STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.:	761024
SERIAL NO.:	0000
DATE RECEIVED BY THE CENTER:	November 24, 2015
DRUG NAME:	ABP 501 (proposed biosimilar to Humira, AbbVie)
DOSAGE FORM:	• Pre-filled Syringes (PFS): (b) (4) 50 mg/1.0 mL • Prefilled autoinjectors for subcutaneous use: 50 mg/1.0 mL
INDICATIONS:	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
APPLICANT:	Amgen Inc.
REVIEW FINISHED:	June 1, 2016
NAME OF STATISTICAL REVIEWER:	Meiyu Shen
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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistics reviewer in the Office of Biostatistics analyzed the comparative results of 2 critical quality attributes: Apoptosis inhibition bioassay and sTNF-α binding, 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 R represents US-licensed reference product variability or the comparator variability. 10 batches of ABP 501 and 21 batches of US-licensed Humira, and 17 batches of EU-approved Humira were used for equivalence testing of apoptosis inhibition bioassay (potency). The results are summarized in Table 1.

Table 1 Results of equivalence testing for apoptosis inhibition bioassay (potency)

Comparison	# of lots	Mean difference, %	90% confidence interval for mean difference, %	Equivalence margin, %	Equivalent
ABP 501 vs. US	(10, 21)	-1.43	(-4.50, 1.93)	(-8.57, 8.57)	Yes
ABP 501 vs. EU	(10, 17)	1.12	(-3.37, 5.82)	(-14.04, 14.04)	Yes
EU vs. US	(17, 21)	-2.55	(-6.97,1.88)	(-8.57, 8.57)	Yes

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

Ten batches of ABP 501, 10 batches of US-licensed Humira, and 10 batches of EU-approved Humira are included in the TNF-α binding dataset for the statistical equivalence testing. The results are shown in Table 2.

Table 2 Results of equivalence testing for sTNF-α binding

Comparison	# of lots	Mean difference, %	90% confidence interval for mean difference, %	Equivalence margin, %	Equivalent
ABP 501 vs. US	(10, 10)	-3.60	(-10,93, 3.73)	(-14.97, 14.97)	Yes
ABP 501 vs. EU	(10, 10)	-3.00	(-9.23, 3.23)	(-10.54, 10.54)	Yes
EU vs. US	(10, 10)	-0.60	(-7.34,6.14)	(-14.97, 14.97)	Yes

As shown in Tables 1 and 2, the results from the statistical equivalence testing of apoptosis inhibition bioassay (potency) and sTNF-α binding support a demonstration that the proposed biosimilar ABP 501 is highly similar to US-licensed Humira and also support the analytical bridge between US-licensed Humira and EU-approved Humira.

2 INTRODUCTION

On November 24, 2015, the applicant (Amgen) submitted to the US Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing ABP 501 and US-licensed Humira.

The applicant characterized multiple batches of US-licensed Humira and EU-approved Humira using a comprehensive set of analytical methods during the ABP 501 development.

The Agency carefully evaluated data for the apoptosis inhibition bioassay and sTNF-α binding provided in the initial BLA submission. Our comments regarding Amgen's statistical equivalence testing (Tier 1 approach) is provided in Section 4, and our independent statistical equivalence testing analyses are present in Section 5.

3 DATA ANALYZED

Amgen submitted the analytical data on November 24, 2015. Note that in Table 3, the apoptosis inhibition bioassay data of 21 US-licensed Humira lots, 17 EU-approved Humira lots, 10 ABP 501 lots were submitted by Amgen.

In addition, Amgen provided and analyzed the sTNF-alpha binding for 10 lot values of EU-approved Humira, 10 lot values of ABP 501, and 10 lot values of US-licensed Humira.

Table 3 Number of batches from each product

Product	Number of batches	
	apoptosis inhibition bioassay (potency)	sTNF-α binding
US-licensed Humira	21	10
ABP 501	10	10
EU-approved Humira	17	10

4 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Amgen conducted Tier 1 statistical equivalence testing with the margin defined as $1.5\hat{\sigma}_R$ for apoptosis inhibition bioassay (potency) and sTNF-α binding. Amgen performed = the Brown and Forsythe's Test for Homogeneity of Variance to determine if sample variances should be pooled in computing the confidence interval for the difference of means between the test product and reference product. If the p-value exceeds 0.05, then the pooled variance is used to compute the confidence interval. If the p-value is less than 0.05, the confidence interval for unequal variances is employed using the Satterthwaite approximation to determine the degrees of freedom. How to calculate the 90% confidence interval depends on the hypothesis test for equal variance. To demonstrate statistical equivalence for apoptosis inhibition bioassay (potency) and sTNF-α binding in this context, the entire two-sided confidence interval must be contained in the range from $-1.5\hat{\sigma}_R$ to $1.5\hat{\sigma}_R$.

Reviewer's comments: Applicant's analyses did not adjust the impact of imbalance sample sizes of the test product and the reference product.

