STATISTICAL REVIEW AND EVALUATION

Date of the review: 7/24/09

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.

Sponsor: Fenwal Inc.

From: Paul B. Hshieh, Ph.D.

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

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

To: Salim Haddad, Medical officer.

cc: HFM-219/ Ghanshyam **Gupta**
HFM-215/ Henry Hsu
HFM-215/Chronnological File

Executive Summary:

1. This review is to comment on the Fenwal's responses to the FDA letter dated 4/06/2009.
2. The detail of comments, suggestions and requests to sponsor and clinical reviewers are all stated following on each Fenwal's responses.
3. Two important issues are stated:
    a. Since the design is paired, the unpaired test is not appropriate.
    b. For the evaluation of in vitro parameters, the lower bound of two-sided 95% confidence interval should be computed based on the hypotheses formulation (Test-0.8*Control).
4. To verify the results of the growth curve analysis, the following information are requested:
    - The data which is ready to be analyzed.
    - All SAS programs which were used (a) to generate all the results of the growth curve analysis and (b) to do all hypotheses testing.

Clinical and Statistics:

18) --(b)(4)--------- of the Platelet products:
a) In your March 11, 2009 facsimile letter you indicate that 'amendment 1' had two incomplete collections and five non evaluable products in the test (PAS III) arm using the Amicus device. Therefore we conclude that out of 101 initial collections seven 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 5.05%.

In 'amendment 2' all procedures were collected using the PAS III. Two of 50 collections were excluded from the study results due to -(b)(4)--, for a rate of -(b)(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 increase in the --(b)(4)----------rate for both test and control arms in the current FCRP-0106 study compared to your previous study FCRP-0303 we may recommend that, following a potential future approval of your solution and its clinical use, you conduct a post marketing ----------(b)(4)------ rate in the collected products.
Details of the post marketing evaluation would be discussed with FDA.

Fenwal appreciates FDA's concern regarding the number of -(b)(4)------ products in the study, but as reported in the literature, the degree of --(b)(4)------ observed in the PAS III clinical studies is not different than seen with platelet products stored in 100% plasma. In a previous study by ---(b)(4)---------- of the normal donor population exhibited varying ---------(b)(4)---------- This response correlated with the degree of frequency that donors exhibited ---(b)(4)----------during apheresis donation. It has also been observed that 2-10% of the normal population exhibits ---(b)(4)----------, an autosomal dominant disorder1. Additionally, in the US Customer Evaluation for AMICUS HUSW Version 3.0 where all platelet products were stored in 100% plasma, --(b)(4)------ was reported in 7 products out of -(b)(4)- evaluable procedures (2.9%).
It is notable that the relative comparison between the PAS III and plasma collections in FCRP-0106 Amendment 1 showed no difference in --(b)(4)----- based on storage solution (total of 5 paired products with --(b)(4)-------). Furthermore, for the additional 2 PAS III collections with --(b)(4)---------- noted in FCRP-0106 Amendment 1, the investigator believed the issue was subject related and the plasma collections were not started. Fenwal also recognizes the rates of --(b)(4)---------- observed in this study may appear to be higher than in FCRP-0303 (1/80 collections = 1.25%), but if the donor that participated in FCRP-0106 Amendment 1 that resulted in -(b)(4)----- was not included in FCRP-0106 Amendment 2, the observed --(b)(4)------ would have been 1/49 collections, for a rate of 2.04%. As such, we have compared the ---(b)(4)---------- between our most recent studies in a pairwise fashion, and found no significant differences in the rates

of ---(b)(4)---------. After controlling for multiplicity by adjusting the Type I error by $\binom{5}{2}$=10, that is, after controlling for multiplicity, there is overlap in the confidence intervals for --(b)(4)-------- for each study. These confidence intervals are one-sample and based on the two-sided normal approximation to the binomial probability density function.

Study	Treatment	Two-sided, n/N (%)	99.5% CI
FCRP 0106 Amend 1	PAS III	7/101 (6.93%)	(0.00, 14.02)
	Plasma	5/99 (5.05%)	(0.00, 11.23)
FCRP 0106 Amend 2	PAS III	2/50 (4.00%)	(0.00, 11.78)
FCRP 0303	Plasma	1/80 (1.25%)	(0.00, 4.74)
Customer Evaluation	Plasma	7/238 (2.94%)	(0.00, 6.02)

Comments to FDA clinical reviewer:

1. For the multiple comparison purpose, the 99.5% CI was computed by adjusting the Type I error by $\binom{5}{2}$=10; however, the statistical approach is not appropriate for two reasons.
    a. The multiple comparisons are not pre-planned in the clinical trial.
    b. The data were collected in different clinical trials. The objective of each trial might be different. They are not appropriate to be compared to each other.
2. The results of FCRP 0106 study in Amend 1 are appropriate for --(b)(4)------- comparison between PAS III and Plasma.

19) In vitro results:
b) Statistical analysis:
i) 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: January 9, 2009, Fenwal questions. Based on these hypotheses formulation we have generated the following table: (table omitted) The 95% confidence intervals that are generated by this table are different from the ones that you have calculated. Please provide an explanation.

