CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761045Orig1s000

STATISTICAL REVIEW(S)

Statistical Review Memo

BLA: 761,045 (SN0048)
Drug Name: zioxtenzo (LA-EP2006)
Indication: Febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs
Sponsor: Sandoz
Statistical Reviewer: Yaping Wang, PhD; Yeh-Fong Chen, PhD
Receipt Date: 02/27/2019
Document Location: \\CDSESUB1\evsprod\BLA761045\0048

There was no new clinical efficacy updates in the submittet documents. Reference is made to the the statistical review dated 6/1/2016.

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/s/

YAPING WANG
08/20/2019 04:02:04 PM

YEH FONG CHEN
08/20/2019 04:06:56 PM

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

STATISTICAL REVIEW AND EVALUATION

BLA NO.	761045
DATE RECEIVED BY THE CENTER	Feburary 27, 2019
DRUG NAME	LA-EP2006
DOSAGE FORM	single-use prefilled syringe
INDICATION	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
SPONSOR	Sandoz
REVIEW FINISHED	May 28, 2019
STATISTICAL REVIEWER	Chao Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Rachel McMullen

Chao Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DBVI
Meiyu Shen, PhD., Lead Mathematical Statistician, CDER/OTS/OB/DBVI

Concur: _____

Thomas Permutt, Ph.D., Associate Director, CDER/OTS/OB

CC List:

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DBVI
Rachel McMullen, CDER/OND/OHOP/DHP

Contents

1 Executive summary and recommendation

I analyzed the applicant's data for two Tier 1 quality attributes, potency and protein concentration.

My independent analysis shows that both attributes pass the equivalence test and support a demonstration that LA-EP2006 is highly similar to US-licensed Neulasta.

The 3-way comparisons between LA-EP2006, US-licensed Neulasta and EU-approved Neulasta for both attributes also support the scientific bridging between the three products.

2 Introduction

On Feburary 27, 2019, Sandoz (the applicant) submitted the Biologics License Application (BLA) 761045 under Section 351 (k) of the PHS Act. In this BLA, the applicant is seeking approval of LA-EP2006 as a biosimilar to US-licensed Neulasta. This is a resubmission which provides a response to the complete response letter (CRL) issued by FDA dated June 24, 2016. While the analysis of two Tier 1 attributes was not a issued raised in the CRL, the applicant updated the analysis of the two Tier 1 attributes in the resubmission. In response, I also updated the analysis of the two Tier 1 attributes in this evaluation.

3 The FDA Statistical reviewer's analysis

3.1 The equivalence test method

In this review, I used the equivalence test method as used by the applicant, which was discussed and agreed during previous meetings between the applicant and the FDA. Below, I briefly discussed the method.

Tn equivalence test concerns testing the means of two normal distributions for Tier 1 QAs between a proposed biosimilar product (B) and a reference product (R). To test the equivalence in mean, the null and alternative hypotheses are formulated as follows:

$$H_0 : \mu_B - \mu_R \leq -\delta \text{ or } \mu_B - \mu_R \geq \delta,$$

and

$$H_a : -\delta < \mu_B - \mu_R < \delta,$$

where μ_B and μ_R are the mean responses of the proposed biosimilar and reference product lots, respectively, and $\delta > 0$ is the equivalence margin which will be specified later.

A test of the equivalence hypothesis can be conducted by requiring simultaneous rejection of the following two one-sided null hypotheses:

$$H_{10} : \mu_B - \mu_R \leq -\delta \text{ versus } H_{1a} : \mu_B - \mu_R > -\delta,$$

and

$$H_{20} : \mu_B - \mu_R \geq \delta \text{ versus } H_{2a} : \mu_B - \mu_R < \delta.$$

Let $(X_{B,j}, j = 1, \cdots, n_B)$ and $(X_{R,j}, j = 1, \cdots, n_R)$ be the two samples for the proposed biosimilar and reference product of sample size n_B and n_R respectively. It is assumed that for $I = B, R$, $X_{I,j} \sim_{IID} N(\mu_I, \sigma_I^2)$

are independent and identically distributed (IID) as a normal distribution with mean μ_I and standard deviation $\sigma_I > 0$.

In practice, $X_{I,j}$ represents the lot value, calculated as the sample mean of multiple replicated measurements for each drug product lot j of drug I. While there is no consensus on how many within-lot replicates should be used, it is known that under independent sampling, the more number of replicates are collected for each lot, the less the variability of lot-average will be.

It is also generally required that the same number of within-lot replicates should be obtained for all drug lots for both test and reference drug products, due to the following reasons. Note that in Tier 1 equivalence test for each drug product (DP) lot, the within-DP lot average is used, whose variance is a function of the number of within-DP lot replicates used in computing the average. Assume that $Y_{I,j,k}$ is the measured value for a QA from the k-th replicate from j-th DP lot for drug I, and $Y_{I,j,k} = \mu + r_j + \epsilon_{j,k}$, with $r_j \sim_{IID} N(0, \sigma^2_{dp})$ and $\epsilon_{j,k} \sim_{IID} N(0, \sigma^2_\epsilon)$ and r_j and $\epsilon_{j,k}$ are mutually independent. Since $X_{I,j} = \frac{1}{K}\sum_{k=1}^{K} Y_{I,j,k}$, $\text{var}(X_{I,j}) = \sigma^2_{dp} + \sigma^2_\epsilon/K$. Different number of within-lot replicates can lead to violation of IID assumption for lot value $X_{I,j}, I = B, R, j = 1, \cdots, n_I$, used in the equivalence test.

Let $\hat{\mu}_I$ and $\hat{\sigma}^2_I$ be the sample mean and unbiased sample variance estimates respectively for $I = B, R$. The test statistics for the two one sided tests H_1 and H_2 are defined respectively as

$$\tau_1 = \frac{\hat{\mu}_B - \hat{\mu}_R + \delta}{\sqrt{\hat{\sigma}^2_B/n^*_B + \hat{\sigma}^2_R/n^*_R}},$$

and

$$\tau_2 = \frac{\hat{\mu}_B - \hat{\mu}_R - \delta}{\sqrt{\hat{\sigma}^2_B/n^*_B + \hat{\sigma}^2_R/n^*_R}},$$

where $n^*_B = \min\{1.5n_R, n_B\}$ and $n^*_R = \min\{1.5n_B, n_R\}$ are the adjusted sample sizes (Dong, Weng, and Tsong 2017). Then H_{10} is rejected if $\tau_1 > t_{1-\alpha,df^*}$ and H_{20} is rejected if $\tau_2 < t_{\alpha,df^*}$, where t_{α,df^*} is α-th upper quantile of the t-distribution with degree of freedom df^*, which is approximated by the Satterthwaite method with sample size adjusted and given as follows,

$$df^* = \frac{\left(\frac{\hat{\sigma}^2_B}{n^*_B} + \frac{\hat{\sigma}^2_R}{n^*_R}\right)^2}{\frac{1}{n_B-1}\left(\frac{\hat{\sigma}^2_B}{n^*_B}\right)^2 + \frac{1}{n_R-1}\left(\frac{\hat{\sigma}^2_R}{n^*_R}\right)^2}.$$

Equivalently, equivalence is accepted for the quality attribute if the following $100(1-2\alpha)\%$ two-sided confidence interval (CI) of the mean difference is within $(-\delta, \delta)$,

$$\left(\hat{\mu}_B - \hat{\mu}_R - t_{1-\alpha,df^*}\sqrt{\hat{\sigma}^2_B/n^*_B + \hat{\sigma}^2_R/n^*_R}, \hat{\mu}_B - \hat{\mu}_R + t_{1-\alpha,df^*}\sqrt{\hat{\sigma}^2_B/n^*_B + \hat{\sigma}^2_R/n^*_R}\right).$$

The equivalence margin is set as $\delta = c\sigma_R$, where c is the margin multiplier and is recommended to be 1.5 (Tsong, Dong, and Shen 2017). In this case, the test would yield a positive result if the 90% confidence interval about the difference in sample means lies within $(-1.5\sigma_R, 1.5\sigma_R)$. For known σ_R, if there were 10 biosimilar and 10 reference product lots, this test would have adequate power (at least 85%) to reject the null hypothesis in favor of equivalence when the true underlying mean difference between the proposed biosimilar and reference product lots is equal to $\sigma_R/8$, assuming a test with $\alpha = 0.05$. If the true difference between products is less than $\sigma_R/8$, the power will increase.

I note that in the applicant's analysis, the margin multiplier seems to be determined in a way so that the test has a 80% power given $\mu_T - \mu_R = 1 \times \sigma_R$ for given available number of observations from the products and

the margin multipliers seem to be different for different comparisons. In this evaluation I used $c = 1.5$ for all comparisons, which is consistent with the FDA reviews.

In practice, σ_R in the proposed margin is unknown and estimated by the sample standard deviation of reference product lots estimated from the reference product lots available to the biosimilar applicant.

In the following analysis, the nominal size is set as $\alpha = 0.05$.

3.2 Data quality

In this section I evaluated the quality of the data for the two Tier 1 quality attributes, potency and protein concentration. The sponsor provided all representative large scale GMP LA-EP2006 DP batches. However, due to the low number of large scale GMP DP batches produced, the applicant also included two large scale non-GMP batches and one pilot scale batch also representative for the commercial product process and quality of LA-EP2006. Note that the pilot scale GMP was manufactured by Sandoz, all the other (including both Non-GMP and GMP) lots were manufactured by (b) (4). The pilot scale batch has lowest potency (96) value but its protein concentration is not extreme.

For Neulasta US and Neulasta EU batches, the applicant used the first result generated after purchase. For US-Neulasta, the applicant tested potency and protein concentration on the same sets of US-Neulasta batches. However, the 24 EU-Neulasta batches tested for the potency constitute a proper subset of the 29 EU-Neulasta batches tested for protein concentration.

The applicant provided the remaining shelf life at date of analysis. Figure 1 and 2 illustrate the assay values with respect to the months from testing date to the end of shelf life, showing no apparent trend with respect to lot age.

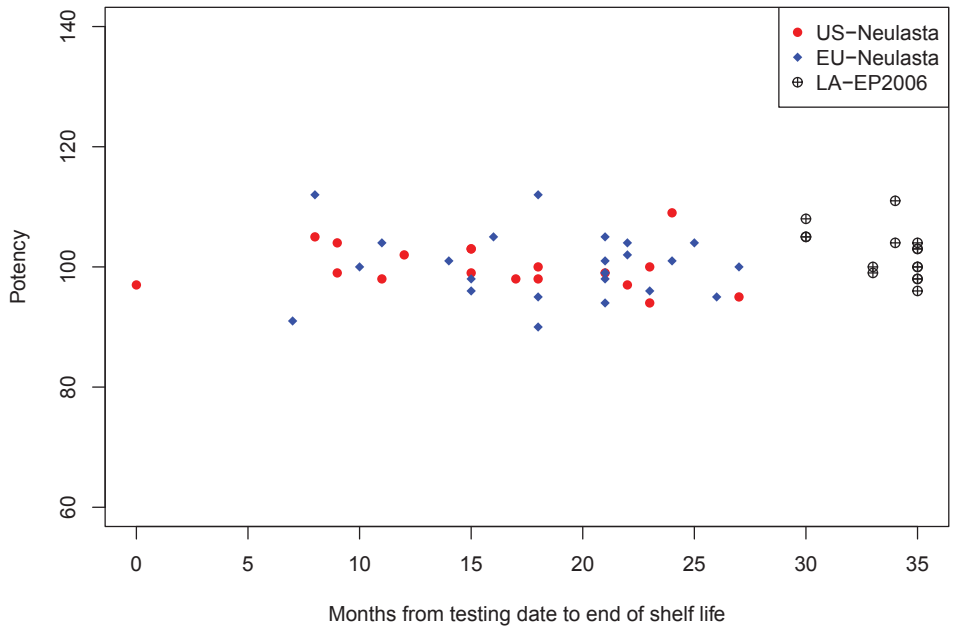

Figure 1: Plot of potency value versus months towards the end of shelf life.

