inhibition of cell growth bioassay

Test Product (Number of lots)	Comparator (Number of lots)	Mean Difference		Equivalence Margin, %	Conclusion
		Estimate	90% CI ¹		
Pfizer (11)	US (64)	-1.22	(-8.86, 6.43)	(-12.33, 12.33)	Pass
Pfizer (11)	EU (74)	-4.34	(-12.33, 3.64)	(-15.31, 15.31)	Pass
EU (74)	US (64)	3.13	(0.53, 5.72)	(-12.33, 12.33)	Pass

1. The 90% confidence interval is adjusted by the sample size imbalance

Samples from 11 batches of PF-05280014 (Pfizer), 27 batches of US-licensed Herceptin (US), and 23 batches of EU-authorized Herceptin (EU) were used for evaluating the similarity of primary NK cell (ADCC) assay using the equivalence testing. The results are summarized in Table 2.

Table 2 Results of Equivalence Testing for the primary NK cell (ADCC) assay

Test Product (Number of lots)	Comparator (Number of lots)	Mean Difference		Equivalence Margin, %	Conclusion
		Estimate	90% CI		
Pfizer (11)	US (27)	14.43	(3.49, 25.36)	(-30.08, 30.08)	Pass
Pfizer (11)	EU (23)	11.91	(-0.26, 24.08)	(-35.65, 35.65)	Pass
EU (23)	US (27)	2.52	(-8.04, 13.08)	(-30.08, 30.08)	Pass

As shown in Tables 1 and 2, the results from statistical equivalence testing of the inhibition of cell growth bioassay and primary NK ADCC support a demonstration that the proposed biosimilar PF-05280014 is similar to US-Herceptin and also support the analytical portion of the scientific bridge to justify the relevance of EU-Herceptin data from the comparative clinical study.

2 Overview

PF-05280014 is a proposed biosimilar to US-licensed Herceptin (trastuzumab) submitted under Section 351(k) of the Public Health Service Act. Following the guidance^[1], the applicant submitted analytical similarity assessments using a three-way bridge approach to demonstrate analytical similarity between PF-05280014, US-Herceptin and to establish a quality bridge between US-Herceptin and EU-Herceptin.

Three critical quality attributes, inhibition of cell growth bioassay, HER2 binding by SPR, and primary NK ADCC were originally assigned as Tier-1 and were tested using samples from multiple biosimilar, US-Herceptin (440 mg presentation) and EU-Herceptin (150 mg presentation) lots. Based on the recommendation of OBP biological reviewer Dr. Kevin Li, HER2 binding by SPR is reassigned as Tier-2 according to the IR response “IR14-09-Feb-2018 QQR1”.

Our comments regarding the applicant’s statistical equivalence testing is provided in Section 3. Our independent statistical analyses and descriptions of received data are summarized in Section 4. Our conclusion is provided in Section 5.

3 Applicant’s statistical equivalence testing

In this submission, the applicant followed the FDA’s recommendation to conduct Tier 1 statistical equivalence testing with the margin defined as $1.5\hat{\sigma}_R$, where $\hat{\sigma}_R$ is the sample standard deviation based on the comparator product lots, for inhibition of cell growth bioassay and primary NK ADCC.

The sponsor observed a shift in total afucosylation, terminal galactosylation and G0 species for US-Herceptin lots with expiration date beyond December 2016 and for EU-Herceptin lots with expiration date beyond June 2018. The sponsor used only ADCC from only pre-glycan shift lots in the statistical analysis. The sponsor claimed that the pre-glycan shift lots were used as targets during the development stage of PF-05280014, and the ADCC from both pre-glycan shift lots and post-glycan shift lots might represent distinct populations due to the shift. From the limited samples, it is challenging to confirm that there is a process shift without the actual knowledge of process.

The CMC statistical reviewer performs an independent statistical analysis in the next section. Because both pre-glycan shift and post-glycan shift EU-Herceptin lots were used in the clinical study, we use all available data that includes data from both pre-glycan shift and post-glycan shift lots for analyses of both Tier-1 QAs.

4 Analytical similarity

To evaluate analytical similarity, the FDA recommended the applicant to apply a tiered approach in the FDA responses to IND meetings with the applicant. That is, product QAs amenable 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. More

details are described in the FDA Draft Guidance on Analytical Similarity (2017)^[1]. This review focuses on the Tier 1 statistical equivalence testing

4.1 Data analyzed

The applicant tested multiple lots of PF-05280014, US- Herceptin and EU- Herceptin for Tier-1 QAs. The numbers of lots tested for Tier-1 QAs are listed in Table 3.

Table 3 Number of lots tested for Tier-1 quality attributes

Quality attribute	PF-05280014	US-Herceptin	EU-Herceptin
Inhibition of cell growth bioassay	11	64	74
Primary NK ADCC	10	27	23

The applicant provided data from 11 independent biosimilar batches, including 5 drug product (DP-440mg) batches and 6 drug substance (DS) batches for assessing analytical biosimilarity. The 5 DP batches correspond to 5 different DS batches that are not include in the similarity assessment. In other words, the 11 biosimilar lots are corresponding to 11 different drug substance lots. Table 4 shows descriptive statistics for the inhibition of cell growth assay grouped by lot type (DS or DP).

In addition to the 11 independent lots, the sponsor tested inhibition of cell growth assay for 17 additional PF-05280014 lots, including 5 clinical lots (150mg). For each of the 5 clinical lots, there is one DP-440mg lot manufactured from the same DS lot included in the analytical similarity assessment. Figure 1 shows the inhibition of cell growth assay against manufacturing dates. No significant difference observed between clinical lots and independent lots.

Table 5 shows descriptive statistics for ADCC activity of 10 independent PF-05280014 lots grouped by lot types. In addition to the 10 independent lots, ADCC test results of 14 additional PF-05280014 lots, including 5 clinical lots and 1 primary reference material (PRM), were provided. Figure 2 shows the ADCC-NK against manufacturing dates.

