Review Memorandum

BN080041

New Drug Application, Original Submission, Fenwal, Platelet Additive Solution III (PAS III, InterSol) for the storage of Amicus-Derived apheresis platelets in a PL 2410 ---(b)(4)---- plastic container with 35% plasma and 65% PAS III for up to 5 days.

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A. Background

Since receiving this submission FDA had a number of interactive communications with Fenwal regarding the clinical study, statistical issues, CMC, manufacturing, and biocompatibility (communications available on file). Additionally, both manufacturing and BIMO inspections were scheduled. As of 4-2-09 BIMO inspection at the Philadelphia site was still pending.
This memo addresses the outstanding issues remaining regarding the clinical study, statistical issues, labeling, and toxicology which will go into the complete response (CR) letter. (Additional CMC, DMPQ, biocompatibility, and inspection issues will be included in the final CR letter).

B. Referral to BPAC

This application need not be referred to the Blood Products Advisory Committee because the candidate drug does not contain active ingredients which have not been previously approved in other FDA applications[1] (CDER).

C. <u>CR letter</u> (clinical studies, statistics, labeling)

I. ----(b)(4)---------- Platelet products:

1. In your March 11, 2009 facsimile letter you indicate that 'amendment 1' had 2 incomplete collections and 5 non evaluable products in the test (PAS III) arm using the Amicus device. Therefore we conclude that out of -(b)(4)- initial collections 7 were excluded from the study results due to --(b)(4)--------, for a rate of 6.9%.
In the control (plasma arm) the exclusion rate was 5 out of 99, for a rate of -(b)(4)-

In 'amendment 2' all procedures were collected using the PAS III. 2 of 50 collections were excluded from the study results due to ---(b)(4)--------, for a rate of 4%.

As a reference, Fenwal (then Baxter) submission BK040059 which cleared 7-day platelets collected by the Amicus device (Study FCRP-0303) had 1/80 collections excluded from the study results due to ---(b)(4)-------, for a rate of 1.25%.

Considering the ---(b)(4)---------- for both test and control arms in the current FCRP-0106 study compared to your previous study FCRP-0303 FDA may recommend that, following a potential future approval of your solution and its clinical use, you conduct a post marketing study to ----(b)(4)---------- in the collected products. Details of the post marketing evaluation would be discussed with FDA.

2. Based on your reply to item 1.b on page 3 of 28 of your Feb 12, 2009 response we recommend you define, in term of hours, the specific rest period for the resolution of -b(4)--------- that you will instruct the user to follow.

II. In vitro results

1. FDA agrees with you that in vitro parameters other than pH are secondary outcomes but may be meaningful when differences between test and control cross a threshold that may impact the safety and efficacy of the product.

Based on FDA statistical analysis, the difference between test and control for some in vitro parameters exceeded the 20% margin which FDA has traditionally considered as potentially clinically meaningful, especially for in vitro parameters such as hypotonic shock response and the extent of shape change which have shown correlation with platelet in vivo viability and performance. Additionally, in the test products, there is increase in the rate of LDH release over the 5-day storage period (potentially associated with cell lysis) and an elevation of CD62 levels for both days 1 and day 5 (potentially associated with platelet activation and poor platelet performance).

Additionally, the sampling volume drawn serially from the product ranged from -(b)(4)- mL (in addition to b(4) mL for bacterial testing on day) and appears larger than the(b)(4)- mL which was suggested in pre-submission meetings (page 4, Fenwal's Aug 22 2006

response). Drawing a series of large volume samples may impact the microenvironment of the platelets and the subsequent in vitro testing results.

Therefore FDA may recommend that, after a potential future approval of your solution and its clinical use, you conduct a post marketing study to generate data on the safety and efficacy of your product. Details of the post marketing evaluation would be discussed with FDA.

2. Statistical analysis

a. In our December 16, 2008 communication to you we listed the hypotheses testing formulation that we recommend for the evaluation of in vitro parameters. These were reiterated in our January 23, 2009 fax to you on pages 6, and on page 7 in response to questions 1 and 2 to 'Amendment 4: Jan 9, 2009 Fenwal questions'.

