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Date: 23-Jan-2009

This Fax is regarding **BN080041** that was received by the agency on 04-Aug-2008 as an original NDA for your InterSol Solution. The reviewers have the following comments:

I. Platelet efficacy study for 5-day platelets stored in a mixture of 35% plasma/65% PAS III

1. FDA comments to the sponsor on the Protocol

a. In volume 2 on page 38 of 287, 2nd bullet from the top, you state that the storage fluid volume was based on -----(b)(4)----------. To our knowledge this appendix pertains only to platelets stored in plasma. Please indicate how was the storage fluid volume determined for the platelet products stored in the mixture of 35% plasma/65% PAS III.

b. In volume 2, page 38 of 287, bottom paragraph, you state that if --(b)(4)------ was observed, products were considered acceptable if --(b)(4)------- was resolved overnight. However in Amendment 2, volume 2, page 245 of 287 you state that the rest period, if --(b)(4)------- is observed, is limited to -(b)(4)- hours. Please 1) explain the discrepancy in handling the presence of ---(b)(4)--- between the two amendments, and 2) clarify the deviation pertaining to ---(b)(4)---- which is listed in volume 3, at the top of 211 of 220.

c. Protocol deviation, volume 3, page 211 of 220, "Samples not collected": If no autologous plasma samples were collected on the two listed subjects, please clarify which diluent was used to generate the in vitro data on these two subjects (----(b)(6)-------).

d. Sampling of day 5 product: Table 9.2a in vol. 2 page 29 of 287 (amendment 1) indicates that the weight of day 5 product is taken --(b)(4)---------, whereas Table 1 of amendment 2, vol. 2 page 274 of 287, shows the weight for day 5 product is taken --(b)(4)-------. Please clarify the discrepancy.

e. Day 1 sampling for microbial testing and white blood cell counts: Section 9.2.3.3 on page 33 of 287 states that such testing was conducted ---(b)(4)----------. However Table 9.2a

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on page 29 of 287, footnote 2 indicates that sampling was conducted --(b)(4)----------. Please clarify and provide rationale for testing pre- or post sampling.

f. Please specify the volume sampled on days 0, 1, and 5 to run the in vitro tests.

g. Platelet collection procedure using PAS III: The successive technical differences between collection in plasma and PAS III are not clearly elucidated, e.g. 1) how the machines are differently programmed in term of yield, volume, concentration, 2) The timepoint at which either plasma or PAS III are added to the collected product, 3) The concentration of platelets when plasma or PAS III are added, 4) the determinants of the fluid storage volume for both plasma and PAS III.

2. FDA comments to the sponsor on the in vitro studies

a. 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.

b. In volume 2, page 55 of 287, you state that an "an analysis of variance with repeated measures (Mixed Effects Model) for the 100% plasma control and PAS III test showed significant differences in treatment day interactions in some secondary in vitro parameters. The results are shown in table 14.8 on page 75/287. 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.

c. Table 14.3 The white blood cell count (/μL) at Day 1 in products collected in plasma are close to double that for products collected using PAS III. Please provide an explanation.

d. Table 14.6, Lactate Dehydrogenase (LDH): please provide an explanation for the doubling of the LDH levels for the products stored with PASIII (average increase of 116%). LDH levels in products stored in plasma increased on average by only 22%.

e. As we have previously indicated any future 510(k) clearance of a Fenwal container for the storage of Amicus platelets in 35% plasma/65% PASIII will be labeled based on the tested range of the bag specifications, and we have traditionally recommended that 30% of the testing occurs at the limits of the bag specifications in term of volume, concentration and yield (Reference April 25, 2006 meeting minutes and Nov 20, 2007 communication to Fenwal). The in vitro data that you have presented in this NDA may provide approval/clearance only for limited specifications on your platelet storage bag.

f. The bicarbonate decrease between day 1 and day 5 is smaller in PAS III than in plasma storage (Table 14.6). Please provide an explanation.

g. Data at site 2 showed 1) site-specific significant decreases in morphology scores between day 1 and day 5 for both plasma and PAS III (Table 14.18), 2) site-specific increase in white blood cell count (Tables 14.14 and 14.15). Please provide an explanation.