Table 4 Descriptive statistics for the Inhibition of cell growth activity of PF-05280014 grouped by type (DS or DP)

Subgroup	Number of lots	Mean, %	Sample standard deviation, %	Min, %	Max, %
DP – 440mg	5	91.20	9.83	80.00	103.00
DS	6	104.50	12.57	89.00	121.00
All (DP+DS)	11	98.45	12.88	80.00	121.00

Table 5 Descriptive statistics for the ADCC activity of PF-05280014 grouped by type (DS or DP)

Subgroup	Number of lots	Mean, %	Sample standard deviation, %	Min, %	Max, %
DP – 440mg	5	112.40	7.37	106.00	124.00
DS	5	107.20	20.14	92.00	142.00
All (DP+DS)	10	109.80	14.56	92.00	142.00

Figure 1 Inhibition of cell growth activity of PF-05280014

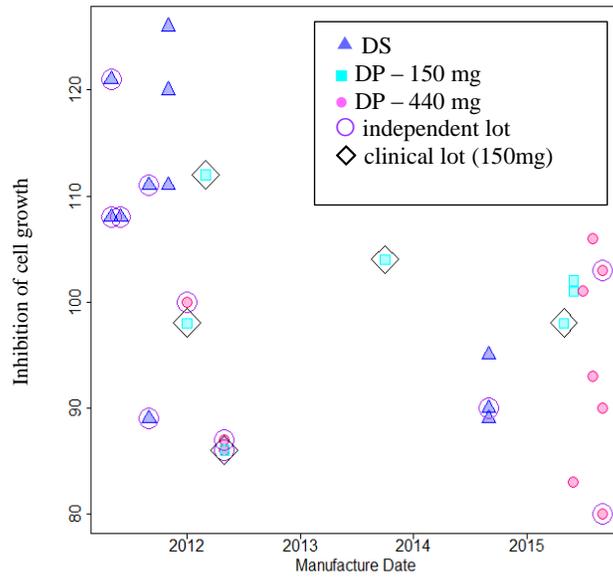
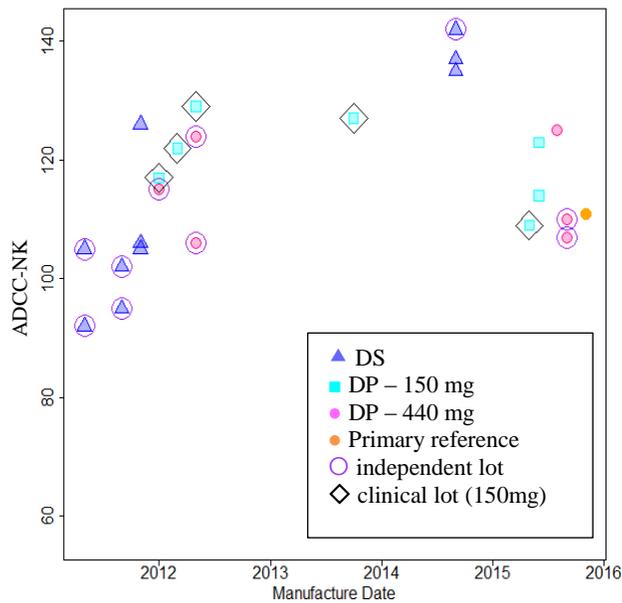


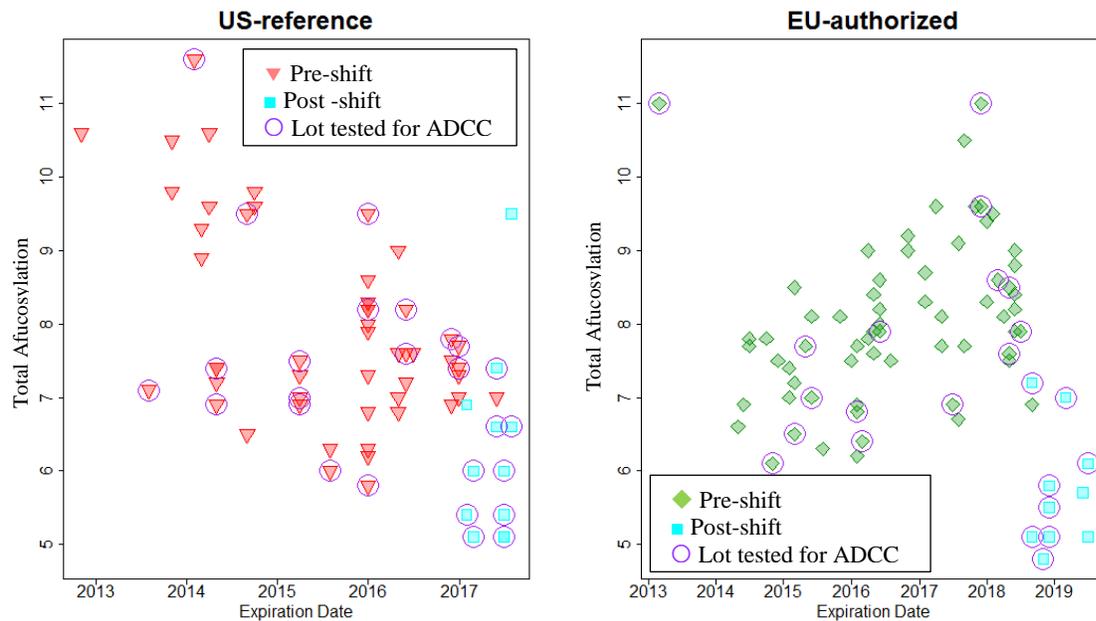
Figure 2 ADCC-NK of PF-05280014



As shown Table 3, the numbers of US-Herceptin tested for inhibition and ADCC are 64 and 27, and the numbers of EU-Herceptin tested for the two Tier-1 QAs are 74 and 23. An IR was sent to clarify the difference between numbers of lots tested for two Tier-1 QAs. According to the “response to FDA IR 09Feb-2018 QQR3”, Pfizer tested all clinical EU-Herceptin lots. However, US-Herceptin and EU-Herceptin sourced after July 2016 were tested but not included in analytical similarity assessment.