Based on these hypotheses formulation we have generated the following table:

Para_c	N	Variable	Mean	Std_D	Prt	95% CLL	95% CLU
Lactate	67	plasma	9.860	2.303	<.0001	9.298	10.421
		pas_3	10.396	2.020	<.0001	9.903	10.888
		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***
pO_2	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
		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***
pCO_2	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
		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****
LDH	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
		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***
CD62	69	plasma	8.102	5.029	<.0001	6.855	9.348
		pas_3	11.297	5.774	<.0001	9.843	12.751
		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****
Morphology	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
		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
HSR	70	plasma	67.271	9.540	<.0001	64.997	69.546
		pas_3	52.829	9.125	<.0001	50.653	55.004
		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

ESC	70	plasma	23.280	4.738	<.0001	22.150	24.410
		pas_3	13.300	6.803	<.0001	11.678	14.922
		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);
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The 95% confidence intervals that are generated by this table are different from the ones that you have calculated. Please provide an explanation.

b. We have not received a response to question 2 in section 'Amendment 3' (p 8 of FDA's Jan 23, 2009 Information Request): "you computed lower limit of 95/95% tolerance limit for pH based on nonparametric approach, we reiterate our request to provide the following detailed information:

i. The references upon which the calculation steps were based.
ii. The SAS program which was developed by following your calculation steps.
iii. The result which was obtained by using your developed SAS program"

Please provide the previously requested information.

3. Bag specifications (item 2 e, page 7 of 28 of your Feb 12, 2009 response)

The previously cleared yield range specification of your platelet container is 1.5-4.7 x 10^{11} platelets. In your response you divide up the range into uneven intervals: --(b)(4)----- --(b)(4)---------- platelets, and --(b)(4)--------- platelets. You additionally state that if the data from amendment 2 are added to the data from amendment 1 you would meet the requirement of 30% of the data generated at each end of the yield range.
However the raw data of amendment 2 (volume 4, p 47 through 61) show identical values for platelet count (x 10^3/µL) and platelet count (10^{11}/product) for each listed product. This renders difficult the assessment of the platelet yield range of your bag.
Please provide the platelet yield data for all products in amendment 2.

III. Irradiation study

1. Comparison of test vs. control

Based on our statistical analysis, all in vitro parameters met the non inferiority criteria except LDH and Extent of Shape Change.
In our December 16, 2008 communication to you we listed the hypotheses testing formulation that we recommend for the evaluation of in vitro parameters. These were reiterated in our January 23, 2009 fax to you on pages 6, and on page 7 in response to questions 1 and 2 to 'Amendment 4: Jan 9, 2009 Fenwal questions'.

Based on these hypotheses formulation we have generated the following table for the irradiation study:

Para_c	N	Var	Mean	Std D	prt	95% CLL	95% CLU
Glucose	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
Lactate	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***
pO_2	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***
pCO_2	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***
Bicarb	18	Non_irrad	4.317	1.210	<.0001	3.715	4.919
		irrad	4.306	1.151	<.0001	3.733	4.878
		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
LDH	18	Non_irrad	223.111	120.132	<.0001	163.371	282.851
		irrad	233.444	116.695	<.0001	175.413	291.476
		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****
CD62	18	Non_irrad	16.167	3.915	<.0001	14.220	18.113
		irrad	16.389	4.286	<.0001	14.258	18.520
		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***
Morph.	18	Non_irrad	297.056	79.196	<.0001	257.672	336.439
		irrad	290.611	73.267	<.0001	254.176	327.046
		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
HSR	18	Non_irrad	52.694	8.095	<.0001	48.669	56.720
		irrad	51.372	8.171	<.0001	47.309	55.436
		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
ESC	18	Non_irrad	10.650	4.102	<.0001	8.610	12.690
		irrad	8.283	3.879	<.0001	6.354	10.212
		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.**

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gdiff_08=irrad-non_irrad*0.8;
gdiff_12=irrad-non_irrad*1.2;
gL_diff=log(irrad)-log(non_irrad);
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The 95% confidence intervals that are generated by this table are different from the ones that you have calculated. Please provide an explanation.

2. Raw data

The raw data of amendment 2 (volume 4, p 47 through 61) show identical values for platelet count (x 10^3/μL) and platelet count (10^{11}/product) for all listed products. Please provide the platelet yield data for all products in amendment 2 for a comprehensive evaluation of the irradiation study data.

3. Labeling

In volume 5, page 2 of 248 you state that the platelets were irradiated at 2500 cGray and that the in vitro parameters showed no statistical difference between test and control. Actually one site tested at 2800 cGray, and some in vitro parameters did show greater than 20% difference. Labeling pertaining to the irradiation study will reflect the outcome of your study.

