CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.	761075
DATE RECEIVED BY THE CENTER	12/09/2016
DRUG NAME	MYL-1401H Solution for Subcutaneous Injection (a proposed biosimilar to pegfilgrastim)
DOSAGE FORM	Prefilled syringe containing 0.6 mL solution
STRENGTH	6 mg/0.6 mL
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	Mylan GmbH
REVIEW FINISHED	08/31/2017
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1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistical reviewer in the Office of Biostatistics analyzed the comparative results of 2 critical quality attributes: Protein Content as assessed by UV-280 and Relative Potency as assessed by Proliferation Inhibition Bioassay, which were 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 Neulasta) or EU-approved reference product variability (EU-approved Neulasta). Ten MYL-1401H drug product lots, 21 US-licensed Neulasta lots and 27 EU-approved Neulasta lots were used for equivalence testing for Protein Content. The results are summarized in Table 1.

Table 1: Equivalence testing results for the Protein Content

Comparison	# of lots	Mean Difference, mg/mL	90% Confidence Interval for Mean Difference, mg/mL	Equivalence Margin, mg/mL	Pass the Equivalence Testing?
MYL-1401H vs. US	(10, 21)*	0.019	(-0.118, 0.155)	(-0.228, 0.228)	Yes
MYL-1401H vs. EU	(10, 27)*	-0.014	(-0.165, 0.137)	(-0.329, 0.329)	Yes
EU vs. US	(27, 21)	0.032	(-0.058, 0.122)	(-0.228, 0.228)	Yes

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

Ten MYL-1401H drug product lots, 18 US-licensed Neulasta lots and 21 EU-approved Neulasta lots were used for equivalence testing for Relative Potency. The results are summarized in Table 2.

Table 2: Equivalence testing results for the Relative Potency

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
MYL-1401H vs. US	(10, 18)*	-0.002	(-0.049, 0.046)	(-0.076, 0.076)	Yes
MYL-1401H vs. EU	(10, 21)*	0.039	(-0.012, 0.091)	(-0.104, 0.104)	Yes
EU vs. US	(21, 18)	-0.041	(-0.073, -0.009)	(-0.076, 0.076)	Yes

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

As shown in Tables 1 and 2, the results from the statistical equivalence testing of Protein Content as assessed by UV-280 and Relative Potency as assessed by Proliferation Inhibition Bioassay support a demonstration that the proposed biosimilar MYL-1401H is highly similar to US-licensed Neulasta. The results also support the analytical portion of the scientific bridge to justify the relevance of EU-approved Neulasta data from the comparative clinical study.

2 INTRODUCTION

On December 9, 2016, Mylan GmbH. 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 attributes for MYL-1401H, US-licensed Neulasta and EU-approved Neulasta.

Mylan GmbH. used 10 MYL-1401H drug product lots for the Tier 1 analytical similarity assessment. This encompasses lots used in stability studies, lots used in clinical studies and process validation. Multiple MYL-1401H drug substance lots manufactured using the proposed commercial process are included to represent the expected MYL-1401H process variability. For parameters primarily influenced by the drug substance manufacturing process, data from a single drug product lot representing each of the 10 unique MYL-1401H drug substance lots is included in the similarity assessment. The 10 MYL-1401H lots used for analytical similarity are summarized in Table 3. MYL-1401H lots used in the analytical similarity assessment are between 2-29 months of age. The approximate ages at testing months for the 10 MYL-1401H drug product lots used for the analytical similiarity assessement were all within the shelf lives.

Neulasta drug product was sourced from both the US and EU on a regular basis, over a period of approximately 5 years by Mylan GmbH. The Neulasta drug product lots used in the similarity assessment had ages at analysis of approximately 8 to 35 months. A total of 30 US-licensed Neulasta lots and 38 EU-approved Neulasta lots, including all lots used in the clinical trials, were tested as part of the analytical similarity assessment. The US-licensed Neulasta and EU-approved Neulasta lots used in the similarity assessment for Tier 1 quality attributes are provided in Table 4 and Table 5, respectively. Some of the US-licensed Neulasta lots and EU-approved Neulasta lots were not used for the Tier 1 analytical similarity assessment and the sponsor justified that “the analytical data generated for US-licensed Neulasta and EU-approved Neulasta lots for a given technique is based on availability of developed and qualified methods for analysis” and “the number of lots chosen for analysis in each individual assay/test was based on the criticality