The inhibition assay was part of the development of PF-05280014 at 2010. The ADCC assay was established later as suggested by the Agency on September 2015. The number of lots tested for ADCC was planned to be sufficient for statistical analysis. The lots tested for NK ADCC assay were selected based on the total afucosylation for the pre-shift lots as shown in Figure 1, and NK ADCC were tested for most of the post-shift lots.

Figure 3 Total afucosylation for US-Herceptin and EU-Herceptin



4.2 Statistical method

Let μ_T and μ_R be the population mean of the QA for the test product and the population mean of the QA for the reference product, respectively. Let σ_R be the standard deviation of the QA of interest for the reference product. To conclude the equivalence in the QA of interest between the test product and the reference product, we test the following null and alternative hypotheses:

$$H_0: \mu_T - \mu_R \leq \theta_1 \text{ or } \mu_T - \mu_R \geq \theta_2$$

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

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

The null hypothesis is rejected with significance level not exceeding $\alpha=0.05$ if the 90% Confidence Interval (CI) of the mean difference, $\mu_T - \mu_R$, of the QA of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude equivalence of the QA of interest between the test product and the reference product if null hypothesis is rejected. Since the margin is conducted with unknown parameter, we replace σ_R by the sample standard deviation of the reference product.

Let X_{Tj} be the observed value of the QA of interest for Lot j of the test product (the proposed biosimilar product), and X_{Rj} be the observed value of the QA of interest for Lot j of the reference product. Since the two products are manufactured by two manufacturers, two products are independent.

Let $\bar{X}_i = \sum_{j=1}^{n_i} X_{Tj}/n_i$ and $S_i^2 = \sum_{j=1}^{n_i} (X_{ij} - \bar{X}_i)^2 / (n_i - 1)$, where n_i is the number of lots of the product i , and $i \in \{T, R\}$. Assuming unequal variances of the test product and the reference product, the $(1 - 2\alpha) * 100\%$ CI of the mean difference in the QA of interest can be calculated as $(\bar{X}_T - \bar{X}_R - t_\alpha(\nu)\sqrt{S_T^2/n_T^* + S_R^2/n_R^*}, \bar{X}_T - \bar{X}_R + t_\alpha(\nu)\sqrt{S_T^2/n_T^* + S_R^2/n_R^*})$, where $t_\alpha(\nu)$ is the $1 - \alpha$ t-distribution quantile and $\nu = \frac{(S_T^2/n_T^* + S_R^2/n_R^*)^2}{\frac{S_T^2/n_T^*}{(n_T-1)} + \frac{S_R^2/n_R^*}{(n_R-1)}}$ is the degrees of freedom calculated by

Welch-Satterthwaite's approximation with adjustment for imbalance sample size. The adjusted value $n_R^* = 1.5n_T$ if $n_R > 1.5n_T$ and $n_R^* = n_R$ otherwise, and $n_T^* = 1.5n_R$ if $n_T > 1.5n_R$ and $n_T^* = n_T$ otherwise.

4.3 Equivalence testing for inhibition of cell growth

Figure 4 shows data of inhibition of cell growth for PF-05280014, US-Herceptin and EU-Herceptin. Table 6 shows descriptive statistics for the inhibition of cell growth. Bridging was conducted using 3-way comparisons. The 3-way equivalence testing results are listed on Table 2. The test results are also expressed graphically in Figure 5, which shows relationships between equivalence margins and confidence intervals. The biosimilar product pass all 3-way equivalence test for inhibition of cell growth assay.

Table 6 Descriptive statistics for inhibition of cell growth

Subgroup	Number of lots	Mean, %	Sample standard deviation, %	Min, %	Max, %
PF-05280014	11	98.45	12.88	80.00	121.00
US-Herceptin	64	99.67	8.22	86.00	124.00
EU-Herceptin	74	102.80	10.20	81.00	126.00

Figure 4 Inhibition of cell growth

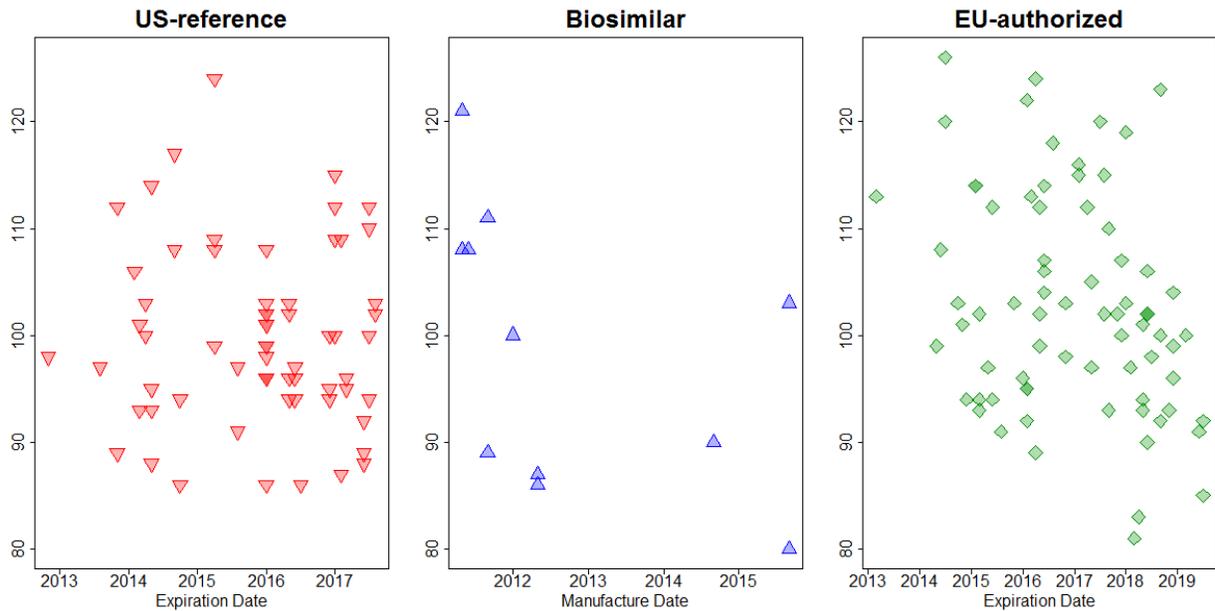
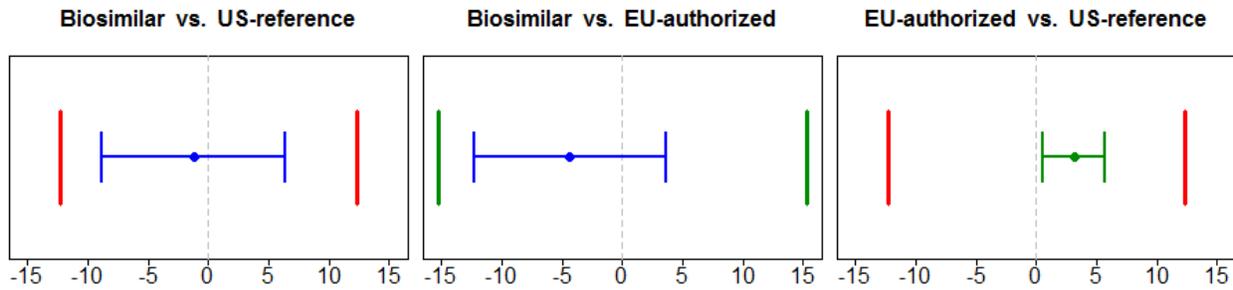