IV. Bacterial study

1. Study comparing bacterial growth in plasma vs. 65% PASIII/35% plasma

a. At the bottom of p 13 of 28 you state that there is no currently available data to suggest that bacterial growth would differ in plasma vs. a mixture of 35% plasma/65% PAS III. Traditionally it has been the sponsor's responsibility to provide supporting evidence for a particular claim and conducting a parallel bacterial growth study in plasma and mixture of 35%plasma/65%PAS III would provide such evidence as we have recommended in our Jan 23, 2009 facsimile letter. We believe such a study is necessary because it has currently been established through published science and through professional standards that the safety of platelet products cannot be divorced from the issue of bacterial contamination of platelets. The PASSPORT study, as well as studies by the American Red Cross[2] and elsewhere[3] have demonstrated a lower than expected clinical sensitivity (higher than expected false negative rate) of the BacT/ALERT device when used early in the storage of platelets. The proposed comparative bacterial growth study would characterize bacterial growth in a mixture of 65%PAS III/35% plasma and provide critical data to ensure safety of the product such as the optimal sampling time to minimize sampling errors.

Your proposed target of --(b)(4)---- and sampling schedule at --(b)(4)--- are acceptable however we continue to recommend that you test at least two slow and two fast growing organisms by inoculating at least 5 different platelet products for each of the two storage conditions with at least 5 replicates per inoculum. The final sample size of the study should be large enough to yield statistically significant results.

b. Following a potential future approval of your solution and its clinical use, FDA may recommend that a post marketing study be conducted to generate data on the safety of your product from bacterial contamination. Details of the post marketing evaluation would be discussed with FDA.

2. Hypothesis testing for each --(b)(4)----- (rather than --(b)(4)----------)

The table on p 15 of 28 of your Feb 12, 2009 response has inaccuracies and internal inconsistencies which may invalidate the results of your hypothesis testing:

a. Raw data

Out of the -(b)(4)- instances in which both -(b)(4)- are negative, -(b)(4)- have occurred at the -b(4)- site with the inoculation of a -(b)(4)- organism at ---(b)(4)----. Please provide an explanation for this outlier result and whether it could be included in the data analysis.

b. 'Aerobic -(b)(4)- only' row:

i. The actual number of -(b)(4)- ------ tested is -(b)(4)- and not -(b)(4)-. You state that ----(b)(4)---------- were only cultured in anaerobic -(b)(4)- however they were inoculated in both aerobic and anaerobic --(b)(4)-----
ii. Based on your raw data the actual number of aerobic --(b)(4)--- which were spiked with aerobic organisms with resulting CFU/ml levels of -(b)(4)- is actually -(b)(4)- and not -(b)(4)-, and the proportion in the '-(b)(4)- column should read --(b)(4)----
iii. You have excluded the aerobic --(b)(4)--- which were spiked with anaerobic organisms however you do not exclude from the 'Anaerobic -(b)(4)- only' row the anaerobic -(b)(4)- which were spiked with aerobic organisms.

c. ---(b)(4)-- column:

Since the (b)(4) were either b(4) aerobic -(b)(4)- or b(4) anaerobic -(b)(4)- (depending on the spiked organism) we believe that only results of the actually tested --(b)(4)-- should be listed in this column. Based on your own definitions ---(b)(4)---------- ---------- column' and the 'Anaerobic -(b)(4)- only' should include a proportion of -(b)(4)-

We recommend you repeat the hypotheses testing taking into account the changes in items a, b, and c above, or that you provide justification for the approach that you have presented in your Feb 23, 2009 response.

V. Labeling

Ultimate labeling for your submission will be a reflection of the basis of approval of

your product.

VI. Toxicology/Leachable materials (Review by Dr. Jaro Vostal)

1. The toxicological evaluation of leachables from PL 2411 plastic platelet additive storage bag should be based on animal studies that defined a toxic dose of an IV administered compound and on the anticipated clinical application of the device. The WHO allowable daily intake for ---(b)(4)---------- applies to oral dosing and is not appropriate for IV application.

2. Please calculate the safety margin for --(b)(4)------ based on toxicity reports (LD50) of an IV administered --(b)(4)------. The calculation should be based on leachables from a 500 ml bag stored with platelets for up to 5 days and a 70 kg patient.

3. Please perform the same calculation for ----(b)(4)---------- using an IV toxic dose (LD50) derived in animal experiments.

4. Please identify the source of ----(b)(4)----------. Could the ink or the adhesive of the label be a source of these compounds?

5. Have the ink and the adhesive been FDA- approved for use on other bags?

6. What is the measured level of -----(b)(4)----- in a platelet products stored up to 5 days at room temperature?

References

1. FDAAA, sec. 918, Referral to advisory committee
2. Eder *et al*. Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross experience (2004-2006) Transfusion 2007;47:1134-1142.
3. Murphy *et al.* Screening platelet concentrates for bacterial contamination: low numbers of bacteria and slow growth in contaminated units mandate an alternative approach to product safety. Vox Sanguinis 2008;95:13-19.