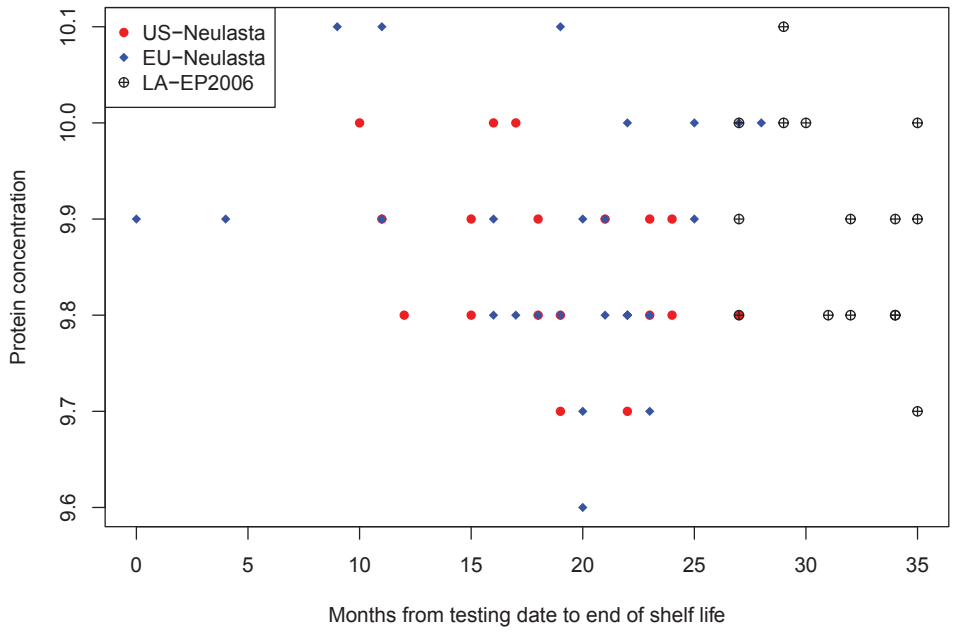

Figure 2: Plot of protein concentration value versus months towards the end of shelf life.

3.3 Analysis of potency

For potency, the data are illustrated in Figure 3 and summarized in Table 1. The equivalence test results are summarized in Table 2, which shows that potency passed the equivalence test.

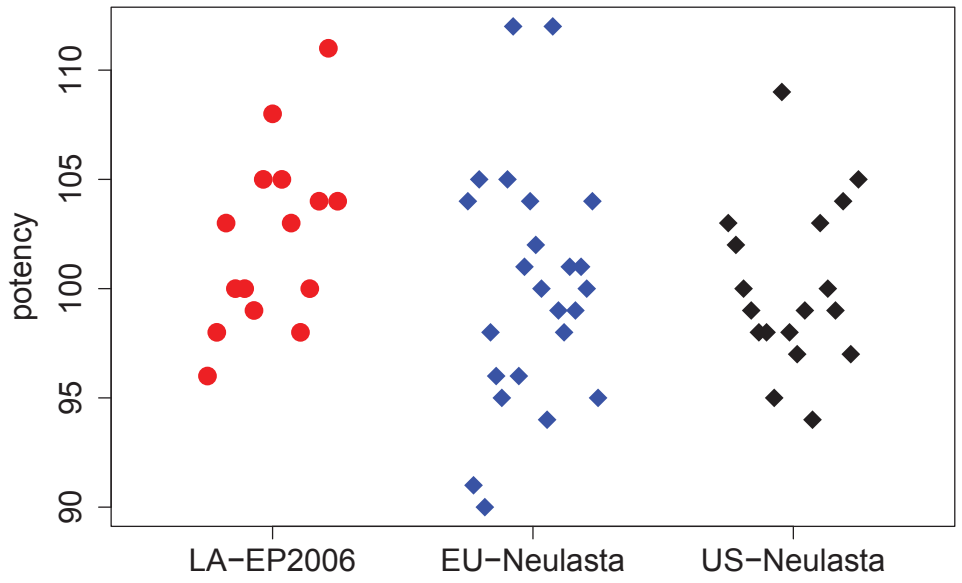

Figure 3: Scatter plot of potency assay values.

Product	n	Min	Max	Mean	SD	CV (%)
LA-EP2006	15	96.00	111.00	102.27	4.08	3.99
EU-Neulasta	24	90.00	112.00	100.08	5.52	5.52
US-Neulasta	18	94.00	109.00	100.00	3.74	3.74

Table 1: Summary of data for potency.

Comparison	Mean Diff. (90% CI)	Margin	Pass ET?
LA-EP2006 vs US-Neulasta	2.27 (-0.07, 4.6)	(-5.61,5.61)	Yes
LA-EP2006 vs EU-Neulasta	2.18 (-0.47, 4.83)	(-8.29,8.29)	Yes
EU-Neulasta vs US-Neulasta	0.08 (-2.33, 2.49)	(-5.61,5.61)	Yes

Table 2: Summary of three-way equivalence test for potency.

3.4 Analysis of protein concentration

For protein concentration, the data are illustrated in Figure 4 and summarized in Table 3. The equivalence test results are summarized in Table 4, which shows that protein concentration passed the equivalence test.

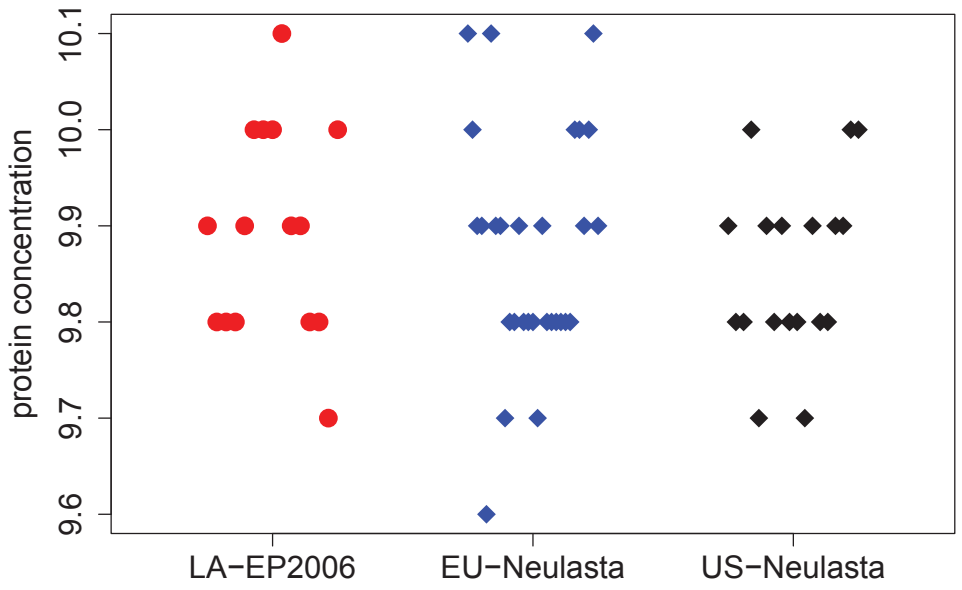

Figure 4: Scatter plot of protein concentration assay values.

Product	n	Min	Max	Mean	SD	CV (%)
LA-EP2006	15	9.70	10.10	9.89	0.11	1.11
EU-Neulasta	29	9.60	10.10	9.87	0.12	1.24
US-Neulasta	18	9.70	10.00	9.86	0.09	0.94

Table 3: Summary of data for protein concentration.

Comparison	Mean Diff. (90% CI)	Margin	Pass ET?
LA-EP2006 vs US-Neulasta	0.04 (-0.02, 0.1)	(-0.14,0.14)	Yes
LA-EP2006 vs EU-Neulasta	0.02 (-0.04, 0.09)	(-0.18,0.18)	Yes
EU-Neulasta vs US-Neulasta	0.02 (-0.04, 0.07)	(-0.14,0.14)	Yes

Table 4: Summary of three-way equivalence test for protein concentration.

4 Conclusion and recommendation

In summary, I analyzed potency and protein concentration as Tier 1 quality attributes. My independent analysis shows that both attributes pass the equivalence test and support a demonstration that LA-EP2006 is highly similar to US-licensed Neulasta. The 3-way comparisons between LA-EP2006, US-licensed Neulasta and EU-approved Neulasta for both attributes also support the scientific bridging between the three products.

Reference

Dong, Xiaoyu, Yu-Ting Weng, and Yi Tsong. 2017. "Adjustment for Unbalanced Sample Size for Analytical Biosimilar Equivalence Assessment." *Journal of Biopharmaceutical Statistics* 27 (2). Taylor & Francis: 220–32.

Tsong, Yi, Xiaoyu Dong, and Meiyu Shen. 2017. "Development of Statistical Methods for Analytical Similarity Assessment." *Journal of Biopharmaceutical Statistics* 27 (2). Taylor & Francis: 197–205.

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/s/

CHAO WANG
07/24/2019 03:58:10 PM

MEIYU SHEN
07/24/2019 03:59:18 PM

THOMAS J PERMUTT
07/25/2019 08:58:30 AM
I concur.

U.S. 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

CLINICAL STUDIES- BIOSIMILAR PRODUCT

NDA/BLA #:	BLA 761045
Supplement #:	Original.
Drug Name:	Zioxtenzo (LA-EP2006)
Indication(s):	Febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs
Applicant:	Sandoz Biopharmaceuticals
Date(s):	Stamp Date: August 27, 2015 BsUFA Goal Date: June 26, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yun Wang, PhD
Concurring Reviewers:	Lei Nie, PhD, Lead Mathematical Statistician Thomas Gwise, PhD, Deputy Director Rajeshwari Sridhara, PhD, Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Dr. Patricia Dinndorf, MD, Clinical Reviewer Dr. Albert Deisseroth, MD, Clinical Team Leader
Project Manager:	Rachel McMullen, RPM
Key words	Biosimilar, non-inferiority, duration of severe neutropenia, febrile neutropenia, equivalence, no clinically meaningful difference

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1 EXECUTIVE SUMMARY

Sandoz submitted a biologics license application BLA761045 under section 351(k) of the Public Health Service Act (PHS Act) to support Zioxtenzo (LA-EP2006) as a biosimilar product to US-licensed Neulasta® (pegfilgrastim). Sandoz is seeking licensure of LA-EP2006 for the indication approved for Neulasta by its submission date of August 26, 2015:

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

To support a demonstration of biosimilarity, a stepwise approach was used following the FDA's scientific recommendation. The stepwise approach starts with structural and functional characterization of both the proposed biosimilar product and the reference product. Results of nonclinical and/or clinical studies follow to assess remaining questions with regards to potential residual uncertainty about biosimilarity.

This review is to evaluate the results of two clinical studies: LA-EP06-301 and LA-EP06-302 which were randomized, double-blind, parallel-group, multi-center studies of LA-EP2006 and EU-licensed Neulasta® in histologically proven breast cancer patients. The purposes of these two studies were to demonstrate that LA-EP2006 is equivalent to EU-Neulasta in the prevention of neutropenic complications in breast cancer patients treated with myelosuppressive chemotherapy. The primary endpoint in both studies was the duration of severe neutropenia (DSN), which was defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5×10^9/L), during Cycle 1 of the neoadjuvant or adjuvant chemotherapy.

A margin of ±1 day for equivalence testing was proposed by the sponsor. LA-EP2006 would be considered equivalent to EU-Neulasta if the two-sided 90% confidence interval for the difference in the mean DSN lies entirely within this equivalence margin. This ±1 day margin for difference in the mean DSN would be anticipated to result in approximately a 10% difference in febrile neutropenia (FN), which is considered not clinically meaningful difference in FN incidence.

In study LA-EP06-301, the mean DSN in Cycle 1 was 0.75 days and 0.83 days for EP2006 and EU-Neulasta, respectively; The difference in the mean DSN and corresponding 90% CI is -0.07 (-0.24, 0.10) days. In study LA-EP06-302, the mean DSN in Cycle 1 was 1.36 days and 1.19 days for EP2006 and EU-Neulasta, respectively; The difference in the mean DSN and corresponding 90% CI is 0.16 (-0.04, 0.37) days. Because 90% CIs from both studies fall within the pre-specified equivalence margin of ±1 day, studies LA-EP06-301 and LA-EP06-302 support that EP2006 is equivalent to EU-Neulasta in terms of efficacy as measured by the mean difference of DSN between EP2006 and EU-Neulasta.