of attribute, availability of an orthogonal technique, assessment of analytical method variability, complexity and suitability of method for large number of lots (e.g.: AUC) and availability of the material at the time of analysis." In the end, 10 MYL-1401H drug product lots, 21 US-licensed Neulasta lots, 27 EU-approved Neulasta lots were used for equivalence testing for Protein Content; and 10 MYL-1401H drug product lots, 18 US-licensed Neulasta lots, 21 EU-approved Neulasta lots were used for equivalence testing for Relative Potency. It is also noted that 2 reference standards (Neulasta US (b) (4) and (b) (4)) were used during the assay of relative potency data for both US-licensed Neulasta and EU-approved Neulasta. FDA CMC reviewer sent out two information requests to Mylan GmbH. on April 19, 2017 and May 10, 2017. FDA requested Mylan GmbH. to compare the relative potency values of the 2 different reference standards and submit data to support the qualification of the reference standards or describe how the data support the bridge. The response from Mylan GmbH. was received on May 11, 2017 and FDA CMC reviwer, Dr. James Kirwan, reviewed data in response to the information request (refer to section 3.2.R for the Analytical Similarity Assessment for information on the comparability of the two reference standards used in the relative potency assay). On August 29, 2017, Dr. James Kirwan concluded that the two reference standards used in the relative potency assay for analytical similarity are comparable.Therefore, in this statistical review report, the potency data is evaluated for statistical equivalence based on individual results obtained using both reference standards.

The Agency carefully evaluated the data for Protein Content and Relative Potency provided in the BLA submission. Our comments regarding Mylan GmbH.'s equivalence testing (Tier 1 approach) is provided in Section 3, and our independent statistical equivalence testing analyses are presented in Section 4.

Table 3: MYL-1401H Drug Product lots used to demonstrate analytical similarity for Tier 1 attributes.

MYL-1401H Drug Product Lot Number	MYL-1401H Drug Substance Lot Number	Date of DS Manufacture	Intended Use
BS14003387	DE-B13-03-000119	Oct 2013	Representative commercial process/ Used for stability studies
BS14005356	DE-B13-03-000372	Jun 2014	Representative commercial process /Phase I clinical trial batch/ Used for stability studies
BS14006052	DE-B14-03-000018	Jul 2014	Representative commercial process/ Used for stability studies
BS14009031	BS14006268	Oct 2014	Representative commercial process/Phase III clinical trial batch/ Used for stability studies
BS 15006245	BS15000682	Dec 2015	Representative commercial process with device / Used for device functional stability studies
BS 15006419	BS15002629	Dec 2015	Representative commercial process with device/Used for device functional stability studies
BS15006420	BS15003287	Dec 2015	Representative commercial process
BS 15007576	BS15004282	Feb 2016	Process validation batch 1/ Used for stability studies
BS15007637	BS15004621	Feb 2016	Process validation batch 2/ Used for stability studies
BS15007635	BS15004783	Feb 2016	Process validation batch 3/ Used for stability studies

Table 4: 30 US-licensed Neulasta Drug Product Lots Information.

Drug Product Lot Number	Expiry date	Protein Content		Relative Potency	
		Used in the Equivalence Test?	Age at analysis (Months)	Used in the Equivalence Test?	Age at analysis (Months)
1026652	Oct/13				
1026653	Oct/13	Yes	14		
1027201	Oct/13				
1028639	Mar/14				
1030206	May/14				
1030012	Apr/14				
1033257	Jun/15				
1037672	Jan/16	Yes	28		
1038206	Feb/16	Yes	27	Yes	26
1039585	Mar/16	Yes	26		
1039586	Apr/16	Yes	25	Yes	23
1044948	Aug/16	Yes	21	Yes	15
1050016	May/17	Yes	12	Yes	10
1051676	Feb/17	Yes	15	Yes	21
1051304	May/17	Yes	12	Yes	11
1048833	May/17	Yes	18	Yes	18
1057095	Sep/17	Yes	14	Yes	14
1055572	Oct/17	Yes	13	Yes	13
1057096	Nov/17	Yes	13		12
1057133	Oct/17	Yes	14	Yes	14
1056762	Oct/17	Yes	15	Yes	14
1056717	Nov/17	Yes	14	Yes	13
1057373	Jan/18	Yes	12	Yes	11
1057097	Feb/18	Yes	11	Yes	10
1057416	Mar/18	Yes	10	Yes	10
1059900	Apr/18	Yes	9	Yes	9
1059221	May/18	Yes	8	Yes	8
1060056	May/18				
1060057	May/18				
1060058	Jun/18				

Table 5: 38 EU-approved Neulasta Drug Product Lots Information.