Figure 5 Equivalence margins and 90%CI of inhibition of cell growth assay



4.4 Equivalence testing for NK ADCC assay

Figure 6 shows data of NK ADCC assay from PF-05280014, US-Herceptin and EU-Herceptin. The average of data from PF-05280014 is slightly higher than the average of data from US-Herceptin and EU-Herceptin. The 3-way equivalence testing results are listed on Table 1. The test results are also displayed in Figure 7, which shows relationships between equivalence margins and confidence intervals of mean difference. All mean difference confidence intervals are within prespecified equivalence margins. The biosimilar product pass all 3-way equivalence test for NK ADCC assay.

Table 7 Descriptive statistics for NK ADCC

Subgroup	Number of lots	Mean, %	Sample standard deviation, %	Min, %	Max, %
PF-05280014	10	109.80	14.56	92.00	142.00
US-Herceptin	27	95.48	20.05	56.00	133.00
EU-Herceptin	23	98.00	23.77	58.00	133.00

Figure 6 NK ADCC Data

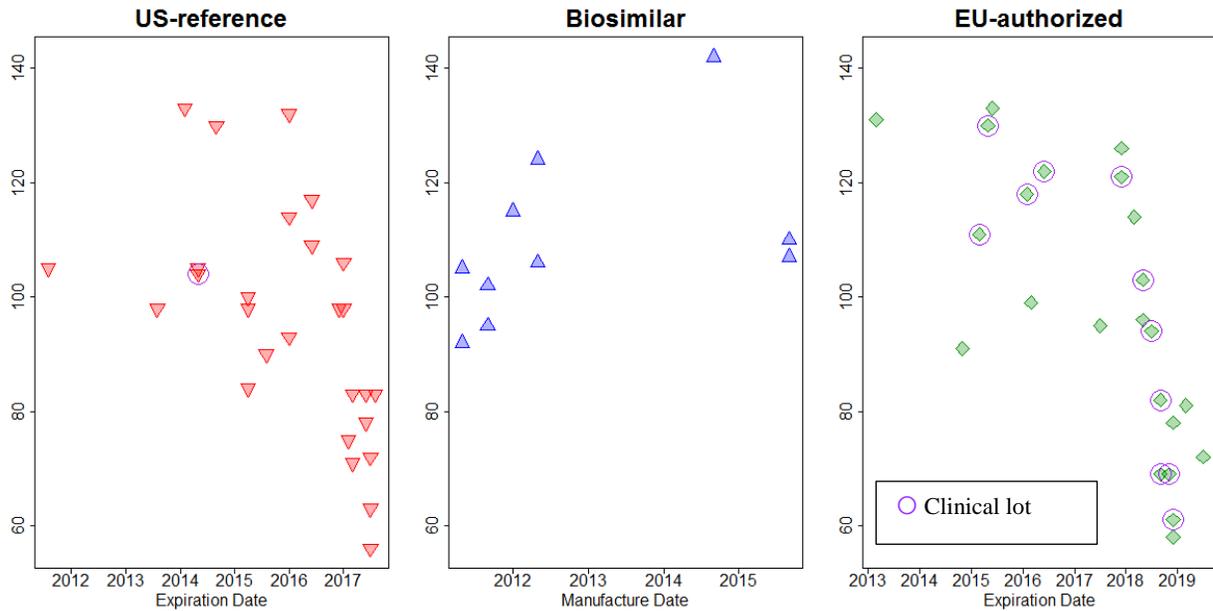
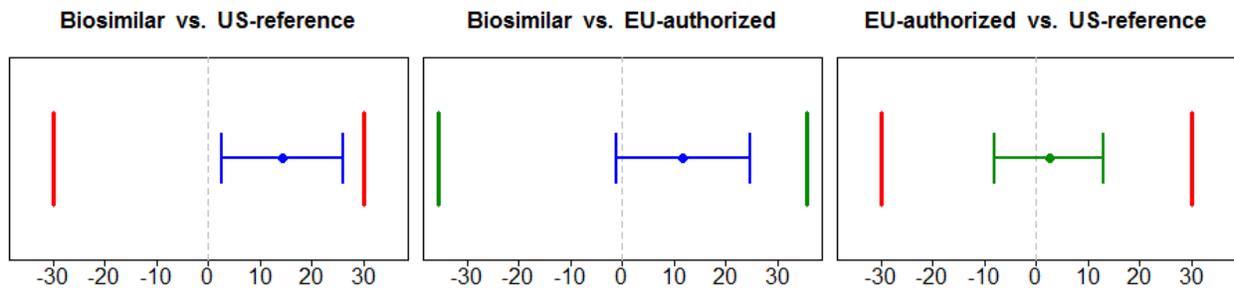


Figure 7 Equivalence margins and 90%CI of TNF- α neutralization assay



5 Conclusion

The results from the statistical equivalence analyses for the inhibition cell growth assay and the NK ADCC assay support a demonstration that the proposed biosimilar PF-05280014 is highly similar to US-Herceptin. In addition, the results support the analytical portion of the scientific bridge to justify the relevance of EU-Herceptin data from the comparative clinical study.

