STATISTICAL REVIEW AND EVALUATION

Date of the review: 3/20/09

Type of submission: BN_080041

Product/Application: New drug application: InterSol Solution for storage of AMICUS-Derived Apheresis Platelets.

Indication: The InterSol Solution is a plasma replacement fluid for storage of platelet using routine blood banking conditions. Platelet products stored in InterSol are transfused to patients with low platelet counts or to decrease bleeding.

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Sponsor: Fenwal Inc.

From: Paul B. Hshieh, Ph.D.

Through: Tie-Hua Ng, PhD., Team leader, Therapeutics Evaluation Branch (HFM-219)

Ghanshyam Gupta, Ph.D.,Chief, Therapeutics Evaluation Branch (HFM-219)

To: Salim Haddad, Medical officer.

cc: HFM-219/ Ghanshyam **Gupta**
HFM-215/ Henry Hsu
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A. Background:

- The plasma and an appropriate container provide the appropriate environment and nutrients to allow platelets to retain their function during storage. InterSol is an isotonic solution designed to replace a proportion of the plasma used in the storage of platelets. InterSol platelets (or PAS III platelets) are defined as platelets stored in 65% InterSol solution and 35% plasma. The solution does not have a pharmacological effect *in vivo*, but rather acts to provide the appropriate nutrients and environment in lieu of a portion of the plasma normally used for platelet storage.
- This study was conducted under two amendments:
  - Amendment 1: Evaluation of Platelets Stored for up to (b)(4)
  - Amendment 2: Evaluation of 5 Day Storage Including *In Vivo* Recovery and Survival and the Effect of Gamma Irradiation.

- Amendment 1 of FCRP 0106 included *in vitro* and *in vivo* evaluations of InterSol platelets stored for (b)(4). These evaluations have been completed; however the results did not meet the requirements for the upper 95% confidence interval as set out in the clinical protocol. Fenwal assessed this failure and the assessment results led to a recalculation of the sample size, resulting in a minimum sample size of 31 subjects for Amendment 2 studies of InterSol platelet recovery and survival following 5-day storage.
- **Only data pertaining to 5-day storage are included in this application.**

OBJECTIVES:
The purpose of this investigational plan was to evaluate leukoreduced platelet products stored in 65% PAS III and 35% plasma in PL 2410 plastic containers **after 5-day storage** to determine whether they met the **storage criteria**.

Study Design:
Amendment 1
- Two platelet collections, separated by one hour, were performed using the AMICUS Separator. The collection sequence of the products, 100% plasma (*in vitro* Control) or 65% PAS III and 35% plasma (PAS III Test), was randomized.
- Products were stored for up to ---(b)(4)--- and evaluated for *in vitro* parameters on Days 1, 5 --(b)(4)--.

Amendment 2
- Platelets were collected as single or double platelet products in 65% PAS III and 35% plasma using the AMICUS Separator and stored for **five days**.
- Platelet **recovery and survival** were compared with that seen with **fresh** autologous whole blood-derived platelets (in vivo Control).
- A subset of these collections and double platelet products were collected for evaluation of **gamma irradiation**. One unit of the paired PAS III platelet product was exposed to approximately 2500 cGy of gamma irradiation on Day 1 of storage (Irradiated Test). The remaining product was not exposed to gamma irradiation and served as both a non-irradiated control, as well as an in vivo test article in the radio-labeled study.
- The **pH and standard in vitro assays** were performed to evaluate irradiated and non-irradiated platelet products stored for 5 days in 65% PAS III and 35% plasma in PL 2410 plastic containers.

ENDPOINT:
Efficacy:
- *In vitro:*
  - ***Primary:*** *the* efficacy of platelet products was determined by **pH** at the end of storage.
  - ***Secondary:*** other accepted biochemical and functional parameters will be assessed. There are:

    Subject Parameter
    - Platelet Count
    - Hemoglobin or Hematocrit

Product Parameter

- Platelet Counts
- Platelet MPV
- White Blood Cell (WBC) Count
- Microbiological Culture
- Product Weight
- ***Biochemical Assessments***-pH (22^oC)
- Glucose
- Lactate
- pO_2
- pCO_2
- Bicarbonate
- Lactate Dehydrogenase
- ***Functional Assessments***-Morphology Score
- Hypotonic Shock Response (HSR)
- Extent of Shape Change (ESC)
- CD62 (p-selectin) Expression5
- Radiolabeled Platelet Recovery/Survival
- ***Other Assessments***
  - Gram Stain
  - Pregnancy Test

- *In vivo* efficacy of platelets was assessed on **Day 5** by radiolabeled platelet **recovery and survival** as a percent of the fresh autologous whole blood-derived platelet control.