Drug Product Lot Number	Expiry date	Protein Content		Relative Potency	
		Used in the Equivalence Test?	Age at analysis (Months)	Used in the Equivalence Test?	Age at analysis (Months)
1022627	Nov/12				
1022425	Jul/12				
1024809	Feb/13				
1023515	Jul/12	Yes	30		
1028409A	Aug/13				
1031110D	Feb/14	Yes	25		
1029962B	Nov/13				
1031742A	Apr/14				
1032243A	Nov/14				
1032339C	May/14				
1031742B	Apr/14				
1036447	Feb/15				
1037627	Jul/15	Yes	35		
1038755B	Jun/15	Yes	35		
1042478E	Jan/16	Yes	28		
1043190	Jan/16	Yes	28	Yes	33
1040664	Nov/15	Yes	30	Yes	35
1044113A	Mar/16	Yes	26	Yes	24
1047632A	Nov/16	Yes	18		
1051893B	Feb/17	Yes	15	Yes	14
1048603D	Jan/17	Yes	21	Yes	21
1053573B	Jun/17	Yes	16	Yes	16
1056938C	Aug/17	Yes	14	Yes	14
1056653B	Aug/17	Yes	18	Yes	14
1058436B	Aug/17	Yes	14	Yes	14
1056658B	Aug/17	Yes	15	Yes	13
1049398B	Jan/17	Yes	21	Yes	23
1054892B	Jan/17	Yes	16	Yes	16
1054893A	Jul/17	Yes	17	Yes	14
1056942B	Jul/17	Yes	19	Yes	18
1057625A	Oct/17	Yes	15	Yes	14
1057625B	Oct/17	Yes	15	Yes	14
1056940D	Aug/17	Yes	18	Yes	17
1059952B	Aug/17	Yes	18	Yes	17
1060059A	Oct/17	Yes	15	Yes	14
1061815C	Nov/17	Yes	14	Yes	14
1063282B	Nov/17	Yes	14	Yes	14
1057623A	Aug/17				

3 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Mylan GmbH. conducted Tier 1 statistical equivalence testing with the margin defined as $(-1.5\hat{\sigma}_R, +1.5\hat{\sigma}_R)$ for Protein Content and Relative Potency. Pairwise comparisions were used for the assessment of the Tier 1 quality attributes. Similarity is demonstrated if all the two-sided 90% confidence intervals of the difference between means for MYL-1401H vs. US-licensed Neulasta, MYL-1401H vs. EU-approved Neulasta, and EU-approved Neulasta vs. US-licensed Neulasta are within the EAC of $(-1.5\hat{\sigma}_R, +1.5\hat{\sigma}_R)$, where R represents the product variability of US-licensed Neulasta or the product variability of EU-approved Neulasta in each of the 3 pairwise comparisions. Mylan GmbH. presumed unequal variances for the two-sided 90% confidence interval. FDA CMC statistics reviewer's conclusion on Mylan GmbH.'s equivalence testing is: Mylan GmbH.'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 Neulasta product. Let σ_R be the standard deviation of the quality attribute of interest for the US-licensed Neulasta. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-

licensed Neulasta 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 Neulasta 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 Neulasta 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 Neulasta 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 Neulasta 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 Neulasta 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 Neulasta product, the $(1-2\alpha)\times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

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

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:

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

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

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 Protein Content

The Protein Content data distributions of MYL-1401H, US-licensed Neulasta and EU-approved Neulasta are displayed in Figure 1. Ten lots of MYL-1401H, 21 lots of US-licensed Neulasta, and 27 lots of EU-approved Neulasta are included in the Protein Content dataset for statistical equivalence testing. Descriptive statistics for the Protein Content data of MYL-1401H, US licensed Neulasta, and EU-approved Neulasta are listed in Table 6.

Figure 1: Scatter plots of Protein Content for US-licensed Neulasta, MYL-1401H, and EU-approved Neulasta.

