STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.	761080
DATE RECEIVED BY THE CENTER	09/28/2017
DRUG NAME	PF-06881893 (filgrastim, proposed biosimilar to US-licensed Neupogen®).
DOSAGE FORM	Injection
STRENGTH	Vials: 300 mcg/mL, 480 mcg/1.6 Ml Prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL
INDICATION	The proposed indication is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia
SPONSOR	Hospira, Inc.
REVIEW FINISHED	06/07/2018
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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistical reviewer in the Office of Biostatistics analyzed the comparative result of one critical quality attribute: In Vitro Potency (%), which was recommended for equivalence testing analysis by Office of Biotechnology. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where R represents US-licensed reference product variability (US-licensed Neupogen). Fourteen PF-06881893 drug product lots, and 15 US-licensed Neupogen lots were used for the equivalence testing of the In Vitro Potency (%). The results are summarized in Table 1.

Table 1: Equivalence testing results for the In Vitro Potency (%)

Comparison	# of lots	Mean Difference, mg/mL	90% Confidence Interval for Mean Difference, mg/mL	Equivalence Margin, mg/mL	Pass the Equivalence Testing?
PF-06881893 vs. US	(14, 15)	2.30	(-0.76, 5.37)	(-8.77, 8.77)	Yes

As shown in Table 1, the results from the statistical equivalence testing of the In Vitro Potency (%) support a demonstration that the proposed biosimilar PF-06881893 is highly similar to US-licensed Neupogen.

2 INTRODUCTION

On September 28, 2017, Hospira submitted to the U.S. Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing the Tier 1 quality attribute for PF-06881893 and US-licensed Neupogen.

In the initial submission, Hospira used 26 PF-06881893 drug product (DP) lots for the Tier 1 analytical similarity assessment, including 16 lots of PF-06881893 drug product in the Prefilled Syringe (PFS) presentation and 10 lots of PF-06881893 drug product in the Single Dose Vial (SDV) presentation. However, these 26 lots of PF-06881893 DP are sourced from 14 independent lots of Drug Substance (DS). FDA's expectation for the analytical similarity assessment is that each value for each attribute being assessed is contributed by an independent drug product lot or drug substance lot. FDA considers an "independent" lot to be a single drug

product lot produced from a single drug substance lot, or a single drug sunstance lot where no subsequent drug product lot is included in the analysis. Additionally, FDA does not consider different drug product lots produced from the same drug substance lot to be independent. Thus, the 26 lots of PF-06881893 were not considered as independent lots. On December 13, 2017, FDA CMC Statistical Reviewer sent out an information request letter. In the letter, the agency requested Hospira to consider FDA's comments regarding the "independent lots" and re-evaluate the equivalence testing for potency using only the first DP lot manufactured from each DS lot. The response from Hospira was received on December 22, 2017. In Hospira's response letter, as per FDA's request, the Tier 1 statistical analysis of In Vitro Potency has been performed using independent lots by including only the result for the first DP lot manufactured from each DS lot.

Secondly, Hospira included 15 lots of US-Licensed Neupogen in their Tier 1 equivalence testing. These 15 lots of US-Licensed Neupogen (7 PFS and 8 SDV) were selected from 25 lots of Neupogen reference product in the PFS presentation and 25 lots of Neupogen reference product in the SDV presentation that were acquired to support the analytical similarity assessment. On December 13, 2017, FDA CMC Statistical Reviewer sent out an information request letter. In this letter, the agency requested Hospira to provide their selection criteria of the reference product lots and the scientific justification to explain why some US-Licensed Neupogen lots were not included in their Tier 1 equivalence testing. Hospira provided their response on December 22, 2017. A total of 15 Neupogen lots were selected for testing by in vitro cell-based bioassay based on availability after final bioassay method implementation. These Neupogen lots were selected across the shelf-life of the product and are representative of both dose strengths and both the prefilled syringe (PFS) and single dose vial (SDV) presentations. The lots include the Neupogen reference product lots (lots 1050859 and 1060852) used in the comparative clinical studies. The in vitro cell-based bioassay was updated on May 2015 to align with the USP Filgrastim Monograph, including changes in detection method from absorbance to luminescence. The In Vitro Potency testing for the final analytical similarity data package using the updated method commenced in July 2015, and was completed in Sep 2016. Hospira also provided the following justifactions for the other 35 purchased Neupogen reference product lots that were excluded from the prospective In Vitro Potency testing plan.