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h. Please explain the large volume removals/reductions that occurred from Day 0 to Day 1 (Appendix 16.3.2 Amendment 1). Examples include but are not limited to the following components:
    - -(b)(6)-: 71 ml in PAS component
    - -(b)(6)-: 146 ml in PAS component
    - -(b)(6)-: 133 ml in PAS component
    - -(b)(6)-: 109 ml in the -(b)(4)- component, 131 ml in the PAS component

i. Please explain the large volume discrepancies between the Plasma/PAS components and the Plasma only components after day 0. Generally the PAS component has less volume than the Plasma component from day 1 through day 5/7. Examples include but are not limited to the following pairs (Appendix 16.3.2, Amendment 1):
    - -(b)(6)-: plasma 304 ml PAS 269 ml
    - -(b)(6)-: plasma 217 ml PAS 183 ml
    - -(b)(6)-: plasma 271 ml PAS 212 ml
    - -(b)(6)-: plasma 339 ml PAS 235 ml

j. Please calculate the mean consumption or production rates for the biochemical parameters for both control and test products between day 1 and day 5 (Table 14.6).
k. Considering that CD 62 expression was higher in PAS III storage than in plasma, please indicate whether PAS III stored platelets demonstrated a higher incidence of --(b)(4)-----.
l. Based on previous discussions (communication March 08), we agreed to exclude the diabetic subject (# -(b)(6)-) in vitro results from analysis. In that same communication, and considering that other diabetic donors such as # -(b)(6)- from study FCRP 0303 did have an acceptable pH, we suggested that you make a proposal on how to address the concern over the quality of platelets collected by from diabetic donors.

II. Irradiation Study

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.
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 per of the study.
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.

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4. You have stated in vol. 2 on page 58 of 287 that a total of 21 subjects participated in both Amendments 1 & 2. Please identify those subjects.
5. Please explain the large volume removals/reductions that occurred from Day 0 to Day 1 (Appendix 16.3.1 Amendment 2). Examples include but are not limited to the following components:
    - -(b)(6)-: 154 ml
    - -(b)(6)-: 73 ml
    - -(b)(6)-: 92 ml
6. Please calculate the mean consumption or production rates for the biochemical parameters for both control and test products, day 1 through day 5 (Table 14.11).
7. Please identify which PAS units were irradiated at the higher dose.

III. Radiolabeling Study

Appendix 16.3.4 (volume 4 p 147 of 274) shows that the recovery and/or survival of the following subjects are higher for the stored test product than the fresh control:

- -(b)(6)-: Recovery of test > recovery of control
- -(b)(6)-: Recovery and survival of test > control
- -(b)(6)-: Recovery test > control

Please provide a possible explanation for these unusual results.

IV. Validation Study for the use of --(b)(4)---------- on platelet stored in 35% plasma/65% PASIII (vol. 4)

1. Bacterial spiking study:

Your spiking study determined the analytical sensitivity of your device based on targeting -(b)(4)- and -(b)(4)- CFU/ml of bacterial inocula into the platelet product. Recent studies such as the PASSPORT study, 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. This concern is especially relevant for new platelet storage solution. Out of such concern we recommended in our April 25, 2006 teleconference that you include a study to determine whether bacterial growth in platelets stored in plasma differs from that in platelets stored in a combination of plasma/platelet additive solution.

We recommend you conduct such a study by inoculating low bacterial targets ((b)(4) CFU/ml, the current estimated initial contamination level) in platelets and compare the time to detection and the bacterial growth curves in plasma and in 35% plasma/65% PAS III storage for the first 48 hours post inoculation by sampling every 12 hours (ideally split products from a double collection would insure a similar plasma environment). You may use two slow growing and two fast growing organisms to inoculate 5 different platelet products for each of the two storage conditions with 5 replicates per inoculum.