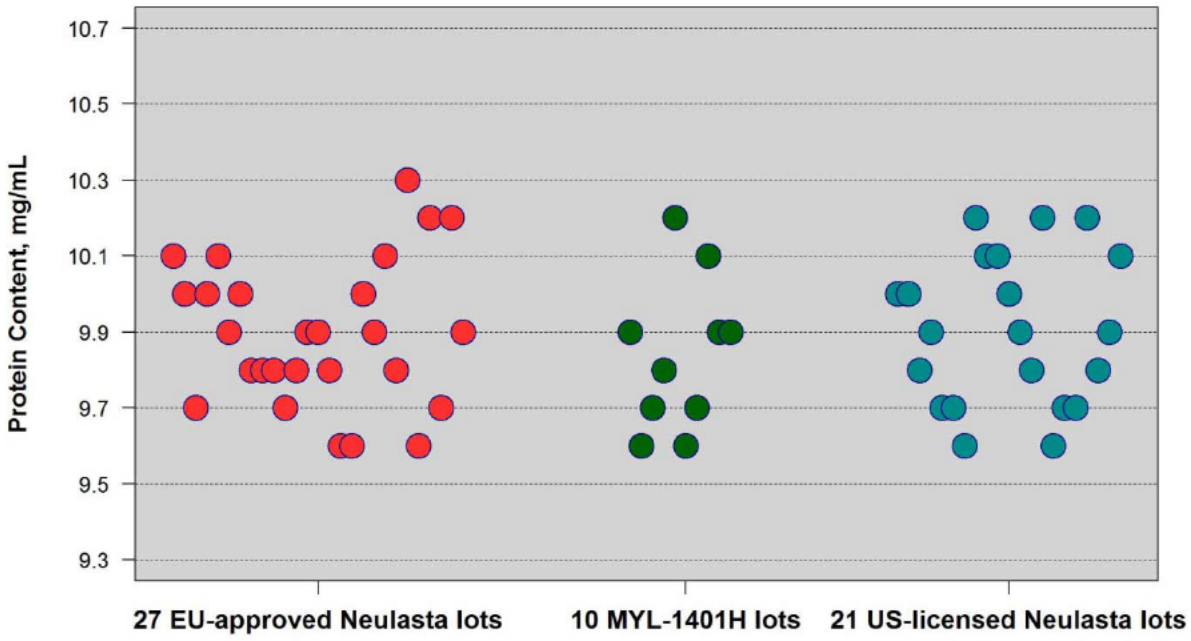

Table 6: Descriptive statistics for the Protein Content data

Product	Number of lots	Sample mean, mg/mL	Sample standard deviation, mg/mL	Min, mg/mL	Max, mg/mL
MYL-1041H	10	9.89	0.213	9.6	10.2
US-licensed Neulasta	21	9.87	0.152	9.6	10.1
EU-approved Neulasta	27	9.90	0.219	9.6	10.3

Table 7 shows that the 90% confidence interval for the mean difference in the Protein Content between MYL-1401H and US-licensed Neulasta is (-0.118, 0.155)mg/mL. It falls entirely within the equivalence margin (-0.228, +0.228)mg/mL. Hence, the results of the Protein Content for MYL-1401H are equivalent to those for US-licensed Neulasta.

It also shows that the 90% confidence interval for the mean difference in Protein Content between MYL-1401H and EU-approved Neulasta is (-0.165, 0.137)mg/mL. It falls within the equivalence margin (-0.329, +0.329)mg/mL. Therefore, the results of the Protein Content for MYL-1401H are equivalent to those for EU-approved Neulasta.

The 90% confidence interval for the mean difference in Protein Content between EU-approved Neulasta and US-licensed Neulasta is (-0.058, 0.122)mg/mL, which falls entirely within the equivalence margin (-0.228, +0.228)mg/mL. Therefore, the results of the Protein Content for EU-approved Neulasta are equivalent to those for US-licensed Neulasta.

The statistical equivalence analyses support that Protein Content as measured by the UV-280 of MYL-1401H is similar to that of US-licensed Neulasta. The results of all three pairwise comparisons support the analytical portion of the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Neulasta and the MYL-1401H product to support a demonstration of biosimilarity to US-licensed Neulasta.

Table 7: Results of equivalence testing for Protein Content

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
MYL-1401H vs. US	(10, 21)*	0.019	(-0.118, 0.155)	(-0.228, 0.228)	Yes
MYL-1401H vs. EU	(10, 27)*	-0.014	(-0.165, 0.137)	(-0.329, 0.329)	Yes
EU vs. US	(27, 21)	0.032	(-0.058, 0.122)	(-0.228, 0.228)	Yes

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

4.3 FDA statistical equivalence testing for Relative Potency

Scatter plots of the Relative Potency for MYL-1401H, US-licensed Neulasta and EU-approved Neulasta are shown in Figure 2. Ten lots of MYL-1401H, 18 lots of US-licensed Neulasta, and 21 lots of EU-approved Neulasta are included in the Relative Potency dataset for statistical equivalence testing. Descriptive statistics for the Relative Potency data of MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta are listed in Table 8.