2 INTRODUCTION

2.1 Overview

Granulocyte colony-stimulating factor (G-CSF) is a lineage-specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSFs restore the number of neutrophils and keep the neutrophil count above the critical level at which febrile neutropenia (FN) can occur. The clinical use of recombinant human G-CSF (rhG-CSF) is to reduce the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients with malignancies treated with myelosuppressive chemotherapy regimens as well as to reduce the duration of neutropenia in patients undergoing myeloablative therapy prior to bone marrow transplantation.

The first approved recombinant human G-CSF is Amgen's filgrastim (Neupogen®). The FDA and European Medicines Agency (EMA) approved in 2002 the first second-generation, recombinant methionyl form of human G-CSF (PEG-r-metHuG-CSF) that is pegylated under the INN pegfilgrastim. It was shown that the mean days of severe neutropenia of pegfilgrastim-treated breast cancer patients did not exceed that of filgrastim-treated patients by more than one day in Cycle 1 of chemotherapy and that the rates of FN in the two studies were similar for pegfilgrastim and filgrastim (in the range of 10% to 20%). In a further placebo-controlled, double blind study in breast cancer patients the incidence of FN was lower for patients randomized to receive pegfilgrastim compared with placebo. Pegfilgrastim is currently marketed in the US, European Union (EU) and other territories by Amgen under the trade name Neulasta®.

Sandoz GmbH has developed LA-EP2006 as a pegfilgrastim product. LA-EP2006 was thoroughly characterized using state-of-the-art analytical procedures in regard to physicochemical properties and impurity profile.

Studies LA-EP06-301 and LA-EP06-302 were designed to investigate the efficacy and safety of LA-EP2006 compared with EU-Neulasta (EU-authorized) in the prevention of neutropenic complications in breast cancer patients treated with established myelosuppressive chemotherapy.

It was planned to randomize 151 patients in each of the treatment groups in a 1:1 ratio in both studies LA-EP06-301 and LA-EP06-302. In Study LA-EP06-301, randomization was stratified by chemotherapy category (adjuvant or neo-adjuvant) and region (geographically located in Europe, Asia, or America). Study LA-EP06-302 had an ECG/PK sub-study planned in a subset of 50 patients. Randomization for patients who did not take part in the ECG sub-study was stratified by chemotherapy category (adjuvant or neo-adjuvant) and region (US, Asia, and 'rest of world'). Patients who took part in the sub-study were stratified by chemotherapy category and weight class (< 65kg; ≥ 65kg to < 80kg; ≥ 80kg).

A total of 316 patients were enrolled and treated in Study LA-EP06-301 between 28 June 2012 and 07 September 2013 from 38 sites in 6 countries. Last patient last visit for 6-month follow-up was 11 February 2014. The original protocol for Study LA-EP06-301 was dated 21 October 2011, and the latest version was Amendment 2 dated 03 September 2012. A total of 308 patients were enrolled and treated in Study LA-EP06-302 between 05 March 2012 and 25 November 2013 from 52 sites in 8 countries. Last patient last visit for 4-week follow-up was 04 December 2013. The original protocol for Study LA-EP06-302 was dated 22 July 2011, and the latest version was Amendment 3 dated 10 May 2012.

Throughout this review, patients received LA-EP2006 or EU-Neulasta for neutropenia while receiving chemotherapy for breast cancer are referred as "LA-EP2006" arm or "EU-Neulasta" arm respectively in the text, the tables/figures.

Table 1 : List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects	Study Population
LA-EP06-301	*Phase 3*	*18 weeks*	*6 months*	*316*	*Breast cancer*
LA-EP06-302	*Phase 3*	*18 weeks*	*4 weeks*	*308*	*Breast cancer*

2.2 Data Sources

The data provided in the submission could be used to evaluate the claim that the products are similar by considering the width of the confidence interval for the difference in mean DSN. The study report and data were provided electronically; the location/names of study report, analysis datasets (ADAM) including STDM datasets and SAS programs are as follows;

Study Reports:

\\cdsesub1\evsprod\BLA761045\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\febrile-neutropenia\5351-stud-rep-contr

Datasets

\\cdsesub1\evsprod\BLA761045\0000\m5\datasets

Programs

\\cdsesub1\evsprod\BLA761045\0020\m5\datasets\la-ep06-301\analysis

\\cdsesub1\evsprod\BLA761045\0020\m5\datasets\la-ep06-302\analysis

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Reviewer reviewed the quality and integrity of the submitted data. Examples of relevant issues include the following:

- It is possible to reproduce the primary analysis dataset, and in particular the primary endpoint, from the original data source.
- The sponsor didn't provide analysis programs at the initial BLA submission, so we requested programs through information request.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies LA-EP06-301 and LA-EP06-302 are randomized, double-blind, parallel-group, multi-center studies comparing the efficacy and safety of LA-EP2006 and EU-Neulasta in histologically proven breast cancer patients treated with TAC combination chemotherapy.

Patients eligible for neoadjuvant or adjuvant treatment were treated with myelosuppressive TAC chemotherapy (Taxotere® [docetaxel 75 mg/m^2] in combination with Adriamycin® [doxorubicin 50 mg/m^2] and Cytoxan® [cyclophosphamide 500 mg/m^2]), all given IV on day 1 of each of six 21-day cycles). After completion of the screening period and first dose of chemotherapy, eligible patients were randomized to either LA-EP2006 or EU-Neulasta. Pegfilgrastim (LA-EP2006 or EU-Neulasta) was administered on Day 2 of each chemotherapy cycle (at least 24 hours after chemotherapy ended). LA-EP2006 and EU-Neulasta were injected subcutaneously with a daily dose of 5 mcg/kg body weight.

For Study LA-EP06-301, the total study duration for the individual patient was approximately 44 weeks. After a screening period of up to 3 weeks, the active treatment period was approximately 18 weeks, i.e. six TAC chemotherapy cycles. The safety follow-up period of 6 months started with the last IMP administration at the beginning of the 6th chemotherapy cycle. For Study LA-EP06-302, the total study duration for the individual patient was up to 22 weeks, including up to 3 weeks screening, approximately 18 weeks of active treatment, i.e. six TAC chemotherapy cycles, and a safety follow-up period of 4 weeks starting after the last IMP administration at the beginning of the sixth TAC chemotherapy cycle.

Patient's ANC, platelet values and hemoglobin values had to be above the defined limits (ANC $\geq$1.5 x 10^9/L, platelets $\geq$100 x 10^9/L, and Hemoglobin $\geq$ 10g/dL) at the Day 1 of Cycle 1. In Cycle 1, blood samples for the determination of the ANC were taken on Day 1, daily until the ANC recovered to 10 × 10^9/L after the nadir or until Day 15, whichever occurred first. In Cycles 2 to 6, blood samples were taken on Day 1 prior to chemotherapy and daily from Day 7 onwards until the ANC recovered to 10 × 10^9/L after the nadir or until Day 15, whichever occurred first.

Primary Endpoint:

The primary efficacy endpoint was the mean DSN in Cycle 1. The DSN was set to 0 in patients who did not experience severe neutropenia in Cycle 1. In patients who experienced several episodes of severe neutropenia, the number of days for each episode was summed up.

Secondary endpoints:

- Incidence of febrile neutropenia
- Fever episode
- Depth and time of ANC nadir in cycle 1
- Time to ANC recovery (> 2*10^9/L)
- Frequency of infection
- Mortality due to infection

If the nadir was $\geq 2 \times 10^9$/L for all time points after administration of chemotherapy the time was set to 0 day. The incidence of FN was calculated as the number of patients with at least one episode of FN divided by the number of patients at risk in a given time interval (in each cycle the period between Day 2 to Day 15 was considered for the analysis). FN was defined as having both an oral temperature $\geq 38.3°C$ and an ANC $< 0.5 \times 10^9$/L on the same day.

3.2.2 Statistical Methodologies

The primary efficacy endpoint was analyzed using an analysis of co-variance (ANCOVA) with treatment group, kind of chemotherapy and baseline ANC value as a covariate. The mean DSN in each treatment group and the difference of means will be presented as well as the 90% confidence limit of the difference between mean DSNs in each treatment group. Equivalence will be concluded, if the confidence interval lies entirely within the equivalence margins of ± 1 day.

Secondary endpoints were analyzed with descriptive statistics.

The equivalence limit of ±1 day was chosen based on the fact that TAC chemotherapy is known to induce a median DSN of seven days in breast cancer patients receiving no G-CSF treatment, while G-CSF treatment reduces the mean DSN for this chemotherapy to 1.4 days (95% CI: 1.07 - 1.69) as shown in Amgen`s pegfilgrastim (Neulasta®) Study. Therefore, a non-inferiority limit of -1 day preserves approximately 80% of the treatment effect of Neupogen®. Moreover, in the Amgen studies conducted to support the approval of the long-acting rh-G-CSF Neulasta®, a single dose of pegfilgrastim (Neulasta®) was compared to daily administrations of filgrastim (Neupogen®) with a non-inferiority margin of -1 day for the duration of Grade 4 neutropenia in breast cancer patients treated with myelosuppressive chemotherapy. This limit was accepted by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the registration of Neulasta®. A limit of -1 day was also accepted by the EMA during the Scientific Advice procedure for the development of LA-EP2006 as a biosimilar to EU-Neulasta. This 1-day difference in DSN would be anticipated to result in approximately a 10% difference in febrile neutropenia, which is considered not clinically meaningful difference in FN incidence.

The missing value imputation refers only to the determination of severe neutropenia and not to the replacement of the ANC value itself. In case an ANC value is missing the following rules may be used:

- The ANC before and after the missing day is ≥ 0.5 x 109/L: the day can likely be ignored as a potential day of severe neutropenia. However, there were exceptions to this rule, in case the potential of the missing ANC to fulfill the severe neutropenia definition was high, e.g. if the missing ANC value could have been the nadir. Such cases were reviewed, decided upon and documented at the BDRM in a completely blinded way.
- If at both neighboring days the ANCs are < 0.5 x 109/L, then set the missing day to severe neutropenia.
- If the day before is < 0.5 x 109/L and the day after ≥ 0.5 x 109/L, then the missing day is set to severe neutropenia.
- If the day before is ≥ 0.5 x 109/L and the day after < 0.5 x 109/L, then the missing day is set to severe neutropenia.

- If any of the neighboring days (i.e. 2 or more missing values in a row) is also missing, severe neutropenia cannot be determined automatically. These cases were discussed in the BDRM.

For the secondary efficacy endpoints no missing value imputation was performed.

Sample Size Calculation

The following assumptions are made for the sample size determination:

- Equivalence limit: ±1 day
- Expected difference in the means: 0 days
- Common standard deviation: 1.6 days
- Power: 90%
- Significance level: 2.5% (two-sided 95% confidence intervals)
- Randomization ratio: 1:1 (LA-EP2006:EU-Neulasta)

Then, 302 evaluable patients are sufficient to achieve at least 90% power for testing equivalence with respect to a margin of ± 1 day using a two one-sided test procedure (TOST) for equivalence in means where each test is performed at the 2.5% level.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The full analysis set (FAS) included all randomized patients who received at least one dose of study medication. FAS was the primary analysis population for all efficacy analyses, and was used for descriptions of patient disposition, demographics, and baseline disease characteristics.

Patient disposition

A total of 316 patients were randomized into Study LA-EP06-301, 159 to LA-EP2006 arm and 157 to EU-Neulasta arm. Twenty-six patients discontinued the study treatment prematurely and 42 patients did not complete the study. The primary reason for premature treatment and study discontinuations are summarized in Table 2.

Table 2 : Patient disposition – FAS, Study LA-EP06-301

	LA-EP2006 N=159 n (%)	**EU-Neulasta N = 157 n (%)**	**Total N = 316 n (%)**
Discontinued treatment	19 (11.9)	7 (4.5)	26 (8.2)
Main Cause of discontinuing treatment			
Withdrawal of informed consent	8 (5.0)	2 (1.3)	10 (3.2)
Adverse event	2 (1.3)	2 (1.3)	4 (1.3)
Death	1 (0.6)	2 (1.3)	3 (0.9)
Investigator's decision	5 (3.1)	1 (0.6)	6 (1.9)
Other	3 (1.9)	0	3 (0.9)
Discontinued study	29 (18.2)	13 (8.3)	42 (13.3)
Main Cause of discontinuing study			
Withdrawal of informed consent	9 (5.7)	2 (1.3)	11 (3.5)
Lost to follow-up	4 (2.5)	2 (1.3)	6 (1.9)
Death	3 (1.9)	2 (1.3)	5 (1.6)
Other	13 (8.2)	7 (4.5)	20 (6.3)

[Source: Study LA-EP06-301 Study CSR Table 10-2 on page 60 and statistical reviewer's analysis]

A total of 308 patients were randomized into Study LA-EP06-302, 155 to LA-EP2006 arm and 153 to EU-Neulasta arm. Thirty-three patients discontinued the study treatment prematurely and 38 patients did not complete the study. The primary reason for premature treatment and study discontinuations are summarized in Table 3.