a) 17 Neupogen reference product lots that expired prior to the May 2015 method update or prior to July 2015 (In Vitro Potency final similarity testing start). Since the Neupogen

reference product lots were stored under the recommended storage condition of 2-8°C, they were not tested beyond the expiry date.

b) 15 Neupogen reference product lots that have expiry within Oct 2015 to Dec 2017, the range of expiry for the Neupogen lots included in the final analytical similarity assessment of In Vitro Potency. These additional available Neupogen lots were not tested as inclusion of these lots does not improve the span of the reference product manufacturing history. The estimated dates of manufacturing for these additional Neupogen lots fall within those of the Neupogen lots prospectively defined in the analytical similarity assessment protocol.

c) Neupogen reference product lot 1038088 (expiry Aug 2015) that was tested in Dec 2014 prior to the method update.

d) Neupogen reference product lot 1062643 (expiry Mar 2018) that was procured for testing by Peptide Mapping and Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS) methods only. Since both Peptide Mapping and CE-SDS analyses were performed at the Hospira Lake Forest site, lot 1062643 was not shipped to the Hospira Zagreb site for any testing.

e) Neupogen reference product lot 1068418 (expiry Jul 2018) that was procured for testing by Nuclear Magnetic Resonance (NMR) method only. The NMR analysis was performed at a Contract Research Organization ((b) (4)) and lot 1068418 was not shipped to Hospira Zagreb site for any testing.

FDA CMC statistical reviewer and the Reviewer from Office of Biotechnology discussed together, and both agreed with Hospira's response. The Agency carefully evaluated the data for In Vitro Potency (%) provided in the BLA submission. Our comments regarding Hospira's equivalence testing (Tier 1 approach) is provided in Section 3, and our independent statistical equivalence testing analyses are presented in Section 4.

Table 2: In Vitro Potency Results for PF-06881893 DP and the Neupogen Reference Product Lots

Test Sample	Lot Number	Dose Strength	Age at Time of Testing (Months)	In Vitro Potency (% Relative Potency)
PF-06881893 DP PFS	2854103	300 mcg/0.5 mL	21	103
	2056024	300 mcg/0.5 mL	17	101
	2053054	300 mcg/0.5 mL	14	104
	2073094	300 mcg/0.5 mL	10	96
	2074114	300 mcg/0.5 mL	7	101
	2572075	300 mcg/0.5 mL	0	110
	2574075	300 mcg/0.5 mL	0	102
	2576075	300 mcg/0.5 mL	2	104
PF-06881893 DP SDV	EX6-049A	300 mcg/1.0 mL	1	97
	EX6-084A	300 mcg/1.0 mL	0	105
	PD6-267	300 mcg/1.0 mL	2	100
	PD6-268	300 mcg/1.0 mL	2	101
	PD6-270	480 mcg/1.6 mL	1	100
	PD6-271	480 mcg/1.6 mL	1	98
Neupogen Reference Product PFS	1042949	300 mcg/0.5 mL	27	92
	1051786	300 mcg/0.5 mL	14	95
	1057139	300 mcg/0.5 mL	9	109
	1047463	480 mcg 0.8 mL	19	94
	1050859	480 mcg 0.8 mL	19	97
	1056459	480 mcg 0.8 mL	9	99
	1060852	480 mcg 0.8 mL	15	98
Neupogen Reference Product SDV	1040808	300 mcg /1.0 mL	27	92
	1051319	300 mcg /1.0 mL	15	93
	1053036	300 mcg /1.0 mL	12	102
	1056454	300 mcg /1.0 mL	11	101
	1041879	480 mcg /1.6 mL	25	106
	1045436	480 mcg /1.6 mL	20	110
	1051323	480 mcg /1.6 mL	18	98
	1058392	480 mcg /1.6 mL	10	103