SAFETY

- To ensure their safety, subjects participating in the study were monitored for adverse events (AEs) during platelet collection and during infusion of the radio-labeled platelets.

Acceptance storage criteria:

Primary Endpoints:

- **In Vitro**: pH ≥ 6.2 with a lower 95% tolerance limit on the 5th percentile (95%, 95%, tolerance limit).
- ***In vivo*** radiolabel assessment:
  - % Recovery at the end of storage compared to fresh autologous whole blood (WB) derived platelets, 0.66 x % recovery fresh WB derived platelets- % recovery at end of storage.
  - Survival (days) at the end of storage compared to fresh autologous whole blood (WB) derived platelets, 0.58 x survival fresh WB derived platelets – survival at end of storage.
  - *In vivo* radiolabel criteria for evaluation and limits calculated:

The upper limit of a two-sided 95% confidence interval on the mean percent recovery of 0.66 x Fresh Survival– 5 Day < 0, then this criterion is satisfied.

Secondary Endpoints:

- The secondary parameters in vitro study, FDA requires the test platelets should not be worse than the control by 20% on day 5 based on the mean response.

B. FDA Statistical Review

Note: After a number of communications between FDA and sponsor, this review report includes the summary results and all statistical comments and responses to the sponsor replies to FDA requests.

I. In-Vivo Study: Parameter Recovery and Survival

Variable	N	Mean	Std Dev	95% CLL	95%CLM
rec_fresh platelet	33	58.042	10.742	54.233	61.851
pas_3_rec	33	46.358	11.886	42.143	50.572
d_recover	**33**	**-8.050**	**9.716**	**-11.495**	**-4.605**
sur_fresh platelet	33	8.039	1.443	7.527	8.550
pas_3_sur	33	5.708	1.431	5.201	6.216
d_survival	**33**	**1.046**	**1.334**	**-1.519**	**-0.573**

note:

1. d_recover =**0.66***fresh-day 5.
2. d_survival=**0.58***survival fresh-day 5.

The upper limit of 95% confidence interval for recovery (0.66*Fresh-Day 5) and survival (0.58*fresh survival-day5) are -4.605, -0.573 respectively, which are less than 0. Therefore, platelets stored for 5 days in PASIII met acceptance criteria for recovery and survival.

II. In Vitro Study:

For the following items, reference is made to FDA's January 23, 2009 Information Request and Fenwal's February 12, 2009 response

a. FDA initial comment: For in vitro parameters other than pH, FDA has traditionally recommended that analyses be conducted to demonstrate a difference of no more than 20% between test and control (FDA Workshop on Platelet evaluation, May 2004, and Communication to Fenwal Nov 20, 2007). We recommend you conduct such studies using the hypotheses testing found in the appendix.

Fenwal's Response: Fenwal respects FDA's right to request information that may be relevant to further evaluate a product under review. Fenwal has completed the additional analyses on the in vitro data requested by FDA, however the primary basis for approval is meeting the primary endpoints of in vivo survival and recovery and pH maintenance. The additional data supplied are supplementary, are consistent with previously reported results

(reference BB IND (b)(4).10: IND Annual Report, 12-Nov-07, pages 23 -82 of 82) and do not raise new questions of safety or effectiveness.

FDA Statistical Comment:

Parameter pH

Variable	Mean	Std Dev	Median	Minimum	Maximum
pas_3	7.187	0.098	7.182	6.940	7.511

- The pH is a primary parameter for the in vitro study. In the process performance qualification in collecting the leukoreduced platelet products, FDA recommends that the lower limit of 95%/95% tolerance interval of pH needs to be bigger than 6.2. Since all pH values are bigger than 6.2, the product PAS-III meets the acceptance criteria.
- **Fenwal did not respond to question 2 of Amendment 3 (p 8 of FDA's Jan 23, 2009 IR):** The sponsor computed lower limit of 95/95% tolerance limit for pH based on nonparametric approach, we requested the sponsor to provide the following detailed information, but the sponsor **has not responded** yet.
    1. The references upon which the calculation steps were based.
    2. The SAS program which was developed by following your calculation steps.
    3. The result which was obtained by using your developed SAS program.