Table 3: Patient disposition – FAS, Study LA-EP06-302

	LA-EP2006 N=155 n (%)	**EU-Neulasta N = 153 n (%)**	**Total N = 308 n (%)**
Discontinued treatment	20 (12.9)	13 (8.5)	33 (10.7)
Main Cause of discontinuing treatment			
Withdrawal of informed consent	10 (6.5)	4 (2.6)	14 (4.5)
Adverse event	4 (2.6)	5 (3.3)	9 (2.9)
Death	3 (1.9)	1 (0.7)	4 (1.3)
Investigator's decision	2 (1.3)	1 (0.7)	3 (1.0)
Other	0	1 (0.7)	1 (0.3)
Lack of efficacy	1 (0.6)	0	1 (0.3)
Protocol deviation	0	1 (0.7)	1 (0.3)
Discontinued study	22 (14.2)	16 (10.5)	38 (12.3)
Main Cause of discontinuing study			
Withdrawal of informed consent	10 (6.5)	4 (2.6)	14 (4.5)
Lost to follow-up	2 (1.3)	0	2 (0.6)
Death	3 (1.9)	1 (0.7)	4 (1.3)
Other	7 (4.5)	11 (7.2)	18 (5.8)

[Source: Study LA-EP06-302 Study CSR Table 10-2 on page 62 and statistical reviewer's analysis]

Patients Demographics

The patients' demographics for Study LA-EP06-301 are summarized in Table 4. Demographic characteristics were balanced between the two treatment groups. Most of the patients were White (81.0%) or Asian (17.1%), and other (1.9%). The number of patients with Hispanic or Latino ethnicity was small (18 patients, 11.5%). The mean (± SD) age of patients was 50.2 (± 10.20) years.

Table 4: Demographics – FAS, Study LA-EP06-301

	LA-EP2006 N=159	**EU-Neulasta N = 157**	**Total N = 316**
Age (Years)			
Mean (SD)	49.9 (9.53)	50.5 (10.87)	50.2 (10.20)
Median	50.0	50.0	50.0
Range	30 – 72	29 – 76	29 – 76
Categorical age, n (%)			
< 65	148 (93.1)	141 (89.8)	289 (91.5)
≥ 65	11 (6.9)	16 (10.2)	27 (8.5)
Race, n (%)			
White	129 (81.1)	127 (80.9)	256 (81.0)
Asian	28 (17.6)	26 (16.6)	54 (17.1)
Other	2 (1.3)	4 (2.5)	6 (1.9)
Ethnicity, n (%)			
Hispanic or Latino	11 (6.9)	18 (11.5)	29 (9.2)
Not Hispanic or Latino	148 (93.1)	139 (88.5)	287 (90.8)
Region, n (%)			
Europe	125 (78.6)	123 (78.3)	248 (78.5)
Asia	27 (17.0)	25 (15.9)	52 (16.4)
America	7 (4.4)	9 (5.7)	16 (5.1)

[Source: Study LA-EP06-301 Study CSR Table 11-2 on page 68 and statistical reviewer's analysis]

The patients' demographics for Study LA-EP06-302 are summarized in Table 5. Demographic characteristics were balanced between the two treatment groups. Most of the patients were White (183 patients, 59.4%) or Asian (120 patients, 39.0%). The number of patients with Hispanic or Latino ethnicity was small (16 patients, 5.2%). The mean age of patients was 48.9 (± 10.27) years.

Table 5: Demographics – FAS, Study LA-EP06-302

	LA-EP2006 N=155	**EU-Neulasta N = 153**	**Total N = 308**
Age (Years)			
Mean (SD)	48.8 (10.50)	49.1 (10.07)	48.9 (10.27)
Median	49.0	50.0	50.0
Range	25 – 75	26 – 68	25 – 75
Categorical age, n (%)			
< 65	144 (92.9)	143 (93.5)	287 (93.2)
≥ 65	11 (7.1)	10 (6.5)	27 (6.8)
Race, n (%)			
White	90 (58.1)	93 (60.8)	183 (59.4)
Asian	62 (40.0)	58 (37.9)	120 (39.0)
Other	3 (1.9)	2 (1.3)	5 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	10 (6.5)	6 (3.9)	16 (5.2)
Not Hispanic or Latino	145 (93.5)	147 (96.1)	292 (94.8)
Region, n (%)			
US	12 (7.7)	11 (7.2)	23 (7.5)
Asia	62 (40.0)	58 (37.9)	120 (39.0)
Rest of world	81 (52.3)	84 (54.9)	165 (53.6)

[Source: Study LA-EP06-302 Study CSR Table 11-2 on page 75 and statistical reviewer's analysis]

Patients Baseline Disease Characteristics

The patients' baseline disease characteristics for Study LA-EP06-301 are summarized in Table 6. Both treatment groups were well matched with regard to baseline disease characteristics.

In both groups, the median duration from time of initial diagnosis of breast cancer to informed consent was about 1.4 months and the disease stage was Stage II (46.5%) or Stage III (50.3%) in most patients. While most of the patients (93.4%) had previous breast cancer surgical procedures, prior radiotherapy was restricted to 5.1 % patients. The majority of patients (79.4%) had an ECOG score of 0. More patients (62.0%) had adjuvant chemotherapy compared to neo-adjuvant therapy (38.0%).

Table 6: Baseline Disease Characteristics – FAS, Study LA-EP06-301

	LA-EP2006 N=159	**EU-Neulasta N = 157**	**Total N = 316**
Time since initial diagnosis (months)	153	147	300
Median	1.35	1.38	1.38
Range	0.1 – 76.0	0.2 – 10.9	0.1 – 76.0
Disease stage at initial dose, n (%)			
I	4 (2.5)	3 (1.9)	7 (2.2)
II	74 (46.5)	73 (46.5)	147 (46.5)
III	81 (50.9)	78 (49.7)	159 (50.3)
IV	0	3 (1.9)	3 (0.9)
Prior breast cancer surgical procedure			
Yes	149 (93.7)	146 (93.0)	295 (93.4)
No	10 (6.3)	11 (7.0)	21 (6.6)
Prior radiotherapy, n (%)			
Yes	7 (4.4)	9 (5.7)	16 (5.1)
No	152 (95.6)	148 (94.3)	300 (94.9)
ECOG performance status, n (%)			
0	128 (80.5)	123 (78.3)	251 (79.4)
1	31 (19.5)	34 (21.7)	65 (20.6)
Type of chemotherapy			
Neo-adjuvant	60 (37.7)	60 (38.2)	120 (38.0)
Adjuvant	99 (62.3)	97 (61.8)	196 (62.0)

[Source: Study LA-EP06-301 Study CSR Table 11-5 on page 70 and statistical reviewer's analysis]

The patients' baseline disease characteristics for Study LA-EP06-302 are summarized in Table 7. There were no considerable differences in disease characteristics between two treatment groups.

In both treatment groups, median time since initial diagnosis was 1.28 months. The majority of patients had cancer of Stage II (42.5%) or Stage III (50.6%). A total of 99.4% patients had prior breast cancer surgery, and 1.0% patients had prior radiotherapy. Most patients were of ECOG status 0 (73.7%) or status 1 (25.6%). More patients (68.2%) had adjuvant chemotherapy compared to neo-adjuvant therapy (31.8%).

Table 7: Baseline Disease Characteristics – FAS, Study LA-EP06-302

	LA-EP2006 N=155	**EU-Neulasta N = 153**	**Total N = 308**
Time since initial diagnosis (months)	155	151	306
Median	1.28	1.28	1.28
Range	0.2 – 42.3	0.3 – 11.2	0.2 – 42.3
Disease stage at initial dose, n (%)			
I	7 (4.5)	13 (8.5)	20 (6.5)
II	70 (45.2)	61 (39.9)	131 (42.5)
III	78 (50.3)	78 (51.0)	156 (50.6)
IV	0	1 (0.7)	1 (0.3)
Prior breast cancer surgical procedure			
Yes	154 (99.4)	152 (99.3)	306 (99.4)
No	1 (0.6)	1 (0.7)	2 (0.6)
Prior radiotherapy, n (%)			
Yes	2 (1.3)	1 (0.7)	3 (1.0)
No	153 (98.7)	152 (99.3)	305 (99.0)
ECOG performance status, n (%)			
0	117 (75.5)	110 (71.9)	227 (73.7)
1	36 (23.2)	43 (28.1)	79 (25.6)
2	2 (1.3)	0	2 (0.6)
Type of chemotherapy			
Neo-adjuvant	48 (31.0)	50 (32.7)	98 (31.8)
Adjuvant	107 (69.0)	103 (67.3)	210 (68.2)

[Source: Study LA-EP06-302 Study CSR Table 11-5 on page 77 and statistical reviewer's analysis]

Protocol deviations

Most frequent reasons for major protocol deviations were use of commercial (peg)filgrastim, IMP-related reasons, and missing ANC data. IMP-related protocol deviations were considered major if they occurred during Cycle 1 of chemotherapy. The distributions of major protocol deviations among treatment groups in both studies do not suggest any impact on the analysis of efficacy.

In Study LA-EP06-301, 22 major protocol deviations occurred in 21 patients (LA-EP2006: 13 patients, EU-Neulasta: 8 patients). ANC data were not evaluable for 9 patients (LA-EP2006: 5 patients ; EU-Neulasta: 4 patients); 4 patients used commercial [peg]filgrastim (LA-EP2006: 1 patient ; EU-Neulasta: 3 patients); major IMP related protocol deviations were reported for 7 patients (LA-EP2006: 5 patients ; EU-Neulasta: 2 patients); 1 patient in LA-EP2006 arm used prohibited medication; and 1 patient in LA-EP2006 arm had randomization error.

In Study LA-EP06-302, 16 patients had major protocol deviations (LA-EP2006: 7 patients, EU-Neulasta: 9 patients). ANC data were not evaluable for 8 patients (4 in each treatment arm respectively); 1 patient in EU-Neulasta arm used commercial [peg]filgrastim; major IMP related protocol deviations were reported for 5 patients (LA-EP2006 : 1 patient ; EU-Neulasta: 4 patients); 2 patients (1 from each treatment arm) used prohibited medication; 1 patient in LA-EP2006 arm had chemotherapy overdose.

3.2.4 Results and Conclusions

3.2.4.1 Primary endpoint

The primary analysis of primary endpoint, duration of severe neutropenia (DSN), for Study LA-EP06-301 is summarized in Table 8. Mean DSN in Cycle 1 was 0.75 days in patients treated with LA-EP2006 and 0.83 days in patients treated with EU-Neulasta. DSN ranged from 0 to 3 days (LA-EP006) and from 0 to 4 days (EU-Neulasta), respectively. The difference in mean DSN was -0.07 days and the corresponding 90% confidence interval was (-0.24, 0.10) which lies within the ±1 day equivalence margin.

Table 8 : Primary analysis for duration of severe neutropenia (DSN) in Cycle 1 – FAS, Study LA-EP06-301

	LA-EP2006 (N=159)	**EU-Neulasta (N=157)**
N	155	155
Mean (SD)	0.75 (0.88)	0.83 (0.90)
Median	1.0	1.0
Range	(0.0, 3.0)	(0.0, 4.0)
Difference in mean (90% CI)	-0.07 (-0.24, 0.10)	
DSN Categorical, n (%)		
0	77 (49.7)	68 (43.9)
1-2	72 (46.4)	79 (51.0)
≥ 3	6 (3.9)	8 (5.2)

- SD: standard deviation; CI: confidence interval;

[Source: CSR for study LA-EP06-301 Tables 11-7 and 11-8 on pages 74 and 85, and statistical reviewer's analysis]

Reviewer's note:

- Six patients (LA-EP2006: 4 patients; EU-Neulasta: 2 patients) were not included in efficacy analysis due to blind date review meeting (BDRM) decision because no ANC profiles available.
- At the clinical site inspection for Study LA-EP06-301, Site 404 (Romania) was determined to have data integrity issues. We checked that efficacy results such as mean of DSN and difference in mean DSN between two treatment arms, excluding the 10 patients (5 in each treatment arm) enrolled at this site, were similar to those based on FAS.