3 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Hospira conducted Tier 1 statistical equivalence testing with the margin defined as $\left(-1.5\hat{\sigma}_R,\ +1.5\hat{\sigma}_R\right)$ for the In Vitro Potency (%). Pairwise comparisions were used for the assessment of the Tier 1 quality attributes. Similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for PF-06881893 vs. US-licensed Neupogen is within the EAC of $\left(-1.5\hat{\sigma}_R,\ +1.5\hat{\sigma}_R\right)$, where R represents the product variability of US-licensed Neupogen. Hospira presumed unequal variances for the two-sided 90% confidence interval. FDA CMC statistics reviewer's conclusion on Hospira's equivalence testing is: Hospira's statistical approach followed the agent's current recommendation for Tier 1 analytical similarity assessment. FDA CMC statistical reviewer also performed the independent analysis and confirmed the results in Section 4.

4 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommends a tiered approach. That is, product quality attributes are assigned to three tiered based on their criticality. The quality attributes with potential highest risk in product quality, efficiency, safety and PK/PD are assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. Quality attributes with lower impact are 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 assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display. This review focuses on the equivalence testing in Tier 1.

4.1 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 Neupogen product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Neupogen. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Neupogen product, we aim to reject the null hypothesis of the following null and alternative hypotheses:

$$H_0: \mu_T - \mu_R \leq \theta_1 \quad \text{or} \quad \mu_T - \mu_R \geq \theta_2$$
$$H_1: \theta_1 < \mu_T - \mu_R < \theta_2$$

.

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 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 Neupogen 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 Neupogen 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 $(-1.5\sigma_R, 1.5\sigma_R)$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 biosimilar lots and 10 US-licensed Neupogen lots. When the number of lots is smaller than 10, the test size may be relaxed somewhat, but agreement on this should be reached in advance with FDA scientists. First we estimate σ_R by the sample variability of the US-licensed Neupogen product 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 Neupogen product. Since the two products are manufactured by two manufacturers, two groups are independent. $\overline{X}_i = \frac{\sum_{j=1}^{n_i} X_{ij}}{n_i}$ and $S_i^2 = \frac{\sum_{j=1}^{n_i} (X_{ij} - \overline{X}_i)}{(n_i - 1)}$, where n_i is the number of lots in the ith product, $i = T,R$.

Under the unequal variance of the test product and the US-licensed Neupogen product, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(v)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}},\ \bar{X}_T - \bar{X}_R + t_\alpha(v)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}\right) \qquad (1)$$

Here $t_\alpha(v)$ is the $(1-\alpha)$ quantile and v is the degrees of freedom calculated by Satterthwaite's approximation.

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

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

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

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 $n_T^* = \min(n_T, 1.5n_R)$ for the confidence interval calculation. In the following analyses, we use $\alpha = 0.05$.

4.2 FDA statistical equivalence testing for In Vitro Potency (%),

The In Vitro Potency (%) data distributions of PF-06881893 and US-licensed Neupogen are displayed in Figure 1. Fourteen lots of PF-06881893 and 15 lots of US-licensed Neupogen are included in the In Vitro Potency (%) dataset for statistical equivalence testing. Descriptive statistics for the In Vitro Potency (%) data of PF-06881893, and US licensed Neupogen are listed in Table 3.

Figure 1: Scatter plots of In Vitro Potency (%) for US-licensed Neupogen and PF-06881893.