Sponsor's further response on in vitro parameters other than pH:

With respect to the data requested, the analyses are presented in **Attachment 2**.

- The PAS III Test is statistically equivalent to the plasma Control for Lactate, pO_2, Lactate Dehydrogenase and Morphology Score. We are not able to claim non-inferiority for CD 62 Expression because the standard deviations are too large in relation to the observed means. The observed differences in values are not considered clinically significant. The PAS III Test is inferior to the plasma Control for Hypotonic Shock Response and Extent of Shape Change. Lower Hypotonic Shock and Extent of Shape Change have been observed in previous studies comparing platelets stored in PAS III and plasma as reported in the PAS III Investigator's Brochure (reference BB IND (b)(4): IND Annual Report, 12-Nov-07, pages 23 -82 of 82). The clinical significance of this finding is not apparent since platelets stored in PAS III demonstrated acceptable in vivo recovery and survival. Additionally, PAS III is currently used effectively in Europe both as a stand-alone platelet storage solution and as part of the INTERCEPT system. The clinical impact of pCO_2 excursions is unclear, so we have presented non-inferiority results for both confidence limits. CO_2 is produced during aerobic respiration and bicarbonate buffering of glycolytic lactate production. A lower pCO_2 in the Test platelets may be expected from the bicarbonate sparing effect of PAS III acetate metabolism and has been observed in previous studies comparing platelets stored in PAS III and plasma as reported in the PAS III Investigator's Brochure (reference BB IND (b)(4): IND Annual Report, 12-Nov-07, pages 23 -82 of 82). These data demonstrate equivalence in clinically relevant parameters, raise no new questions of safety and effectiveness or questions regarding the primary endpoint analysis, and thus support the safety and effectiveness of PAS III for its intended purpose.

FDA Statistical Comment:

In-Vitro Study: Secondary Parameters

- For the secondary parameters in the in vitro study, FDA recommended that the test platelets should not be worse than the control by 20% on day 5 based on the mean response. For parameters with a higher value corresponding to a better outcome, the acceptance criteria should be based on the lower limit of 95% confidence interval for μ_t-0.8*μ_c (or μ_t / μ_c) being greater than 0 (or 0.8). For parameters with a lower value corresponding to a better outcome the upper limit of 95% confidence interval for μ_t-1.2*μ_c (or μ_t / μ_c) should be less than 0 (or 1.2).
- The parameters with a higher value corresponding to a better outcome are **Glucose, Morphology Score, Hypotonic Shock Response, Extent of Shape Change and Bicarbonate.** The parameters with a lower value corresponding to a better outcome are **Lactate, Lactate Dehydrogenase, CD62 Expression; however, the PO_2 and PCO_2 may vary**.
- Based on the above discussion, the parameters pCO_2 (if higher pCO_2 is considered better), CD62 Expression, Hypotonic Shock Response, Extent of Shape Change **do not meet the acceptance criteria.**
- The 95% confidence intervals of all the secondary parameters obtained by the sponsor were different from those obtained by FDA statistical reviewer. **Please compare your confidence intervals to the ones in the table below and comment**.