The primary analysis of primary endpoint duration of severe neutropenia (DSN) for Study LA-EP06-302 is summarized in Table 9. Mean DSN in Cycle 1 was 1.36 days in patients treated with LA-EP2006 and 1.19 days in patients treated with EU-Neulasta. DSN ranged from 0 to 6 days (LA-EP006) and from 0 to 4 days (EU-Neulasta), respectively. The difference in mean DSN was 0.16 days and the corresponding 90% confidence interval was (-0.04, 0.37) which lies within the ±1 day equivalence margin.

Table 9 : Primary analysis for duration of severe neutropenia (DSN) in Cycle 1 – FAS, Study LA-EP06-302

	LA-EP2006 (N=155)	**EU-Neulasta (N=153)**
N	151	149
Mean (SD)	1.36 (1.13)	1.19 (0.98)
Median	1.0	1.0
Range	(0.0, 6.0)	(0.0, 4.0)
Difference in mean (90% CI)	0.16 (-0.04, 0.37)	
DSN Categorical, n (%)		
0	42 (27.8)	40 (26.9)
1-2	89 (58.9)	95 (63.8)
≥ 3	20 (13.2)	14 (9.4)

- SD: standard deviation; CI: confidence interval;

[Source: CSR for study LA-EP06-302 Tables 11-7 and 11-8 on pages 81 and 83, and statistical reviewer's analysis]

Reviewer's comment:

- Eight patients (4 from each treatment arm) were not included in efficacy analysis due to blind date review meeting (BDRM) decision because no ANC profiles available.
- Both studies LA-EP06-301 and LA-EP06-302 support that LA-EP2006 is similar to EU-Neulasta in terms of efficacy.
- We believe that the equivalence margin of 1 day is appropriate. Please refer to clinical review in STN125031, dated Jan 31, 2002, for the basis for use of DSN as a surrogate for FN and the non-inferiority margin of 1 day in DSN was used.

  "A 1-day difference in DSN would be anticipated to result in approximately a 10% difference in febrile neutropenia. This was felt to be a meaningful and practical difference to exclude when comparing Pegfilgrastim and Filgrastim."

3.2.4.2 Secondary Endpoints

Descriptive statistics were summarized for secondary endpoints. In both studies, there were no marked differences between two treatment arms in the analysis results for secondary endpoints.

Incidence of Febrile Neutropenia

In Study LA-EP06-301, 21 (6.6%) patients (LA-EP2006: 5.7%; EU-Neulasta: 7.6%) experienced at least one episode of febrile neutropenia across all cycles.

In Study LA-EP06-302, 36 (11.7%) patients (LA-EP2006: 10.3%; EU-Neulasta: 13.1%) experienced at least one episode of febrile neutropenia across all cycles.

Fever Episode

In Study LA-EP06-301, 52 (16.5%) patients (LA-EP2006: 16.4%; EU-Neulasta: 16.6%) experienced at least one episode of fever across all cycles.

In Study LA-EP06-302, 67 (21.8%) patients (LA-EP2006: 20.6%; EU-Neulasta: 22.9%) experienced at least one episode of fever across all cycles.

Depth and Time of Absolute Neutrophil Count (ANC) Nadir in Cycle 1

In Study LA-EP06-301, the mean (SD) depth of ANC nadir in cycle 1 was 1.12 (1.55) for patients in LA-EP2006 arm and 0.94 (1.19) for patients in EU-Neulasta arm.

In Study LA-EP06-302, the mean (SD) depth of ANC nadir in cycle 1 was 0.49 (0.72) for patients in LA-EP2006 arm and 0.44 (0.57) for patients in EU-Neulasta arm.

The daily mean ANC in Cycle 1 for Studies LA-EP06-301 and LA-EP06-302 are plotted in Figure 1 and 2 respectively.

Figure 1: Daily Mean ANC in Cycle 1 – FAS population, Study LA-EP06-301

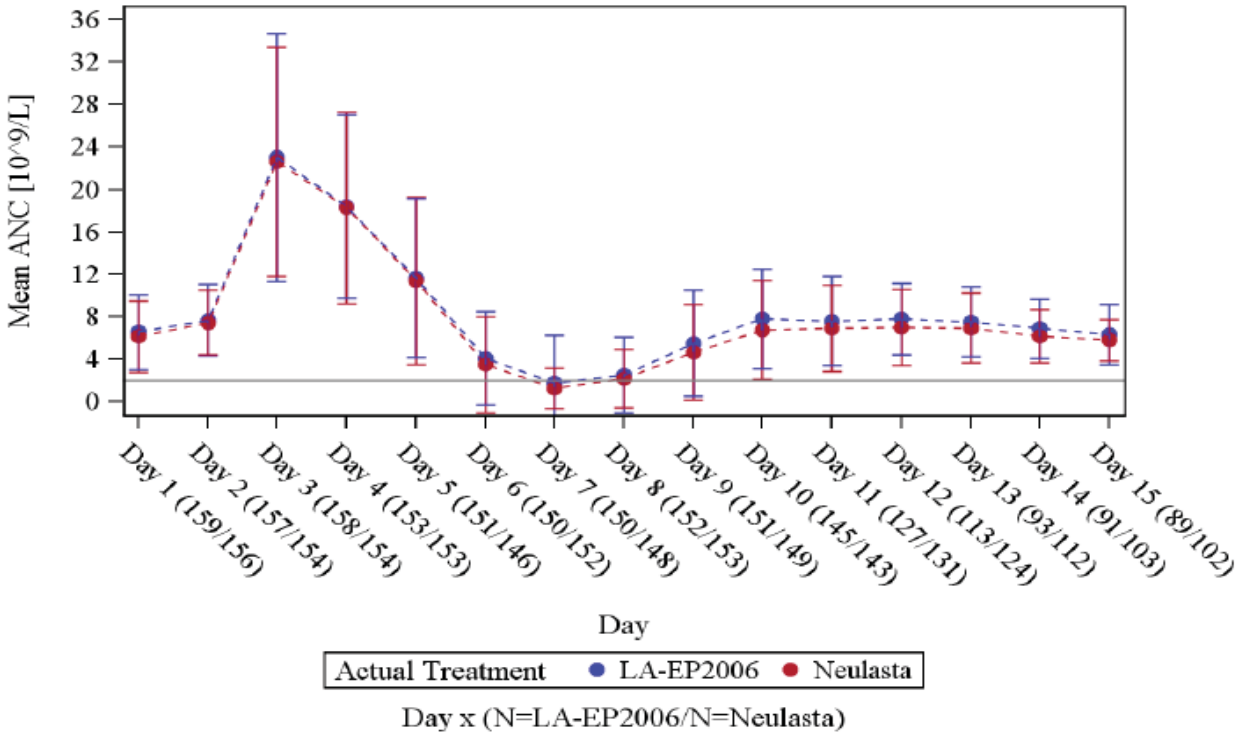
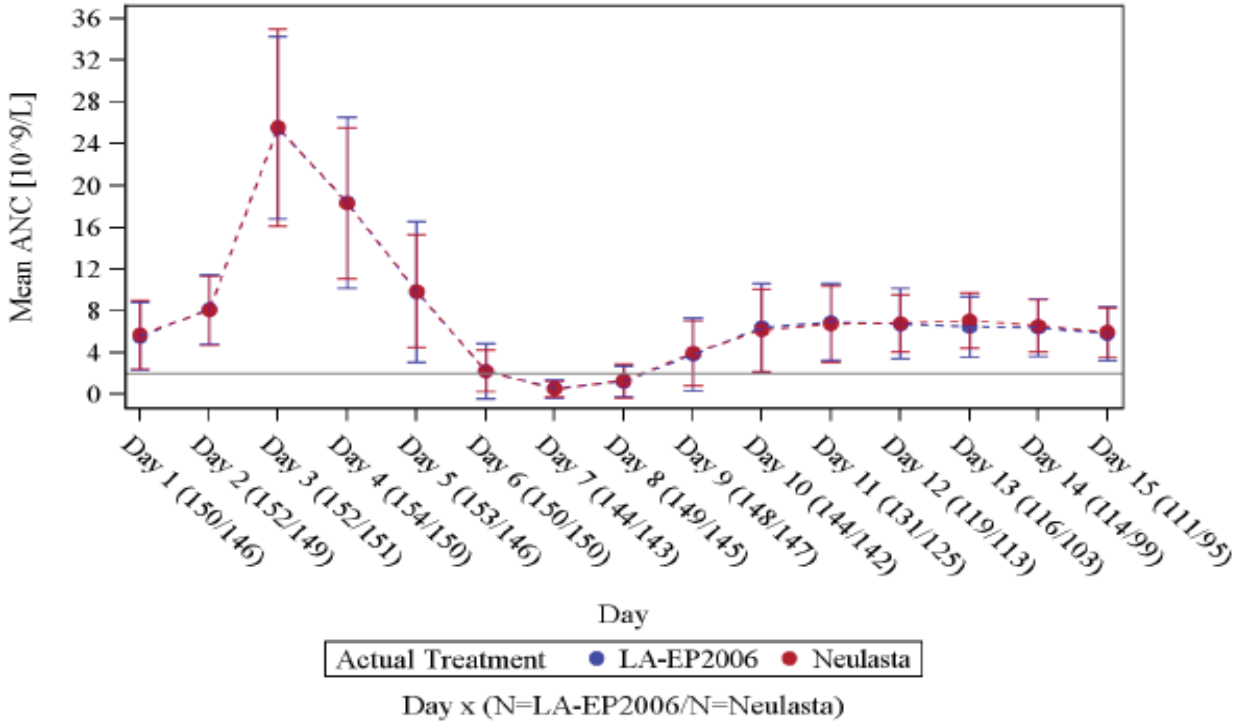


Figure 2: Daily Mean ANC in Cycle 1 – FAS population, Study LA-EP06-302



Time to Recovery of ANC Nadir

In Study LA-EP06-301, the mean (SD) time to recovery from ANC nadir were 1.58 (1.05) days and 1.72 (1.10) days, for EP2006 and EU-Neulasta, respectively.

In Study LA-EP06-302, the mean (SD) time to recovery from ANC nadir were 2.11 (0.89) days and 2.04 (0.95) days, for EP2006 and EU-Neulasta, respectively.

Frequency of infection

In Study LA-EP06-301, 46 (14.6%) patients (LA-EP2006: 13.8%; EU-Neulasta: 15.3%) experienced at least one episode of infection across all cycles.

In Study LA-EP06-302, 58 (18.8%) patients (LA-EP2006: 16.8%; EU-Neulasta: 20.9%) experienced at least one episode of fever across all cycles.

Mortality Due to Infection

In Study LA-EP06-301, 2 patients in EU-Neulasta arm died due to infection. In Study LA-EP06-302, no patient died due to an infection.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Race, Age, Geographic Region, and Type of Chemotherapy

Table 10 and 11 summarize the subgroup analyses of primary endpoint of mean DSN by age, race, region, and type of chemotherapy for Study LA-EP06-301 and Study LA-EP06-302 respectively.