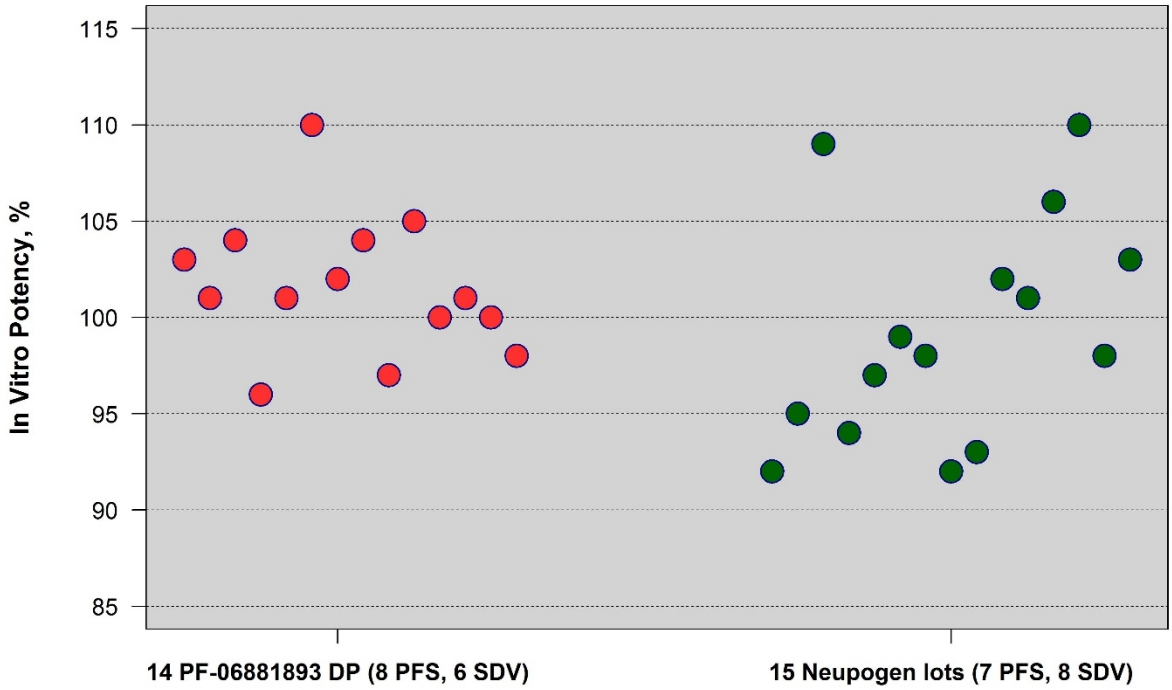

Table 3: Descriptive statistics for the In Vitro Potency (%) data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
PF-06881893	14	101.57	3.59	96	110
US-licensed Neupogen	15	99.27	5.85	92	110

Table 4 shows that the 90% confidence interval for the mean difference in the In Vitro Potency (%) between PF-06881893 and US-licensed Neupogen is (-0.76, 5.37)%. It falls entirely within the equivalence margin (-8.77, +8.77)%. Hence, the results of the In Vitro Potency (%) for PF-06881893 are equivalent to those for US-licensed Neupogen.

The statistical equivalence analyses support that the In Vitro Potency (%) of PF-06881893 is similar to that of US-licensed Neupogen.

Table 4: Results of equivalence testing for the In Vitro Potency (%)

Comparison	# of lots	Mean Difference, mg/mL	90% Confidence Interval for Mean Difference, mg/mL	Equivalence Margin, mg/mL	Pass the Equivalence Testing?
PF-06881893 vs. US	(14, 15)	2.30	(-0.76, 5.37)	(-8.77, 8.77)	Yes

5 CONCLUSION AND RECOMMENDATION

The statistical equivalence analyses shown above regarding the In Vitro Potency (%) support a demonstration that PF-06881893 is highly similar to US-licensed Neupogen.

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