Para_c	N	Variable	Mean	Std_D	Prt	95% CLL	95% CLU
3	67	plasma	9.860	2.303	<.0001	9.298	10.421
		pas_3	10.396	2.020	<.0001	9.903	10.888
low		diff_0	0.536	1.459	0.0037	0.180	0.892
		diff_08	2.508	1.293	<.0001	2.192	2.823
		diff_12	-1.436	1.735	<.0001	-1.859	-1.013
		Ratio	0.060	0.144	0.0011	1.025	**1.100***
4	70	plasma	146.886	31.609	<.0001	139.349	154.423
		pas_3	145.143	33.521	<.0001	137.150	153.136
		diff_0	-1.743	13.243	0.2747	-4.901	1.415
varies		diff_08	27.634	14.324	<.0001	24.219	31.050
		diff_12	-31.120	15.017	<.0001	-34.701	-27.539
		Ratio	**-0.018**	**0.208**	**0.4770**	**0.935**	**1.033***
5	70	plasma	30.786	6.157	<.0001	29.318	32.254
		pas_3	21.971	4.625	<.0001	20.869	23.074
		diff_0	-8.814	4.202	<.0001	-9.816	-7.812
varies		diff_08	-2.657	3.513	<.0001	-3.495	-1.820
		diff_12	-14.971	5.100	<.0001	-16.188	-13.755
		Ratio	**-0.341**	**0.147**	**<.0001**	**0.687**	**0.736****
7	70	plasma	153.871	57.227	<.0001	140.226	167.517
		pas_3	146.729	83.649	<.0001	126.783	166.674
		diff_0	-7.143	68.892	0.3887	-23.570	9.284
low		diff_08	23.631	68.355	0.0051	7.333	39.930
		diff_12	**-37.917**	**71.288**	**<.0001**	**-54.915**	**-20.919**
		Ratio	-0.112	0.374	0.0149	0.818	**0.978***
8	69	plasma	8.102	5.029	<.0001	6.855	9.348
		pas_3	11.297	5.774	<.0001	9.843	12.751
low		diff_0	3.195	4.060	<.0001	2.173	4.218
		diff_08	4.816	3.961	<.0001	3.818	5.813
		diff_12	**1.575**	**4.400**	**0.0061**	**0.467**	**2.683**
		Ratio	0.378	0.444	<.0001	1.305	**1.632****
9	70	plasma	303.343	69.368	<.0001	286.803	319.883
		pas_3	294.700	70.505	<.0001	277.889	311.511
		diff_0	-8.643	16.576	<.0001	-12.595	-4.691
high		**diff_08**	**52.026**	**21.073**	**<.0001**	**47.001**	**57.050**

		diff_12	-69.311	22.144	<.0001	-74.592	-64.031
		Ratio	-0.032	0.062	<.0001	**0.954***	0.983
10	70	plasma	67.271	9.540	<.0001	64.997	69.546
		pas_3	52.829	9.125	<.0001	50.653	55.004
high		diff_0	-14.443	10.366	<.0001	-16.915	-11.971
		diff_08	**-0.989**	**9.384**	**0.3812**	**-3.226**	**1.249**
		diff_12	-27.897	11.582	<.0001	-30.659	-25.136
		Ratio	-0.247	0.181	<.0001	**0.748****	0.815
11	70	plasma	23.280	4.738	<.0001	22.150	24.410
		pas_3	13.300	6.803	<.0001	11.678	14.922
high		diff_0	-9.980	6.554	<.0001	-11.543	-8.417
		diff_08	**-5.324**	**6.327**	**<.0001**	**-6.833**	**-3.815**
		diff_12	-14.636	6.905	<.0001	-16.283	-12.989
		Ratio	-0.684	0.572	<.0001	**0.440****	0.579

***** : The parameter meets the acceptance criteria.
****** : The parameter does not meet the acceptance criteria.

```
diff_08=pas_3-plasma*0.8,
diff_12=pas_3-plasma*1.2;
L_diff=log(pas_3)-log(plasma);
```

III. Irradiation Study:

Regarding items 1, 2, and 3 below, reference is made to FDA's January 23, 2009 Information Request and Fenwal's February 12, 2009 response

1. As we indicated in our Nov 20, 2007 communication to you, FDA recommends a demonstration of no more than 20% difference between test and control for the in vitro parameters other than pH. We recommend you conduct such analyses using the hypotheses listed in the appendix.

Response: Fenwal respectfully understands FDA's recommendation, however as stated in the comments presented in the cover letter to this response, Fenwal is unaware of any published regulation or guidance documents establishing this recommendation as a requirement for approval. Additionally, Fenwal notes that there are no published or publicly disclosed standards on the required quality of irradiated platelets. Nonetheless, the analyses are presented in **Attachment 4**.
The study presented was designed to show that there is no unexpected impact of irradiation on platelets stored in PAS III as compared to non-irradiated platelets.