Table 10: Subgroup Analyses of mean DSN: Age, Race, Region, and Type of Chemotherapy (90% CI) – FAS, Study LA-EP06-301

	LA-EP2006 (N=155)		EU-Neulasta (N=155)		
	N	**Mean (SD)**	**N**	**Mean (SD)**	**Difference (90% CI)**
Age					
< 65	145	0.75 (0.86)	140	0.78 (0.83)	-0.03 (-0.20, 0.13)
≥ 65	10	0.90 (1.10)	15	1.27 (1.33)	-0.37 (-1.20, 0.47)
Race					
White	127	0.65 (0.84)	125	0.72 (0.87)	-0.07 (-0.24, 0.11)
Asian	27	1.22 (0.93)	26	1.19 (0.90)	0.03 (-0.39, 0.45)
Other	1	1.0	4	1.75 (0.96)	-0.75
Region					
Europe	122	0.61 (0.81)	121	0.72 (0.87)	-0.10 (-0.28, 0.07)
Asia	27	1.22 (0.93)	25	1.24 (0.88)	-0.02 (-0.44, 0.40)
America	6	1.50 (1.05)	9	1.11 (1.05)	0.39 (-0.59, 1.37)
Type of chemotherapy					
Neo-adjuvant	59	0.69 (0.79)	59	0.81 (0.96)	-0.12 (-0.39, 0.15)
Adjuvant	96	0.79 (0.93)	96	0.83 (0.87)	-0.04 (-0.26, 0.17)

[Source: statistical reviewer's analysis]

Table 11: Subgroup Analyses of mean DSN: Age, Race, Region, and Type of Chemotherapy (90% CI) – FAS, Study LA-EP06-302

	LA-EP2006 (N=151)		EU-Neulasta (N=149)		
	N	**Mean (SD)**	**N**	**Mean (SD)**	**Difference (90% CI)**
Age					
< 65	140	1.36 (1.09)	140	1.17 (0.98)	0.19 (-0.02, 0.39)
≥ 65	11	1.36 (1.69)	9	1.56 (1.01)	-0.19 (-1.31, 0.92)
Race					
White	88	1.27 (1.19)	89	1.06 (0.87)	0.22 (-0.04, 0.48)
Asian	60	1.42 (1.00)	58	1.41 (1.12)	0.003 (-0.32, 0.33)
Other	3	2.67 (1.53)	2	1.00 (0)	1.67 (-1.01, 4.35)
Region					
USA	12	2.25 (1.29)	10	0.80 (0.79)	1.45 (0.64, 2.26)
Asia	60	1.42 (1.00)	58	1.41 (1.12)	0.003 (-0.32, 0.33)
Rest of World	79	1.18 (1.15)	81	1.09 (0.87)	0.09 (-0.18, 0.36)
Type of chemotherapy					
Neo-adjuvant	47	1.15 (1.08)	49	1.24 (1.09)	-0.10 (-0.46, 0.27)
Adjuvant	104	1.45 (1.15)	100	1.17 (0.93)	0.28 (0.04, 0.52)

[Source: statistical reviewer's analysis]

Reviewer's note:

- All patients are female. Therefore, no subgroup analysis by gender can be performed.
- For both studies, the differences in mean DSN between the two groups and the 90% CI lie within the equivalence margin of ±1 day except for few subgroups with small sample sizes.

5 SUMMARY AND CONCLUSIONS

The analyses of the primary endpoint (DSN) as well as secondary endpoints of both studies LA-EP06-301 and LA-EP06-302 support that there was no clinically meaningful difference with respect to efficacy between LA-EP2006 and EU-licensed Neulasta.

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/s/

YUN WANG
05/27/2016

LEI NIE
05/27/2016

THOMAS E GWISE
06/01/2016

RAJESHWARI SRIDHARA
06/01/2016

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

APPLICATION NUMBER	BLA 761045
REFERENCE PRODUCT	Neulasta® (pegfilgrastim)
ESTABLISHED NAME	pegfilgrastim
STRENGTH	6 mg/0.6mL
DOSAGE FORM	single-use prefilled syringe
Route of Administration	subcutaneous injection
PROPOSED INDICATIONS	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
APPLICANT	Sandoz, Inc.
REVIEW FINISHED	May 25, 2016
STATISTICAL REVIEWER	Xiaoyu (Cassie) Dong, Ph.D.

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Reviewer: Xiaoyu Dong, Ph.D., Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____

Meiyu Shen, Ph.D., Team Leader, CDER/OTS/OB/DB VI
Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI

Distribution: BLA 761045

CDER/OTS/OB/DB VI/ Yi Tsong
CDER/OTS/OB/DB VI/ Meiyu Shen
CDER/OTS/OB/ Lillian Patrician
CDER/TBBS

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I. EXECUTIVE SUMMARY

This review provides statistical evaluation on the two Tier 1 quality attributes, Potency (%) and Content (mg/mL), to support a demonstration of analytical similarity between the proposed biosimilar LA-EP2006 and US-licensed Neulasta. The summarized conclusions based on the reviewer's independent analysis are provided below.

- For both Potency(%) and Content (mg/mL), the results of statistical equivalence test support the demonstration that LA-EP2006 is highly similar to US-licensed Neulasta because statistical equivalence in means is established between the proposed biosimilar LA-EP2006 and US-licensed Neulasta.
- In addition, the results of statistical equivalence test also support an analytical bridge between US-licensed and EU-approved Neulasta because the three-way comparison passes the statistical equivalence test.

The obtained confidence interval and corresponding equivalence margin ($\pm 1.5\sigma_{ref}$) for each comparison in Tier 1 are provided in Table A. Please see Section III for detailed analyses.

Table A – Summarized Results of Statistical Equivalence Testing for Potency (%) on the Log-Scale and Content mg/mL) based on the Reviewer's Analyses

Potency(%)	# of Lots	Mean Difference	90% Confidence Interval	Equivalence Margin	Statistical Equivalence? [a]
LA-EP2006 vs. US	9 vs. 12	0.0130	(-0.0205, 0.0465)	(-0.0581, 0.0581)	Yes
LA-EP2006 vs. EU	9 vs. 15	0.0265	(-0.0122, 0.0652)	(-0.0911, 0.0911)	Yes
EU vs. US	15 vs. 12	-0.0135	(-0.0464, 0.0195)	(-0.0581, 0.0581)	Yes
Content (%)	# of Lots	Mean Difference	90% Confidence Interval	Equivalence Margin	Statistical Equivalence? [a]
LA-EP2006 vs. US	8 vs.10	0.0025	(-0.0897, 0.0947)	(-0.1761, 0.1761)	Yes
LA-EP2006 vs. EU	8 vs.17	-0.0140	(-0.1087, 0.0808)[b]	(-0.2090, 0.2090)	Yes
EU vs. US	17 vs.10	0.0165	(-0.0722, 0.1051)[b]	(-0.1761, 0.1761)	Yes

[a] Statistical equivalence in mean values is established if the obtained confidence interval of the mean difference is completely covered by the equivalence margin.

[b] the 90% confidence interval is computed using the sample size imbalance adjustment

II. INTRODUCTION

On August 27 2015, the applicant Sandoz submitted their Biologics License Application (BLA) 761045 under Section 351 (k) of the PHS Act. In this BLA, Sandoz is seeking approval of LA-EP2006 as a proposed biosimilar to US-licensed Neulasta.

LA-EP2006 is provided in pre-filled syringes (0.6 mL) with pegfilgrastim (an N-terminally pegylated form of G-CSF) as the active ingredient. In each syringe, pegfilgrastim has a nominal concentration at 6 mg / 0.6 mL.

To demonstrate the analytical similarity between LA-EP2006 and US-licensed Neulasta, Sandoz performed a risk-based tiered approach which is recommended by the Agency. Specifically, Potency and Content are the two quality attributes assigned to Tier 1 because they directly link to product efficiency. To assess their similarity between LA-EP2006 and US-licensed Neulasta, Sandoz applied the statistical equivalence test. In addition, because EU-approved Neulasta served as the sole comparator in the comparative clinical studies LA-EP06-301 and LA-EP06-302, Sandoz also performed a three-way comparison to establish the scientific bridge between US-licensed and EU-approved Neulasta.

Regarding the data used in Tier 1 equivalence test, Sandoz intended to use the batch release data for LA-EP2006 although Sandoz submitted other stability data in the original package. This data selection plan was pre-specified in 3.2.R Statistical similarity evaluation of BLA 761045 as "*in case of LA-EP2006, release data for the DP were used for evaluations. For Neulasta US and Neulasta EU batches, the first result generated after purchase was used*". The Agency identified this issue in the Information Request Letter dated January 11, 2016. Per the Agency's request, Sandoz provided corrected data of LA-EP2006 (release data) with individual replicates on January 22, 2016. The Tier 1 evaluation performed by the reviewer is based on this updated data set. A few expired batches of US-licensed and EU-approved Neulasta were excluded from Tier 1 analysis.

The following section provides a detailed evaluation of analytical similarity for Potency and Content among LA-EP2006, US-licensed and EU-approved Neulasta. In addition, statistical issues in Sandoz's analyses are also discussed.

III. EVALUATION OF ANALYTICAL SIMILARITY

III.1 OVERVIEW OF EQUIVALENCE TEST

To evaluate analytical similarity, the Agency recommends a tiered approach. That is, product quality attributes amendable to statistical evaluation 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 test in Tier 1 for Potency and Content. In Tier 1, we evaluate the analytical similarity by statistical equivalence test in terms of the mean difference using the following hypotheses:

$$H_0: \mu_B - \mu_R \leq \text{-EAC or } \mu_B - \mu_R \geq \text{EAC}$$

versus

$$H_a: \text{- EAC} < \mu_B - \mu_R < \text{EAC}$$

where μ_B and μ_R are the mean responses of the proposed biosimilar (LA-EP2006) and reference (US-licensed Neulasta) or the comparator (EU-approved Neulasta), respectively. Statistical equivalence is established if the (1-2α)100% two-sided confidence interval (CI) of the mean differenc is completely within (-EAC, EAC), where EAC equals to $1.5\sigma_{ref}$. σ_{ref} here is the variability of US-licensed reference product or the comparator depending on the specific comparison being conducted. The confidence interval can be obtained using formula (1).

$$\text{Confidence Interval} = \text{Mean Diff.} \pm t_{1-\alpha,\ v} \times \sqrt{\frac{S_B^2}{N_B} + \frac{S_R^2}{N_R}} \qquad (1)$$

where $t_{v,df}$ is the (1-α)100% percentile of the *t*-distribution with degrees of freedom *v* approximated by Satterthwaite Approximation. n_B and n_R are respectively the number of the proposed biosimilar lots and the number of the reference product lots; S_B^2 and S_R^2 are respectively the sample variance estimated by all the biosimilar lots and the sample variance estimated by all the reference lots. Please note, here we do not assume equal variances to construct the test statistics or the confidence interval. With the normality assumption, the decision rule of using the confidence interval is consistent with that of using test statistics.

The EAC of $1.5\sigma_{ref}$ gives us at least 85% power of passing equivalence test if we have at least 10 biomilar lots and 10 reference lots when the mean different is 0.125 σ_{ref}. In practice, σ_R in the proposed margin is usually unknown and must be estimated from the reference product lots available to the biosimilar sponsor. With a limited number of lots, all reference product lots can be used to compute the confidence interval and to estimate the equivalence margin. In general, we also recommend a similar number of lots for both the proposed biosimilar and the reference products. When the number of reference product lots is much larger than the number of proposed biosimilar lots (e.g., more than 50 % larger, we recommend the following sample size imbalance adjustment to calculate the confidence interval of the mean difference:

$$\left(\bar{X}_B - \bar{X}_R\right) \pm t_{1-\alpha,df*} \times \sqrt{S_B^2 / n_B + S_R^2 / n_R^*} \quad (2)$$

where $n_R^* = \min(1.5 \times n_B, n_R)$, n_B and n_R are respectively the number of the proposed biosimilar lots and the number of the reference product lots; $\bar{X}_B$ and $\bar{X}_R$ are respectively the sample mean of the proposed biosimilar lots and the sample mean of the reference product lots; S_B^2 and S_R^2 are respectively the sample variance estimated by all the biosimilar lots and the sample variance estimated by all the reference lots; $t_{1-\alpha, df*}$ is 1-α quantile of the *t*-distribution with degrees of freedom *df** where *df** can be approximated by the Satterthwaite method. If the number of biosimilar lots, n_B, is 50% more than the number of reference lots, n_R, a similar approach can be applied with n_B* = min (1.5×n_R, n_B) for the confidence interval calculation.

The reviewer applied the equivalence test described above to assess the analytical similarity for Potency and Content among LA-EP2006, US-licensed and EU-approved Neulasta in Section III.3 and III.4, respectively.

III.2 COMMENTS ON THE APPLICANT'S ANALYSIS

The applicant, Sandoz, performed the statistical equivalence test for both Potency and Content. However, the reviewer does not fully agree with the applicant's approach for the following two reasons.