5 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommended that Amgen apply a tiered approach in the Agency's responses to IND meetings with Amgen. 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 Humira product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Humira. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Humira product, we aim to reject the null hypothesis of the following null and alternative hypotheses:

$$H_0 : \mu_T - \mu_R \le \theta_1 \text{ or } \mu_T - \mu_R \ge \theta_2$$
$$H_1 : \theta_1 < \mu_T - \mu_R < \theta_2 \quad .$$

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 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 that the equivalence in the quality attribute of interest between the test product and the US-licensed Humira product if 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 Humira 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 Humira lots. First we estimate σ_R by the sample variability of the US-licensed Humira product (or by the sample variability of EU-approved Humira in the comparison between ABP 501 and EU-approved Humira) 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 Humira 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 Humira 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:

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

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 apoptosis inhibition bioassay

The apoptosis inhibition bioassay data points of ABP 501, US-licensed Humira, and EU-approved Humira are displayed in Figure 1. There appears a small mean difference among the 3 products. The variability of ABP 501 is smallest among 3 products.

Ten batches of ABP 501, 21 batches of US-licensed Humira, and 17 batches of EU-approved Humira are included for the statistical equivalence testing for the apoptosis inhibition bioassay. Descriptive statistics for the apoptosis inhibition bioassay data are listed in Table 4.

Figure 1 Scatter plot of Apoptosis inhibition bioassay for US-licensed Humira, ABP 501, and EU-approved Humira

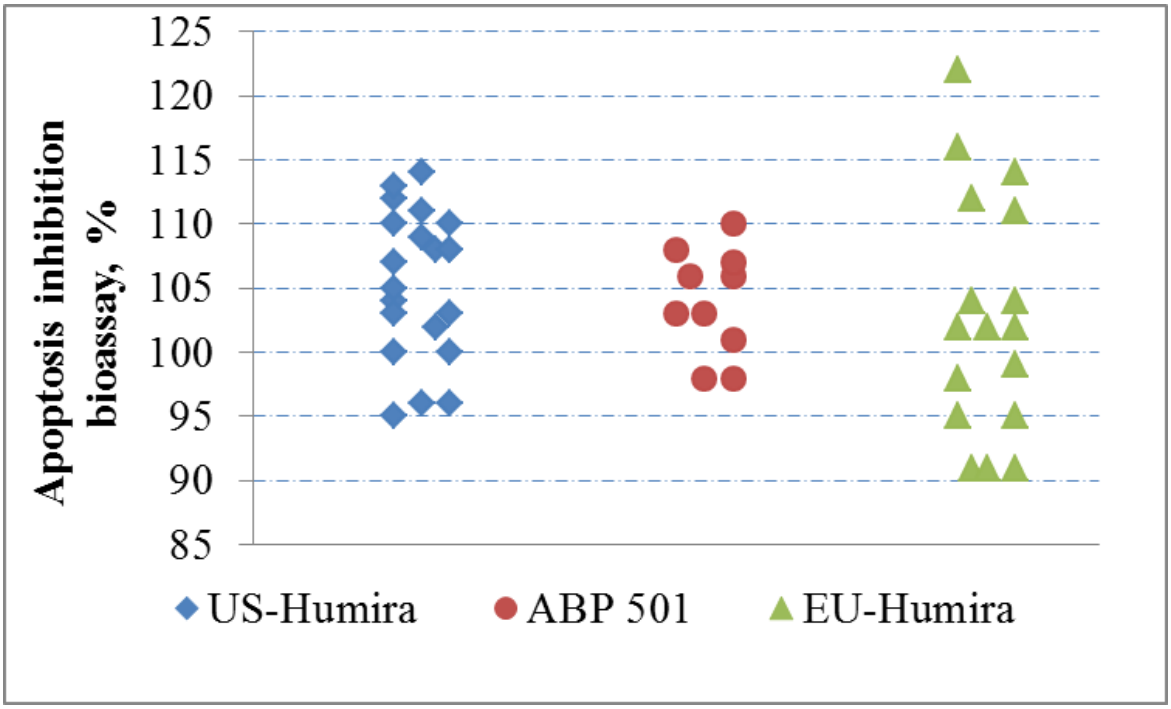

Table 4 Descriptive statistics for the apoptosis inhibition bioassay data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
US-licensed Humira	21	105.43	5.71	95	114
ABP 501	10	104	4.11	98	110
EU-approved Humira	17	102.88	9.36	91	114

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 Humira and ABP 501. From Table 5, it is seen that the apoptosis inhibition bioassay of ABP 501 is equivalent to the apoptosis inhibition bioassay of US-licensed Humira. Similarly, the apoptosis inhibition bioassay of ABP 501 is equivalent to the apoptosis inhibition bioassay of EU-approved Humira, and the apoptosis inhibition bioassay of EU-approved Humira is equivalent to the apoptosis inhibition bioassay of US-licensed Humira.