- The irradiated PAS III Test is statistically equivalent to the non-irradiated PAS III Control for Glucose, Lactate, pO_2, pCO_2, Bicarbonate, Lactate Dehydrogenase, CD62 Expression, Morphology Score and Hypotonic Shock.
- We are not able to claim non-inferiority for the Extent of Shape Change. The observed differences in values are not clinically significant.

These data support the safety and effectiveness of the PAS III solution for its intended use and raise no new questions of safety or effectiveness.

2. As per our April 1st 2008 teleconference, please determine 1) whether the results of the irradiation study are statistically significant and 2) the statistical power of the study.

Response: See response directly above (Section II, 1.) and **Attachment 4**.

3. In volume 2, page 56 of 287, you state that an analysis of variance with repeated measures

using the Mixed Effects Model was used to evaluate the effect of irradiation on 18 paired platelet products. The results are shown in table 14.13 on page 80/287. Please provide a more complete interpretation of these results such as the effect of the choice of storage solution and that of the day of storage on the in vitro parameter results, and please elaborate on the meaning of treatment day interactions on the interpretation of the results.

Response: There is no significant treatment (irradiated vs. non-irradiated) by day (day 1 vs. day 5 storage) interaction for any of the parameters tested for the irradiated compared to non-irradiated PAS III platelets. Therefore, as previously shown for platelets in plasma, there appears to be no significant impact of irradiation on PAS III platelets.
The electronic files containing the SAS data sets to generate the results in Tables 14.13 (volume 2, page 80 of 287) are provided in the attached file GAMPLATE.sas7bdat and A2_POP.sas7bdat. For all parameters in GAMPLATE.sas7bdat merge platelet.sas7bdat and A2_POP.sas7bdat by subject id PT. Retain records only where EVAL2=1 (Evaluable = Yes). Refer to **Attachment 5** for the instructions needed to reproduce Table 14.13.

FDA Statistical Response:

- In Irradiation Study, FDA recommends a demonstration of no more than 20% difference between test and control **on day 5** based on the mean response. Thus, an analysis of variance with repeated measure using the Mixed Effects Model is not necessary. The hypotheses setting and acceptance criteria are the same as in vitro study. Our analysis results were presented on the table below. We conclude that the parameter **Lactate Dehydrogenase and Extent of Shape Change** do **not meet** the acceptance criteria.

- The 95% confidence intervals of all secondary parameters obtained by the sponsor were different from that obtained by the reviewer; and the conclusions are also different. The sponsor needs to **comment.**

Para_c	N	Var	Mean	Std_D	prt	95% CLL	95% CLU
2 (high)	18	Non_irrad	27.444	11.908	<.0001	21.523	33.366
		irrad	27.611	12.010	<.0001	21.638	33.584
		gdiff_0	0.167	2.229	0.7550	-0.942	1.275
		gdiff_08	**5.656**	**3.184**	**<.0001**	**4.072***	**7.239**
		gdiff_12	-5.322	3.338	<.0001	-6.982	-3.662
		gRatio	0.006	0.103	0.8133	**0.956***	1.05856
3 (Low)	18	Non_irrad	11.972	1.442	<.0001	11.255	12.689
		irrad	11.889	1.460	<.0001	11.163	12.615
		gdiff_0	-0.083	0.342	0.3153	-0.253	0.087
		gdiff_08	2.311	0.433	<.0001	2.096	2.526
		gdiff_12	-2.478	0.461	<.0001	-2.707	-2.248
		gRatio	-0.007	0.029	0.3022	**0.978**	**1.007***
4 (Varies)	18	Non_irrad	147.278	20.719	<.0001	136.975	157.581
		irrad	151.889	16.421	<.0001	143.723	160.055
		gdiff_0	4.611	15.451	0.2225	-3.072	12.295
		gdiff_08	34.067	13.275	<.0001	27.465	40.668
		gdiff_12	-24.844	18.318	<.0001	-33.954	-15.735
		gRatio	0.035	0.113	0.2037	**0.979***	**1.0960***
5 (Varies)	18	Non_irrad	20.500	3.915	<.0001	18.553	22.447
		irrad	20.333	3.710	<.0001	18.488	22.178
		gdiff_0	-0.167	1.383	0.6156	-0.854	0.521
		gdiff_08	3.933	1.353	<.0001	3.261	4.606
		gdiff_12	-4.267	1.794	<.0001	-5.159	-3.374