First, the applicant computed the confidence interval of the mean difference assuming the variances among the three products are the same (using the pooled variance). This is a strong assumption and is unlikely to be true in practice. Thus, the reviewer performed independent analysis without the assumption of equal variance (using Satterthwaite Approximation). Please note, when the true variances are equal, the confidence interval results using Satterthwaite Approximation are very close to the results using the pooled variance. But, when the true variances are unequal, the confidence interval results incorrectly using equal variances assumption can be significantly different from the results without using equal variance assumption. Thus, the reviewer applied Satterthwaite Approximation to compute all the confidence intervals for Tier 1 analysis.

Second, the applicant applied a much wider equivalence margin (about 3~4σ_{ref}) compared to the margin of 1.5 σ_{ref} recommended by the Agency. To determine this wider margin, the applicant set an acceptable mean different at $\sigma_{ref,}$ which is much bigger than the mean different of 0.125 σ_{ref} used by the Agency.

With the above considerations, the reviewer conducted independent equivalence test using Satterthwaite Approximate and an equivalence margin of 1.5σ_{ref} for Tier 1 analysis.

III.3 REVIEW'S EQUIVELNECE TEST FOR POTENCY

III.3.1 BIOASSAY MODEL

Potency is selected as a Tier 1 quality attribute because it closely relates to the mechanism of action and directly links to the efficacy of the product. Specifically, "*the biological potency of a G-CSF sample is determined by measuring its ability to stimulate proliferation of NFS-60 cells compared to the LA-EP2006 in-house reference material. The NFS-60 cell line was derived from mouse myelogenous leukemia cells.*" (3.2.S.4.2 Analytical procedure – Bioactivity) As shown in **Table 1**, the in-vitro potency data (proliferative effect on NFS-60 cells) were measured by a 96-well micro-titer plate in which three replicates of two samples (A, B) and the reference standard (R) were tested in each plate (assay). The rows A – H represent a 2-fold dilution series. Relative potency of each sample (A or B) was measured as the potency relative to the reference standard (R). The reportable value of the relative potency of each batch was computed as the average of at least 4 compliant determinations for release and at least 2 compliant determinations for stability testing.

Table 1 – Example of a schematic representation of the black microtiter plate
(Sponsor's Table 2-1 in 3.2.S.4.2 Analytical procedure – Bioactivity)

	1	2	3	4	5	6	7	8	9	10	11	12
A	BL	A,#1	R,#1	B,#1	A,#1	R,#1	B,#1	A,#1	R,#1	B,#1	NEG	POS
B	BL	A,#2	R,#2	B,#2	A,#2	R,#2	B,#2	A,#2	R,#2	B,#2	NEG	POS
C	BL	A,#3	R,#3	B,#3	A,#3	R,#3	B,#3	A,#3	R,#3	B,#3	NEG	POS
D	BL	A,#4	R,#4	B,#4	A,#4	R,#4	B,#4	A,#4	R,#4	B,#4	NEG	POS
E	BL	A,#5	R,#5	B,#5	A,#5	R,#5	B,#5	A,#5	R,#5	B,#5	NEG	POS
F	BL	A,#6	R,#6	B,#6	A,#6	R,#6	B,#6	A,#6	R,#6	B,#6	NEG	POS
G	BL	A,#7	R,#7	B,#7	A,#7	R,#7	B,#7	A,#7	R,#7	B,#7	NEG	POS
H	BL	A,#8	R,#8	B,#8	A,#8	R,#8	B,#8	A,#8	R,#8	B,#8	NEG	POS

BL	blank: no sample, no cells.
R	dilution series of LA-EP2006 in-house reference material
A	dilution series of sample 1
B	dilution series of sample 2
POS	positive control: LA-EP2006 in-house reference material with concentration of 10.0 ng/mL
NEG	negative control: no sample, but cells present

The statistical model to calculate the relative potency is the parallel-line model. In this model, the concentration-response curve for each sample is modeled by the linear regression with log-concentration (dose) as the X-axis as shown in **Figure 1.** When the two lines are parallel with the same slope, relative potency is the horizontal shift on the X-axis from Test to Standard to achieve the same response. By the definition of the slope, we have

$$\begin{aligned} Y_S &= \alpha_S + \beta \log(conc_S) + \varepsilon_S \\ Y_T &= \alpha_T + \beta \log(conc_T) + \varepsilon_T \end{aligned} \tag{3}$$

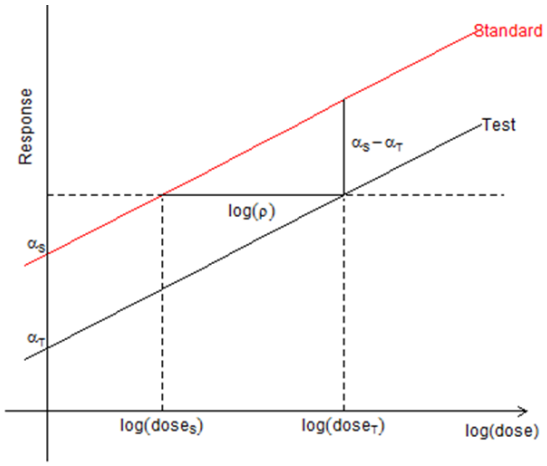

Figure 1 – Parallel Line Model

$$\beta = \frac{\Delta y}{\Delta x} = \frac{\alpha_S - \alpha_T}{\log(\text{conc.}_S) - \log(\text{conc.}_T)} \tag{4}$$

Then,

$$\log(\text{conc.}_S) - \log(\text{conc.}_T) = \log \frac{\text{conc.}_S}{\text{conc.}_T} = \frac{\alpha_S - \alpha_T}{\beta}$$

Thus

$$\text{Relative Potency} = \frac{\text{conc.}_S}{\text{conc.}_T} = \text{antilog}\left(\frac{\alpha_S - \alpha_T}{\beta}\right) \tag{5}$$

Note: $\hat{\alpha} = \bar{Y} - \beta \bar{X}$, then we have $\hat{\alpha}_S - \hat{\alpha}_T = (\bar{Y}_S - \bar{Y}_T) - \beta(\bar{X}_S - \bar{X}_T) = \bar{Y}_S - \bar{Y}_T$ because S and T samples have the same dilution, then the average values of X are the same. As we can see from (4) and (5), the original value of relative potency is expressed on the log-scale. Thus, both the sponsor and reviewer conducted equivalence test for Potency on the log-scale. The reviewer and the sponsor also performed the analysis on the percentage scale as a sensitivity analysis.

III.3.2 POTENCY DATA

The potency data for equivalence test consist of nine LA-EP2006 batches at either the pilot scale or at the commercial scale. The manufacture date of the nine LA-EP2006 batches ranges from 2010 to 2015. Among those batches, two batches were used in the comparative clinical

studies LA-EP06-301 and LA-EP06-302. The batch manufactured in 2015 was provided by Sandoz in their responses to FDA's Day 74 Letter. For more detailed information on the batch record of LA-EP2006, please refer to *3.2.P.5.4 Batch analyses* in BLA 761045 submission. The estimated manufacture year of the 12 batches of US-licensed Neulasta and the 15 batches of EU-approved Neulasta ranges from 2005 to 2013. The release and stability specifications are the same (b) (4) considering there is no indication that potency is a stability-indicating attribute.

The reviewer plotted the average relative potency values for each batch of LA-EP2006, US-licensed Neulasta and EU-approved Neulasta in **Figure 2.** In this figure, the blue squares denote the values from nine LA-EP2006 batches, the empty red squares are the values from 12 batches of US-licensed Neulasta, and the green triangles represent the values from 15 batches of EU-approved Neulasta. As we can see from **Figure 2,** the data largely overlap among the three products. The descriptive statistics, such as minimum, maximum, mean and sample standard deviation, of the three products also appear similar in **Table 2.**

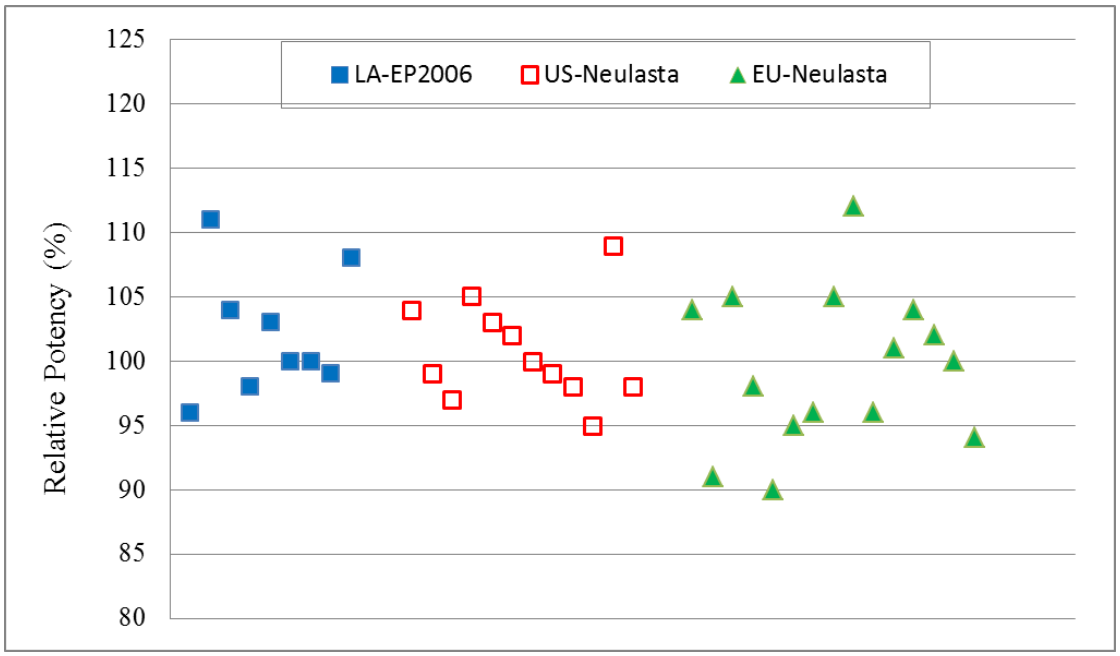

Figure 2 – Reviewer's Plot on Relative Potency (%)

Table 2 - Descriptive Statistics for Relative Potency (%) based on FDA Reviewer's Analyses

	Number of Lots	Min	Max	Mean	Standard Deviation	Data Selection
LA-EP2006	9	96	111	102.11	4.88	Release
US-licensed Neulasta	12	95	109	100.75	3.96	The earliest testing results
EU-approved Neulasta	15	90	112	99.53	6.01	

III.3.3 EQUIVAELNCE TEST OF POTENCY DATA

To formally evaluate the analytical similarity among the three products, the review applied statistical equivalence test for the mean values. This approach has been discussed in the previous section. The summarized results of the equivalence test are presented in **Table 3**. Please note, the reviewer transformed the relative potency data to the natural log scale before applying the equivalence test because the potency is measured by the parallel line model. The batch value was calculated as the geometric mean of independent samples from 1 to 2 micro-titer plates. **Table 3** shows that all the 90% confidence intervals of the mean different are completely covered by the equivalence margin. The equivalence test results are also plotted in **Figure 3.** Thus, statistical equivalence test results support a demonstration of analytical similarity between LA-EP2006 and US-licensed Neulasta.