Table 5 Equivalence testing results for the apoptosis inhibition bioassay

Comparison	# of lots	Mean difference, %	90% confidence interval for mean difference, %	Equivalence margin, %	Equivalent
ABP 501 vs. US	(10, 21)	-1.43	(-4.50, 1.93)	(-8.57, 8.57)	Yes
ABP 501 vs. EU	(10, 17)	1.12	(-3.37, 5.82)	(-14.04, 14.04)	Yes
EU vs. US	(17, 21)	-2.55	(-6.97,1.88)	(-8.57, 8.57)	Yes

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

5.3 FDA statistical equivalence testing for sTNF-α binding

The sTNF-α binding data points of ABP 501, US-licensed Humira, and EU-approved Humira are displayed in Figure 2. Clearly there is a mean shift between the US-licensed Humira and ABP 501.

Ten batches of ABP 501, 10 batches of US-licensed Humira, and 10 batches of EU-approved Humira are included in the sTNF-α binding dataset for the statistical equivalence testing. Descriptive statistics for the sTNF-α binding data of ABP 501, US-licensed Humira, and EU-approved Humira are listed in Table 6.

From Table 7, it is seen that the equivalence of sTNF-α binding between ABP 501 and US-licensed Humira is supported. The equivalence of sTNF-α binding between ABP 501 and EU-approved Humira is supported. The equivalence of sTNF-α binding between US-licensed Humira and EU-approved Humira is supported.

Figure 2 Scatter plot of sTNF-α binding for US-licensed Humira, ABP 501, and EU-approved Humira

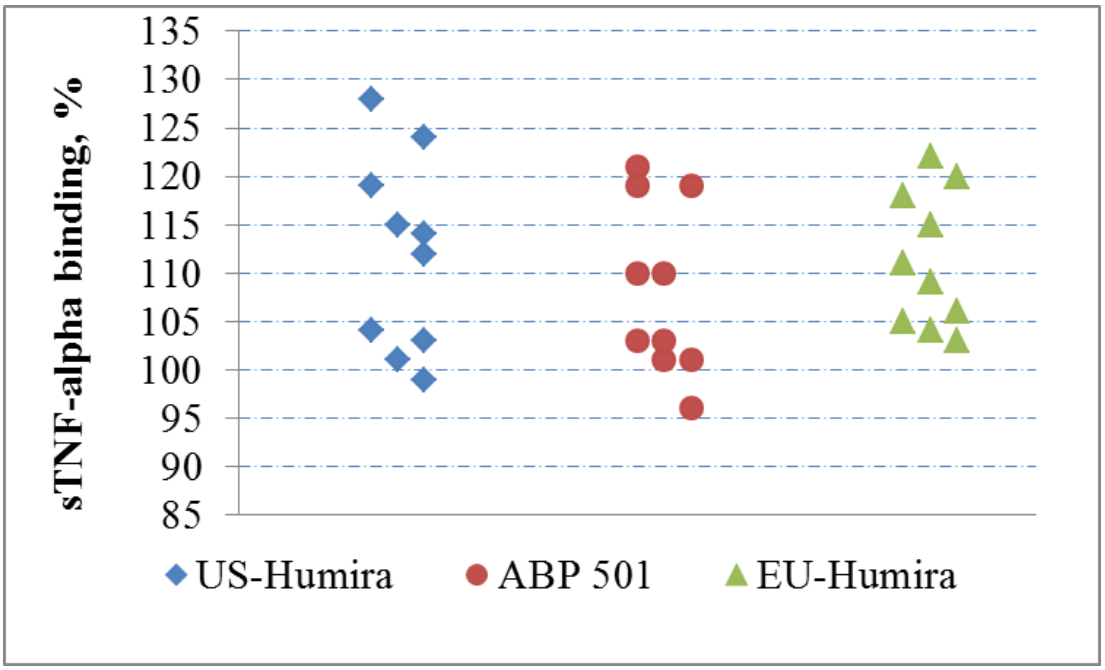

Table 7 Descriptive statistics for the sTNF-α binding data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
US-licensed Humira	10	111.9	9.98	99	128
ABP 501	10	108.3	8.88	96	121
EU-approved Humira	10	111.3	7.02	103	122

Table 8 Equivalence testing results for the sTNF-α binding

Comparison	# of lots	Mean difference, %	90% confidence interval for mean difference, %	Equivalence margin, %	Equivalent
ABP 501 vs. US	(10, 10)	-3.60	(-10,93, 3.73)	(-14.97, 14.97)	Yes
ABP 501 vs. EU	(10, 10)	-3.00	(-9.23, 3.23)	(-10.54, 10.54)	Yes
EU vs. US	(10, 10)	-0.60	(-7.34,6.14)	(-14.97, 14.97)	Yes

6 CONCLUSION AND RECOMMENDATION

The results from the statistical equivalence testing of the apoptosis inhibition bioassay and the sTNF-α binding support a demonstration that the proposed biosimilar ABP 501 is highly similar to US-licensed Humira. The statistical analyses of the apoptosis inhibition bioassay and the sTNF-α binding in the three pair-wise comparisons (ABP 501, US-licensed Humira, and EU-approved Humira) also support the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Humira and the ABP 501 product to support a demonstration of biosimilarity to US-licensed Humira.

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/s/

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08/17/2016

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