Figure 2: Scatter plots of Relative Potency for US-licensed Neulasta, MYL-1401H, and EU-approved Neulasta

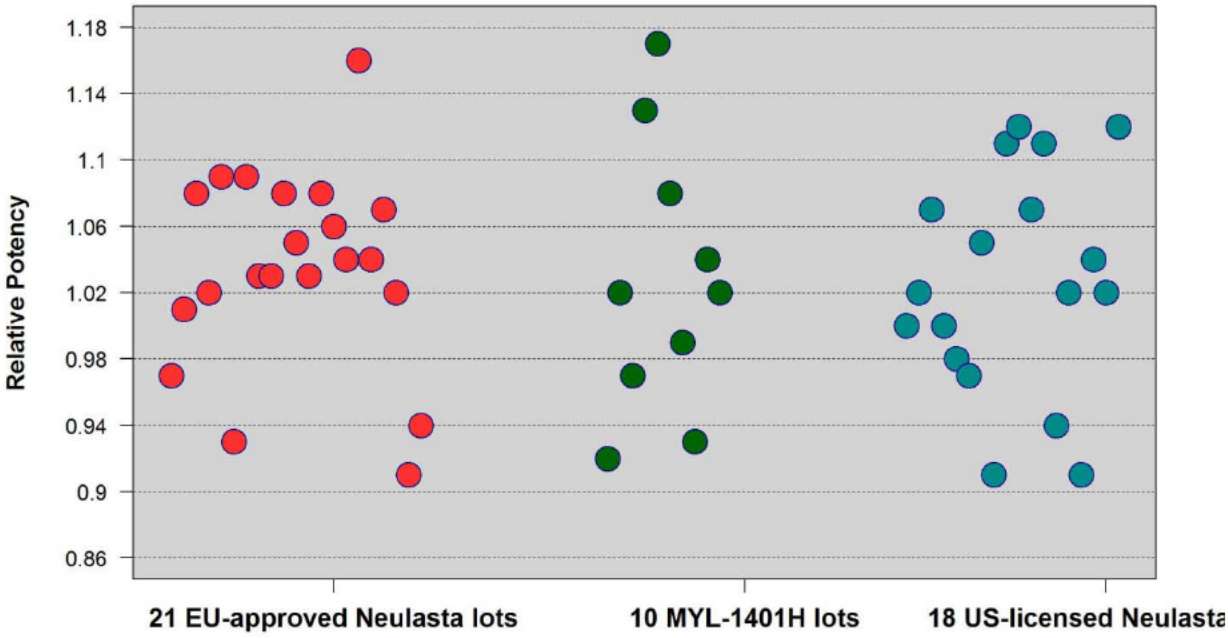

Table 8: Descriptive statistics for the Relative Potency data

Product	Number of lots	Sample mean	Sample standard deviation	Min	Max
MYL-1041H	10	1.046	0.075	0.91	1.12
US-licensed Neulasta	18	1.048	0.050	0.93	1.16
EU-approved Neulasta	21	1.007	0.069	0.91	1.17

Table 9 shows that the 90% confidence interval for the mean difference in the Relative Potency between MYL-1401H and US-licensed Neulasta is (-0.049, 0.046). It falls entirely within the equivalence margin (-0.076, +0.076). Hence the Relative Potency of MYL-1401H is equivalent to the Relative Potency of US-licensed Neulasta.

It also shows that the 90% confidence interval for the mean difference in the Relative Potency between MYL-1401H and EU-approved Neulasta is (-0.012, 0.091). It falls within the

equivalence margin (-0.104, +0.104). Therefore, the Relative Potency of MYL-1401H is equivalent to the Relative Potency of EU-approved Neulasta.

The 90% confidence interval for the mean difference in the Relative Potency between EU-approved Neulasta and US-licensed Neulasta is (-0.073, -0.009), which falls entirely within the equivalence margin (-0.076, +0.076). Therefore, the the Relative Potency of EU-approved Neulasta is equivalent to the the Relative Potency of US-licensed Neulasta.

The statistical equivalence analyses support that the Relative Potency of MYL-1401H is similar to that of US-licensed Neulasta. The results of all three pairwise comparisons support the analytical portion of the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Neulasta and the MYL-1401H product to support a demonstration of biosimilarity to US-licensed Neulasta.

Table 9: Equivalence testing results for the the Relative Potency

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
MYL-1401Hvs. US	(10, 18)*	-0.002	(-0.049, 0.046)	(-0.076, 0.076)	Yes
MYL-1401Hvs. EU	(10, 21)*	0.039	(-0.012, 0.091)	(-0.104, 0.104)	Yes
EU vs. US	(21, 18)	-0.041	(-0.073, -0.009)	(-0.076, 0.076)	Yes

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

5 CONCLUSION AND RECOMMENDATION

The statistical equivalence analyses shown above regarding Protein Content and the the Relative Potency of MYL-1401H support a demonstration that MYL-1401H is highly similar to US-licensed Neulasta. They also support the analytical portion of the scientific bridge to justify the relevance of EU-approved Neulasta data from the comparative clinical study.

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