		gRatio	-0.007	0.067	0.6790	**0.961***	**1.027***
6	18	Non_irrad	4.317	1.210	<.0001	3.715	4.919
		irrad	4.306	1.151	<.0001	3.733	4.878
(high)		gdiff_0	-0.011	0.307	0.8796	-0.164	0.141
		gdiff_08	0.852	0.325	<.0001	0.691	1.014
		gdiff_12	-0.874	0.447	<.0001	-1.097	-0.652
		gRatio	0.001	0.082	0.9698	**0.961***	1.0421
7	18	Non_irrad	223.111	120.132	<.0001	163.371	282.851
		irrad	233.444	116.695	<.0001	175.413	291.476
(low)		gdiff_0	10.333	67.241	0.5231	-23.105	43.772
		gdiff_08	54.956	63.495	0.0019	23.380	86.531
		gdiff_12	-34.289	78.522	0.0814	-73.337	4.759
		gRatio	0.066	0.310	0.3811	0.91525	**1.246****
8	18	Non_irrad	16.167	3.915	<.0001	14.220	18.113
		irrad	16.389	4.286	<.0001	14.258	18.520
(low)		gdiff_0	0.222	1.665	0.5786	-0.606	1.050
		gdiff_08	3.456	1.854	<.0001	2.533	4.378
		gdiff_12	-3.011	1.825	<.0001	-3.918	-2.104
		gRatio	0.010	0.108	0.7133	0.95676	**1.065***
9	18	Non_irrad	297.056	79.196	<.0001	257.672	336.439
		irrad	290.611	73.267	<.0001	254.176	327.046
(High)		gdiff_0	-6.444	19.098	0.1704	-15.942	3.053
		gdiff_08	52.967	19.023	<.0001	43.507	62.426
		gdiff_12	-65.856	29.485	<.0001	-80.518	-51.193
		gRatio	-0.016	0.065	0.3027	**0.953***	1.01620
10	18	Non_irrad	52.694	8.095	<.0001	48.669	56.720
		irrad	51.372	8.171	<.0001	47.309	55.436
(high)		gdiff_0	-1.322	4.380	0.2175	-3.500	0.856
		gdiff_08	9.217	4.268	<.0001	7.094	11.339
		gdiff_12	-11.861	5.040	<.0001	-14.367	-9.355
		gRatio	-0.026	0.083	0.1981	**0.934***	1.01527
11	18	Non_irrad	10.650	4.102	<.0001	8.610	12.690
		irrad	8.283	3.879	<.0001	6.354	10.212
(high)		gdiff_0	-2.367	4.303	0.0322	-4.507	-0.227
		gdiff_08	-0.237	3.890	0.7994	-2.171	1.698
		gdiff_12	-4.497	4.822	0.0010	-6.895	-2.099
		gRatio	-0.282	0.447	0.0193	**0.600****	0.94927

*** : The parameter meets the acceptance criteria.**
**** : The parameter does not meet the acceptance criteria.**

```
gdiff_08 = irrad-non_irrad*0.8;
gdiff_12 = irrad-non_irrad*1.2;
gL_diff = log(irrad)-log(non_irrad);
```

IV. Bacterial Validation Study

Regarding items 3a through 3d below, reference is made to FDA's January 23, 2009 Information Request and Fenwal's February 12, 2009 response

3. Statistical Methods (vol 4 page 246 of 274)

a) Under experimental design you state that (b)(4) results from each sample drawn from each inoculated bag and dispensed into ---(b)(4)---------- and -----(b)(4)---------- will constitute a matched set of results. However on p. 217 of 274, under 'Organism Recovery' section you indicate that each test set consists of –(b)(4)------

----------. Please clarify the contradiction and elaborate on any impact on the outcomes.

Response:

Each ----------**(b)(4)**---------- was compared to the overall result of -(b)(4)---------- for a total of (b)(4) results. If ----(b)(4)---- was positive, the overall (b)(4) was considered positive.