6 Reference

- [1] Scientific considerations in demonstrating biosimilarity to a reference product (2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>
- [2] Statistical Approaches to Evaluate Analytical Similarity Guidance for Industry (2017)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM576786.pdf>

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Test Product (Number of lots)	Comparator (Number of lots)	Mean Difference		Equivalence Margin, %	Conclusion
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Pfizer (11)	US (64)	-1.22	(-8.86, 6.43)	(-12.33, 12.33)	Pass
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1. The 90% confidence interval is adjusted by the sample size imbalance

Samples from 11 batches of PF-05280014 (Pfizer), 27 batches of US-licensed Herceptin (US), and 23 batches of EU-authorized Herceptin (EU) were used for evaluating the similarity of primary NK cell (ADCC) assay using the equivalence testing. The results are summarized in Table 2.

Table 2 Results of Equivalence Testing for the primary NK cell (ADCC) assay

Test Product (Number of lots)	Comparator (Number of lots)	Mean Difference		Equivalence Margin, %	Conclusion
		Estimate	90% CI		
Pfizer (11)	US (27)	14.43	(3.49, 25.36)	(-30.08, 30.08)	Pass
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Three critical quality attributes, inhibition of cell growth bioassay, HER2 binding by SPR, and primary NK ADCC were originally assigned as Tier-1 and were tested using samples from multiple biosimilar, US-Herceptin (440 mg presentation) and EU-Herceptin (150 mg presentation) lots. Based on the recommendation of OBP biological reviewer Dr. Kevin Li, HER2 binding by SPR is reassigned as Tier-2 according to the IR response “IR14-09-Feb-2018 QQR1”.

Our comments regarding the applicant’s statistical equivalence testing is provided in Section 3. Our independent statistical analyses and descriptions of received data are summarized in Section 4. Our conclusion is provided in Section 5.

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In this submission, the applicant followed the FDA’s recommendation to conduct Tier 1 statistical equivalence testing with the margin defined as $1.5\hat{\sigma}_R$, where $\hat{\sigma}_R$ is the sample standard deviation based on the comparator product lots, for inhibition of cell growth bioassay and primary NK ADCC.

The sponsor observed a shift in total afucosylation, terminal galactosylation and G0 species for US-Herceptin lots with expiration date beyond December 2016 and for EU-Herceptin lots with expiration date beyond June 2018. The sponsor used only ADCC from only pre-glycan shift lots in the statistical analysis. The sponsor claimed that the pre-glycan shift lots were used as targets during the development stage of PF-05280014, and the ADCC from both pre-glycan shift lots and post-glycan shift lots might represent distinct populations due to the shift. From the limited samples, it is challenging to confirm that there is a process shift without the actual knowledge of process.

The CMC statistical reviewer performs an independent statistical analysis in the next section. Because both pre-glycan shift and post-glycan shift EU-Herceptin lots were used in the clinical study, we use all available data that includes data from both pre-glycan shift and post-glycan shift lots for analyses of both Tier-1 QAs.

4 Analytical similarity

To evaluate analytical similarity, the FDA recommended the applicant to apply a tiered approach in the FDA responses to IND meetings with the applicant. That is, product QAs amenable 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. More details are described in the FDA Draft Guidance on Analytical Similarity (2017)^[1]. This review focuses on the Tier 1 statistical equivalence testing

4.1 Data analyzed

The applicant tested multiple lots of PF-05280014, US- Herceptin and EU- Herceptin for Tier-1 QAs. The numbers of lots tested for Tier-1 QAs are listed in Table 3.

Table 3 Number of lots tested for Tier-1 quality attributes

Quality attribute	PF-05280014	US-Herceptin	EU-Herceptin
Inhibition of cell growth bioassay	11	64	74
Primary NK ADCC	10	27	23

The applicant provided data from 11 independent biosimilar batches, including 5 drug product (DP-440mg) batches and 6 drug substance (DS) batches for assessing analytical biosimilarity. The 5 DP batches correspond to 5 different DS batches that are not include in the similarity assessment. In other words, the 11 biosimilar lots are corresponding to 11 different drug substance lots. Table 4 shows descriptive statistics for the inhibition of cell growth assay grouped by lot type (DS or DP).

In additional to the 11 independent lots, the sponsor tested inhibition of cell growth assay for 17 additional PF-05280014 lots, including 5 clinical lots (150mg). For each of the 5 clinical lots, there is one DP-440mg lot manufactured from the same DS lot included in the analytical similarity assessment. Figure 1 shows the inhibition of cell growth assay against manufacturing dates. No significant difference observed between clinical lots and independent lots.