Table 3 - Reviewer's Statistical Equivalence Test Results on Potency (%) on the Natural Log-scale

Natural Log Scale	Number of Lots	Std. Dev	Mean Diff	Confidence Interval	Equivalence Margin	Stat. Equiv.?
LA-EP2006 vs. US	9 vs. 12	0.0466 vs. 0.0387	0.0130	(-0.0205, 0.0465)	(-0.0581, 0.0581)	Yes
LA-EP2006 vs. EU	9 vs. 15	0.0466 vs. 0.0608	0.0265	(-0.0122, 0.0652)	(-0.0911, 0.0911)	Yes
EU vs. US	15 vs. 12	0.0608 vs. 0.0387	-0.0135	(-0.0464, 0.0195)	(-0.0581, 0.0581)	Yes

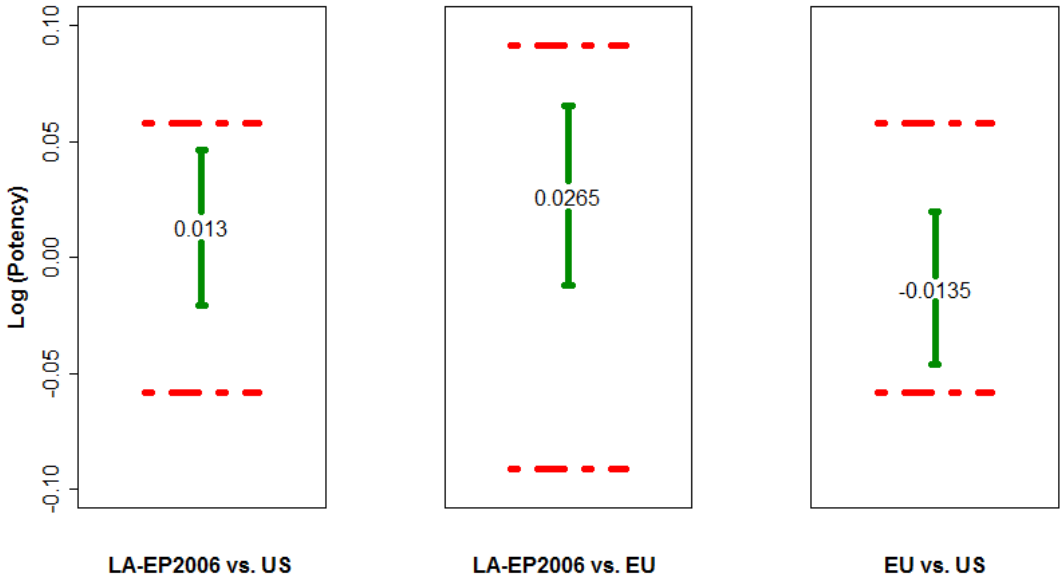

Figure 3 – Reviewer's Plot on the 90% Confidence Intervals of the Mean Difference (green lines) and the Equivalence Margins (red dashed lines) for Potency on the Natural Log Scale for the three-way Comparison

In addition to the analysis on the natural log-scale, the reviewer performed the equivalence test on the 100% scale as a sensitivity analysis. Again, the confidence intervals from **Table 4** are

all covered by the equivalence margin. This result further supports the analytical similarity of Potency.

Table 4 - Reviewer's Statistical Equivalence Test Results on Potency (%) on the 100% scale

100% Scale	Nu**mber of Lots**	**Std. Dev (%)**	**Mean Diff. (%)**	**Confidence Interval**	**Equivalence Margin**	**Stat. Equiv.?**
LA-EP2006 vs. US	9 vs. 12	4.88 vs. 3.96	1.36	(-2.12, 4.85)	(-5.94, 5.94)	Yes
LA-EP2006 vs. EU	9 vs. 15	4.88 vs. 6.01	2.58	(-1.30, 6.46)	(-9.02, 9.02)	Yes
EU vs. US	15 vs. 12	6.01 vs. 3.96	-1.22	(-4.51, 2.08)	(-5.94, 5.94)	Yes

III.4 **EQUIVELNECE TEST FOR CONTENT**

III.4.1 **CONTENT DETERMINATION**

Content is also selected as a Tier 1 quality attribute because it "*directly links to the efficacy of the product*". In this submission, content refers to the protein concentration measured by UV spectroscopy at a wavelength of 279 nm using the same extinction coefficient for all products. The following calculation of the content by UV is provided in "*3.2.S.4.2 Analytical procedure - Assay: Content by UV*" of BLA 761045.

III.4.2 CONTENT DATA

The content data for equivalence test consist of eight LA-EP2006 batches at either the pilot scale or at the commercial scale. , 10 batches of US-licensed Neulasta and 17 batches of EU-approved Neulasta. For more detailed information on the batch record of LA-EP2006, please refer to *3.2.P.5.4 Batch analyses* in BLA 761045 submission. The applicant's proposed release specification for content (spectroscopy) is both [redacted] (b) (4)) and the proposed stability specification for content is [redacted] (b) (4) mg/mL.

The reviewer plotted the average content values for each batch of LA-EP2006, US-licensed Neulasta and EU-approved Neulasta in **Figure 5.** In this figure, the blue squares denote the values from eight LA-EP2006 batches, the red squares are the values from 10 batches of US-licensed Neulasta, and the green triangles represent the values from 17 batches of EU-approved Neulasta. As we can see from **Figure 5,** the data largely overlap among the three products.

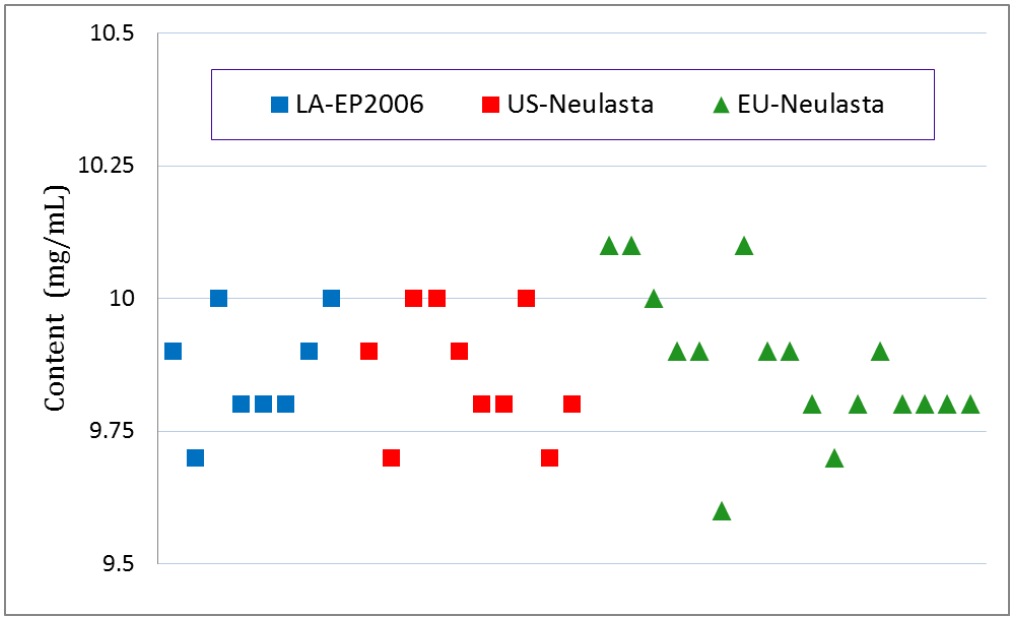

Figure 5 – Reviewer's Plot on Content (mg/mL)

The descriptive statistics, such as minimum, maximum, mean and sample standard deviation, of the three products also appear similar in **Table 5.**

Table 5 - Descriptive Statistics for Content (mg/mL) based on FDA Reviewer's Analyses

	Number of Lots	Min	Max	Mean	Standard Deviation	Data Selection
LA-EP2006	8	9.7	10.0	9.863	0.106	Release
US-licensed Neulasta	10	9.7	10.0	9.860	0.117	The earliest testing results
EU-approved Neulasta	17	9.6	10.1	9.876	0.139	

III.4.3 EQUIVALENCE TEST OF CONTENT

To formally evaluate the analytical similarity for Content among the three products, the reviewer applied statistical equivalence test for the mean values. This approach has been discussed in the previous section. **Table 6** shows that all the 90% confidence intervals of the mean different are completely covered by the equivalence margin. Please note, because the sample size (number of batches) of EU-approved Neulasta is 50% more than that of LA-EP2006 and US-licensed Neulasta, the reviewer applied the sample size imbalance adjustment (2) to the confidence interval calculation in **Table 6**. The equivalence test results are also plotted in **Figure 6.**

Table 6– Reviewer's Statistical Equivalence Test Results on Content (mg/mL) using Sample Size Imbalance Adjustment

	Number of Lots	Std. Dev (mg/mL)	Mean Diff. (mg/mL)	Confidence Interval	Equivalence Margin	Stat. Equiv.?
LA-EP2006 vs. US	8 vs.10	0.1061 vs. 0.1174	0.0025	(-0.0897, 0.0947)	(-0.1761, 0.1761)	Yes
LA-EP2006 vs. EU	8 vs.17	0.1061 vs. 0.1393	-0.0140	(-0.1087, 0.0808)[a]	(-0.2090, 0.2090)	Yes
EU vs. US	17 vs.10	0.1393 vs. 0.1174	0.0165	(-0.0722, 0.1051)[a]	(-0.1761, 0.1761)	Yes

[a] the 90% confidence interval is computed using the sample size imbalance adjustment

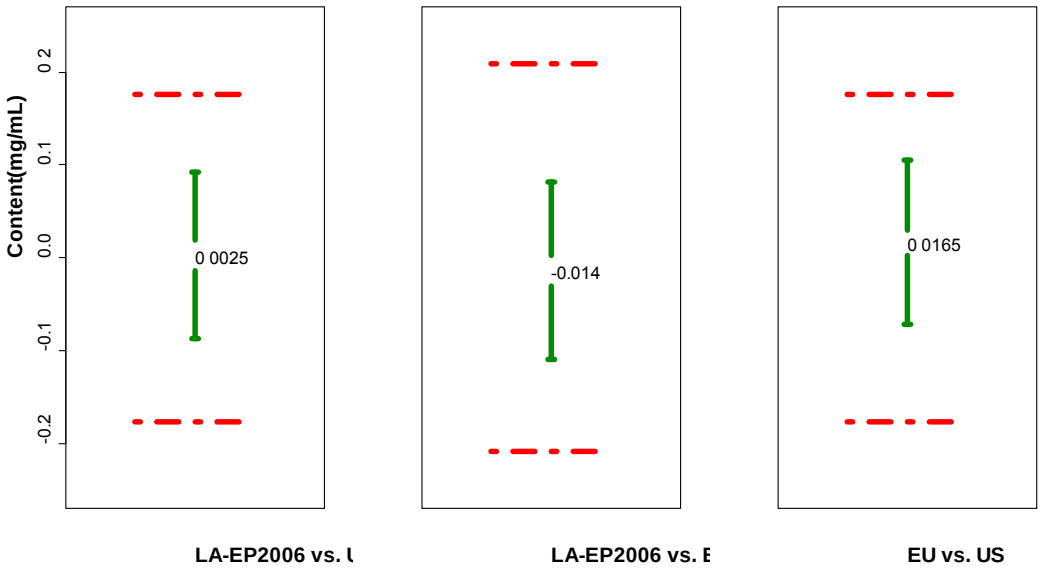

Figure 6 – Reviewer's Plot on the 90% Confidence Intervals of the Mean Difference (green lines) and the Equivalence Margins (red dashed lines) for Content (mg/mL) for the three-way Comparison

In addition, the reviewer also performed the equivalence test using all the sample sizes without imbalance adjustment. As shown in **Table 7**, we can see that the confidence interval using the total sample sizes are also covered by the equivalence margins. Thus, statistical equivalence test results with and without sample size imbalance adjustment all support a demonstration of analytical similarity in Content between LA-EP2006 and US-licensed Neulasta as well as the scientific bridge between US-licensed Neulasta and EU-approved Neulasta.

Table 7– Reviewer's Statistical Equivalence Test Results on Protein Content (mg/mL) using the Total Sample Size

	Number of Lots	Std. Dev (mg/mL)	Mean Diff. (mg/mL)	Confidence Interval	Equivalence Margin	Stat. Equiv.?
LA-EP2006 vs. US	8 vs.10	0.1061 vs. 0.1174	0.0025	(-0.0897, 0.0947)	(-0.1761, 0.1761)	Yes
LA-EP2006 vs. EU	8 vs.17	0.1061 vs. 0.1393	-0.0140	(-0.1015, 0.0736)[b]	(-0.2090, 0.2090)	Yes
EU vs. US	17 vs.10	0.1393 vs. 0.1174	0.0165	(-0.0698, 0.1027)[b]	(-0.1761, 0.1761)	Yes

[b] the 90% confidence interval is computed using the total sample size

IV. CONCLUSIONS

The summarized conclusions based on the reviewer's independent evaluation of the Tier 1 data are provided as follows.

- For both Potency(%) and Content (mg/mL), the results of statistical equivalence test support the demonstration that LA-EP2006 is highly similar to US-licensed Neulasta because statistical equivalence in means is established between the proposed biosimilar LA-EP2006 and US-licensed Neulasta.
- In addition, the results of statistical equivalence test also support an analytical bridge between US-licensed and EU-approved Neulasta because the three-way comparison passes the statistical equivalence test.

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XIAOYU DONG
06/01/2016

MEIYU SHEN
06/01/2016

YI TSONG
06/01/2016