The Fenwal results from the 20% post-hoc analyses differ from the FDA results for two reasons:
(1) Fenwal presented results on the two-sample t-test, as noted in the footnote of the associated table and agreed to by the FDA in the letter dated January 23, 2009. The FDA appears to have presented results using the paired t-test.
(2) Fenwal presented results for two one-sided 95% confidence limits based on ICH guidelines and as noted in the applicable column headers of the analysis table. The FDA appears to have presented two one-sided 97.5% confidence limits.

Although these methods differ, the same conclusions for both sets of 20% analyses were reached for all of the assays presented, thus supporting the safety and effectiveness of InterSol solution (PAS III) for its intended use.

Comments to sponsor:

1. Since the design is paired, the unpaired test is not appropriate.
2. In our January 23, 2009 communication we indicated that the acceptance criteria should be based on the lower bound of the two-sided 95% confidence interval.
3. For the evaluation of in vitro parameters, the two-sided 95% confidence interval should be computed based on the hypotheses formulation (Test-0.8*Control). Please comment.

ii) We have not received a response to question 2 in section 'Amendment 3' (page 8 of FDA's January 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:
(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.
Please provide the previously requested information.

Item (1): Fenwal provided the requested information to the FDA in regards to the above correspondence on December 23, 2008. Please see the references below.
Guenther, W.C. (Feb., 1970). Determination of sample size for distribution-free tolerance limits. *The American Statistician*, 24, 44-46.
Somerville, P.N. (1958). Tables for obtaining non-parametric tolerance limits. *Annals of Mathematical Statistics*, 29, 599-601.
Item (2) and Item (3): Fenwal provided the requested information to the FDA in regards to the above correspondence on January 23, 2009. Fenwal previously provided the SAS analysis dataset for the production of Table 11.4a on January 23, 2009, entitled EFFSUM.sas7bdat. Please see this information below.
SAS Code Used to Generate Tolerance Interval in Table 11.4a.

Comment: The response is acceptable.

20) Irradiation study:
a) Comparison of test vs. control:
Based on FDA 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 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: (table omitted).

The 95% confidence intervals that are generated by this table are different from the ones that you have calculated. Please provide an explanation.

The Fenwal results from the 20% post-hoc analyses differ from the FDA results because Fenwal presented results for two one-sided 95% confidence limits based on ICH guidelines and as noted in the applicable column headers of the analysis table. The FDA appears to have presented two one-sided 97.5% confidence limits.
The FDA analysis resulted in not being able to claim non-inferiority for LDH and Extent of Shape Change, while the Fenwal analysis resulted in not being able to claim non-inferiority just for Extent of Shape Change. Fenwal does not believe that the observed differences in mean values, 233 (Irradiated) / 223 (Non-irradiated) for LDH, and 8.3 (Irradiated) / 10.7 (Nonirradiated) for ESC are clinically significant.
As stated in our previous response of 12 February 2009, Fenwal concurs with FDA's own position as noted in the FDA Workshop on Use of Radiolabeled Platelets for Assessment of In vivo Viability of Platelet Products presentation, *in vitro* parameters are not valid surrogate endpoints for clinical endpoints, and in this case Fenwal has met the gold standard endpoint of *in vivo* recovery and survival.

Comments to sponsor:

1. In our January 23, 2009 communication, we indicated that the acceptance criteria should be based on the lower bound of the two-sided 95% confidence interval.

Growth Curve Study:

Objective:
The objective of this study was to determine if the growth kinetics of a select panel of bacteria were different in apheresis platelets stored in platelet additive solution PAS III compared to the kinetics in apheresis platelets stored in plasma.

Methods:
This study was executed as described in ------(b)(4)----------, December 2, 2008 found in Appendix A. The detailed methods for seeding and recovery can be found in Appendix B and Appendix C.

Statistical Methods:

- -------(b)(4)----------
- ----(b)(4)----------
- ----(b)(4)----------
- ---(b)(4)----------

- ----(b)(4)----------

Results and discussion:

The results were discussed on pages 215-217 of 279 in the submission.

Comments to sponsor:

- To verify the results of the growth curve analysis, the statistical reviewer would like to request the sponsor to provide the following information:
  1. The data which is ready to be analyzed without further data manipulation. The data should include all necessary parameters.
  2. All SAS programs which were used (a) to generate all the results of the growth curve analysis and (b) to do all hypotheses testings.

Note: The following is to comment on the Fenwal's responses to the FDA letter dated 1/23/2009.

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.

Fenwal response: Each ---(b)(4)----- (anaerobic and aerobic) was compared to the overall result of --(b)(4)---- for a total of -b(4)- results. If either -(b)(4)- was positive, the overall -(b)(4)- was considered positive.

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 either -(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.

Fenwal 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)----------aerobic--b(4)---------- (p value=-(b)(4)-) and -(b)(4)- (p value=-(b)(4)-), respectively. Because these limits are greater than -0.055 (NI margin), each --(b)(4)-- is non-inferior to -(b)(4)-. This discrepancy does not impact the original conclusions.

Comments: The response is acceptable.