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DS	6	104.50	12.57	89.00	121.00

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DP – 440mg	5	112.40	7.37	106.00	124.00
DS	5	107.20	20.14	92.00	142.00
All (DP+DS)	10	109.80	14.56	92.00	142.00

Figure 1 Inhibition of cell growth activity of PF-05280014

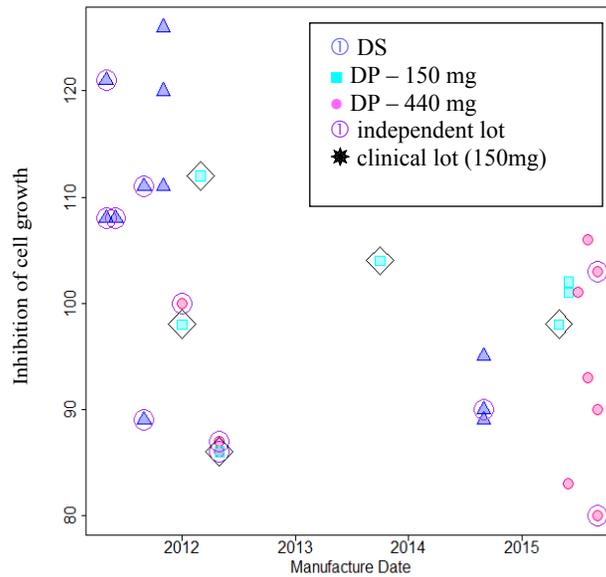
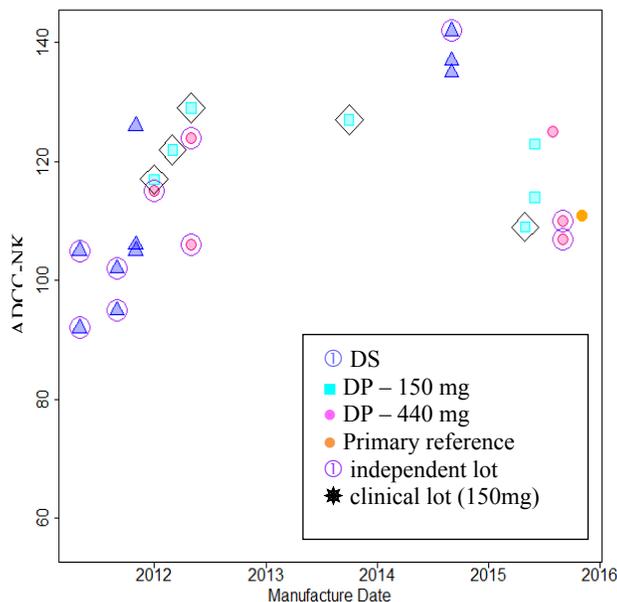


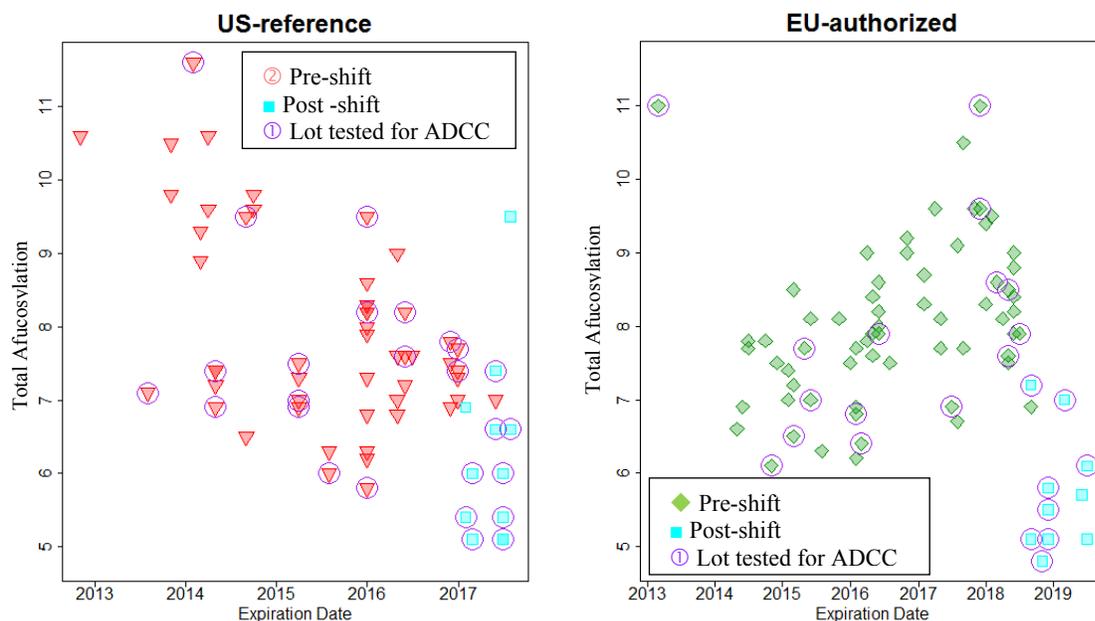
Figure 2 ADCC-NK of PF-05280014



As shown Table 3, the numbers of US-Herceptin tested for inhibition and ADCC are 64 and 27, and the numbers of EU-Herceptin tested for the two Tier-1 QAs are 74 and 23. An IR was sent to clarify the difference between numbers of lots tested for two Tier-1 QAs. According to the “response to FDA IR 09Feb-2018 QQR3”, Pfizer tested all clinical EU-Herceptin lots. However, US-Herceptin and EU-Herceptin sourced after July 2016 were tested but not included in analytical similarity assessment.

The inhibition assay was part of the development of PF-05280014 at 2010. The ADCC assay was established later as suggested by the Agency on September 2015. The number of lots tested for ADCC was planned to be sufficient for statistical analysis. The lots tested for NK ADCC assay were selected based on the total afucosylation for the pre-shift lots as shown in Figure 1, and NK ADCC were tested for most of the post-shift lots.

Figure 3 Total afucosylation for US-Herceptin and EU-Herceptin



4.2 Statistical method

Let μ_T and μ_R be the population mean of the QA for the test product and the population mean of the QA for the reference product, respectively. Let σ_R be the standard deviation of the QA of interest for the reference product. To conclude the equivalence in the QA of interest between the test product and the reference product, we test the following null and alternative hypotheses:

$$H_0: \mu_T - \mu_R \leq \theta_1 \text{ or } \mu_T - \mu_R \geq \theta_2$$

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

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

The null hypothesis is rejected with significance level not exceeding $\alpha=0.05$ if the 90% Confidence Interval (CI) of the mean difference, $\mu_T - \mu_R$, of the QA of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude equivalence of the QA of interest between the test product and the reference product if null hypothesis is rejected. Since the margin is conducted with unknown parameter, we replace σ_R by the sample standard deviation of the reference product.