FDA Statistical Response:

Acceptable.

b) Under sample size you state, in the last sentence of the paragraph, that the hypothesis will be tested ---(b)(4)--- for ---(b)(4)----- type, however on page 218 of 274, in the 2nd and 3rd paragraphs, you indicate that the ---(b)(4)---------- tests were analyzed as a set (considered positive if ---(b)(4)------ was positive) and that a single hypothesis was tested. Please clarify the contradiction and indicate whether the conclusions would differ based on the different hypothesis testing.

Response:

The original intent was to test a single non-inferiority hypothesis for each **---(b)(4)-------** type. The non-inferiority (NI) margin of -0.055 was used for testing. Inadvertently, only the combined results (**---(b)(4)-------**) were provided. In addition to the combined results, the results for each single **---(b)(4)----** type are provided below (**---(b)(4)----------** were removed from the aerobic only analysis since **--(b)(4)**were incubated only under anaerobic conditions). The one-sided lower 97.5% confidence limits on the difference between the **(b)(4)** anaerobic (b)(4) and **----------(b)(4)**-----aerobic------**(b)(4)**---------- are 0.033 (p value=0.0002) and 0.024 (p value=0.0023), respectively. Because these limits are greater than -0.055 (NI margin), **---(b)(4)**---------- is non-inferior to **-(b)(4)**- . This discrepancy does not impact the original conclusions.

FDA Statistical Response:

- The comparisons between Anaerobic**---(b)(4)**---------- , and between Aerobic**---(b)(4)**---------- are acceptable. Both reviewer and sponsor have the same conclusion- ---**(b)(4)**-- is non-inferior to **(b)(4)** however, the results are slightly different. From SAS results, the one-sided lower 97.5% confidence limits on the difference between the (b)(4) anaerobic ---- **(b)(4)**--------aerobic---------- 0.027 (compare to 0.033) and 0.015 (compare to 0.024), respectively.

			(Exact) 95%	
	Risk	ASE	Confidence Limits	
(b)(4)	1.0000	0.0000	0.9841	1.0000
(b)(4)	0.9435	0.0152	0.9053	0.9696
Diff	0.0565	0.0152	0.0267	0.0864

			(Exact) 95%	
	Risk	ASE	Confidence Limits	

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(b)(4)	0.9435	0.0152	0.9053	0.9696
Diff	0.0565	0.0152	0.0267	0.0864

			(Exact) 95% Confidence Limits	
	Risk	ASE		
ƒƒ				
(b)(4)	1.0000	0.0000	0.9785	1.0000
(b)(4)	0.9529	0.0162	0.9094	0.9795
Diff	0.0471	0.0162	0.0152	0.0789

Note: According to clinical reviewer, there is some discrepancy in the submitted data and need to be resolved.

c) Since your -----(b)(4)------ validation study was conducted using the --(b)(4)-- system (----(b)(4)----) as a set, any future approval would require the concurrent use of ------(b)(4)----.

Response:

There are no FDA requirements for bacterial testing of platelet products. However, since this is a common practice in the blood banking industry, Fenwal did conduct a study to understand if PAS III would affect the performance of either --**(b)(4)**-- being used by some customers for QC testing of platelets. A non-inferiority hypothesis was tested for each --------**(b)(4)**--- separately and also for ----**(b)(4)**-------- types. The non-inferiority (NI) margin of -0.055 was used for testing. Inadvertently, only the results of ------**(b)(4)**-- tests were provided. The results for -----**(b)(4)**-------- and the-------**(b)(4)**---------- type are provided above in 3b (--------**(b)(4)**------- were removed from the --------**(b)(4)**------ analysis since --**(b)(4)** were ----------**(b)(4)**-------------------------). As demonstrated by the one-sided lower 97.5% confidence limits, the ----------**(b)(4)**---------- the --**(b)(4)**---------- , and ----**(b)(4)**---------- are non-inferior to ----**(b)(4)**------- . Therefore Fenwal has data to support the use of PAS with the ----**(b)(4)**----- whether customers use -**(b)(4)**- , as is the practice with some customers, or **(b)(4)** which is the practice for others.

FDA Statistical Response:

- The explanation is acceptable.