Let X_{Tj} be the observed value of the QA of interest for Lot j of the test product (the proposed biosimilar product), and X_{Rj} be the observed value of the QA of interest for Lot j of the reference product. Since the two products are manufactured by two manufacturers, two products are independent.

Let $\bar{X}_i = \sum_{j=1}^{n_i} X_{Tj}/n_i$ and $S_i^2 = \sum_{j=1}^{n_i} (X_{ij} - \bar{X}_i)^2/(n_i - 1)$, where n_i is the number of lots of the product i , and $i \in \{T,R\}$. Assuming unequal variances of the test product and the reference product, the $(1 - 2\alpha) * 100\%$ CI of the mean difference in the QA of interest can be calculated as $(\bar{X}_T - \bar{X}_R - t_\alpha(\nu) \sqrt{S_T^2/n_T^* + S_R^2/n_R^*}, \bar{X}_T - \bar{X}_R + t_\alpha(\nu) \sqrt{S_T^2/n_T^* + S_R^2/n_R^*})$, where $t_\alpha(\nu)$ is the $1 - \alpha$ t-distribution quantile and $\nu = \frac{(S_T^2/n_T^* + S_R^2/n_R^*)^2}{\frac{(S_T^2/n_T^*)}{(n_T - 1)} + \frac{(S_R^2/n_R^*)}{(n_R - 1)}}$ is the degrees of freedom calculated by

Welch-Satterthwaite's approximation with adjustment for imbalance sample size. The adjusted value $n_R^* = 1.5n_T$ if $n_R > 1.5n_T$ and $n_R^* = n_R$ otherwise, and $n_T^* = 1.5n_R$ if $n_T > 1.5n_R$ and $n_T^* = n_T$ otherwise.

4.3 Equivalence testing for inhibition of cell growth

Figure 4 shows data of inhibition of cell growth for PF-05280014, US-Herceptin and EU-Herceptin. Table 6 shows descriptive statistics for the inhibition of cell growth. Bridging was conducted using 3-way comparisons. The 3-way equivalence testing results are listed on Table 2. The test results are also expressed graphically in Figure 5, which shows relationships between equivalence margins and confidence intervals. The biosimilar product pass all 3-way equivalence test for inhibition of cell growth assay.

Table 6 Descriptive statistics for inhibition of cell growth

Subgroup	Number of lots	Mean, %	Sample standard deviation, %	Min, %	Max, %
PF-05280014	11	98.45	12.88	80.00	121.00
US-Herceptin	64	99.67	8.22	86.00	124.00
EU-Herceptin	74	102.80	10.20	81.00	126.00

Figure 4 Inhibition of cell growth

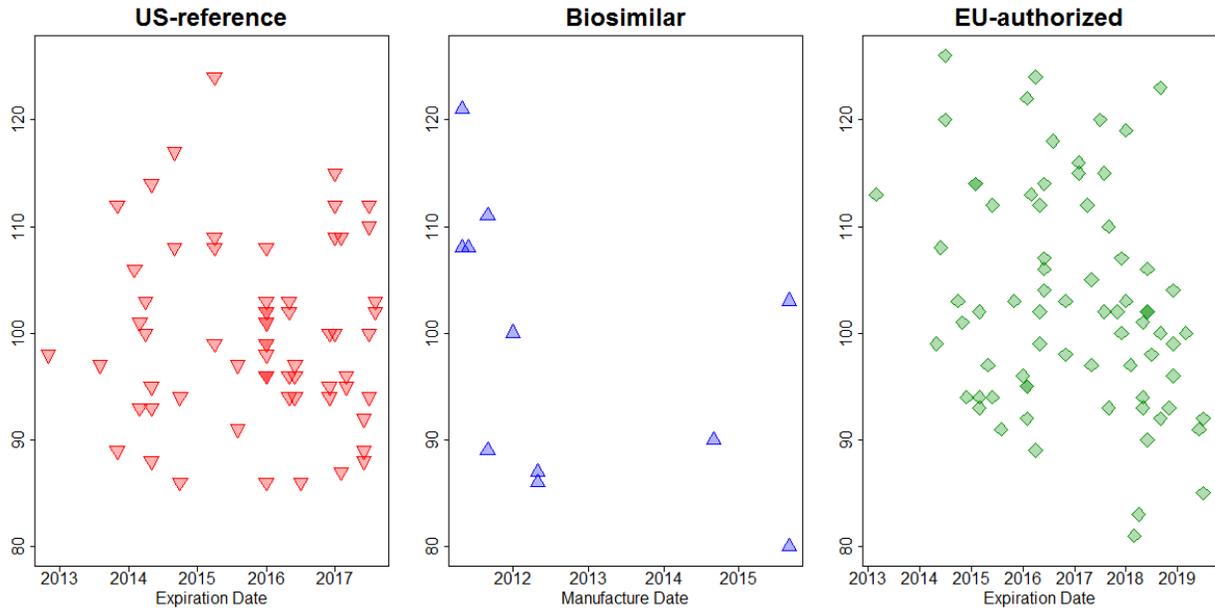
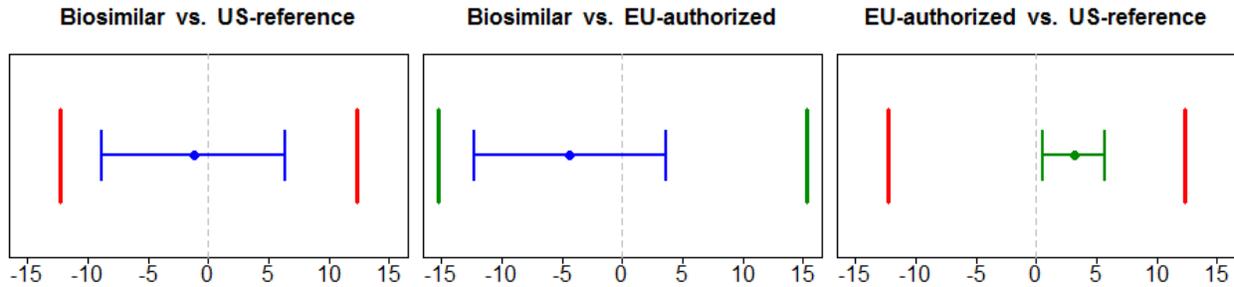


Figure 5 Equivalence margins and 90%CI of inhibition of cell growth assay



4.4 Equivalence testing for NK ADCC assay

Figure 6 shows data of NK ADCC assay from PF-05280014, US-Herceptin and EU-Herceptin. The average of data from PF-05280014 is slightly higher than the average of data from US-Herceptin and EU-Herceptin. The 3-way equivalence testing results are listed on Table 1. The test results are also displayed in Figure 7, which shows relationships between equivalence margins and confidence intervals of mean difference. All mean difference confidence intervals are within prespecified equivalence margins. The biosimilar product pass all 3-way equivalence test for NK ADCC assay.

Table 7 Descriptive statistics for NK ADCC

Subgroup	Number of lots	Mean, %	Sample standard deviation, %	Min, %	Max, %
PF-05280014	10	109.80	14.56	92.00	142.00
US-Herceptin	27	95.48	20.05	56.00	133.00
EU-Herceptin	23	98.00	23.77	58.00	133.00

Figure 6 NK ADCC Data

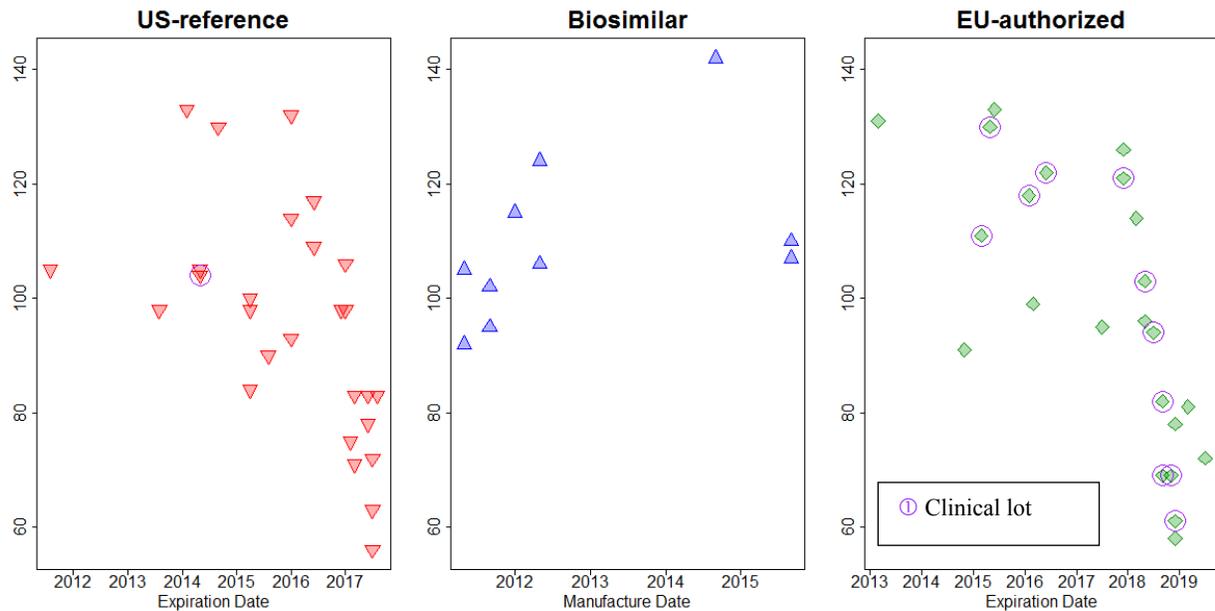
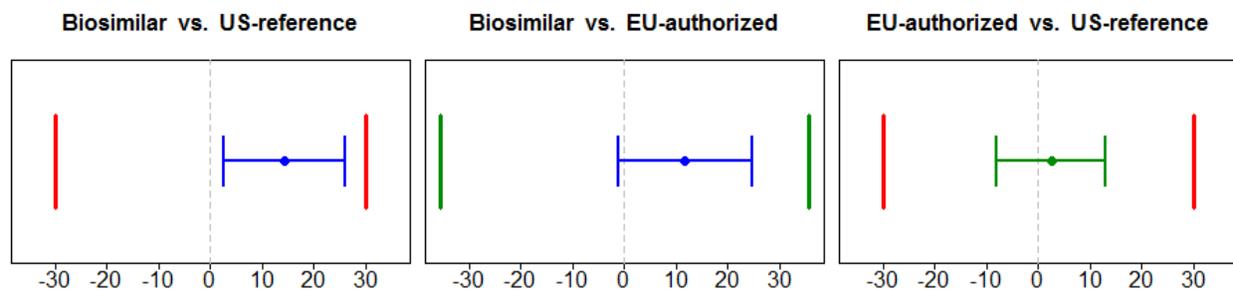


Figure 7 Equivalence margins and 90%CI of TNF- α neutralization assay



5 Conclusion

The results from the statistical equivalence analyses for the inhibition cell growth assay and the NK ADCC assay support a demonstration that the proposed biosimilar PF-05280014 is highly similar to US-Herceptin. In addition, the results support the analytical portion of the scientific bridge to justify the relevance of EU-Herceptin data from the comparative clinical study.

6 Reference

[1] Scientific considerations in demonstrating biosimilarity to a reference product (2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

[2] Statistical Approaches to Evaluate Analytical Similarity Guidance for Industry (2017)
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