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2. Results (vol. 4, page 218 of 274)

You state, in the first paragraph, that --(b)(4)---------- had the lowest percent recoveries. In fact other organisms (e.g. --(b)(4)----------) had lower percent recoveries than --(b)(4)--- for both target concentrations.

You additionally state, in the first paragraph, that the actual concentrations for -(b)(4)---------- ---------- for the target concentration of -(b)(4)- CFU/ml were low. However those --(b)(4)----------were even lower, respectively at 10 CFU/ml and 15.5 CFU/ml.

Please indicate whether these observations would alter the primary data analysis that you performed using bacterial concentrations at -(b)(4)- CFU/ml.

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)---------- ---------- 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.
   b. Under sample size you state, in the last sentence of the paragraph, that the hypothesis will be tested --(b)(4)---- for each --(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.
   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 ---(b)(4)----------
   d. You conducted your hypothesis testing (vol. 4, p 218 of 274) using the --(b)(4)--- inoculum levels -(b)(4)- CFU/ml i.e. with a sample size of -(b)(4)-. Please indicate whether the results are statistically significant with this sample size as well as the statistical power of the study.

V. Labeling:

Final labeling will depend, as in all submissions, on the basis of the submission approval.

VI. Appendix:

For in vitro tests that do not have a pre-set standard, the study should be designed to

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demonstrate that the test platelets should not be worse than the control by 20% based on the mean response. The appropriate hypotheses and statistical methods should be stated clearly.

For parameters where a higher value corresponds to a better outcome, the hypotheses may be formulated as follows.

$H_0 : \mu_t - \mu_c \le -0.2\mu_c$ vs. $H_1 : \mu_t - \mu_c > -0.2\mu_c$ … (1)

or equivalently

$H_0 : \mu_t - 0.8\mu_c \le 0$ vs. $H_1 : \mu_t - 0.8\mu_c > 0$, … (2)

or

$H_0 : \mu_t / \mu_c \le 0.8$ vs. $H_1 : \mu_t / \mu_c > 0.8$, … (3).

where μ_t and μ_c denote the mean response of the test and control, respectively.
The acceptance criteria should be based on the 95% confidence interval for μ_t - 0.8 μ_c in (2) or μ_t/μ_c in (3). More specifically, the lower limit of 95% confidence interval for μ_t - 0.8 μ_c or μ_t/μ_c should be greater than 0 or 0.8, respectively.

For parameters where a lower value corresponds to a better outcome, the hypotheses may be formulated as follows

$H_0 : \mu_t - 1.2\mu_c \ge 0$ vs. $H_0 : \mu_t - 1.2\mu_c < 0$, (1)

or

$H_0 : \mu_t / \mu_c \ge 1.2$ vs. $H_1 : \mu_t / \mu_c < 1.2$ (2).

FDA RESPONSE TO SPONSOR'S DECEMBER 23, 2008 and JANUARY 9 2009 COMMUNICATIONS

Amendment 4: Jan 9, 2009 Fenwal questions

1. While hypotheses (1) and (2), listed below, are algebraically equivalent, we understand, per the ICH E9 Statistical Principles for Clinical Trials and EMEA guidance documents, that hypotheses (1) are concerned with establishing non-inferiority of test to control with an equivalence margin of 20%, and hypotheses (2) are concerned with establishing superiority of test to 0.8*control. Fenwal believes that the in vitro parameters should be evaluated using a non-inferiority analysis (Hypothesis 1). Does FDA agree?

$H_0 : \mu_t - \mu_c \le -0.2\mu_c$ vs. $H_1 : \mu_t - \mu_c > -0.2\mu_c$ (1)

$H_0 : \mu_t - 0.8\mu_c \le 0$ vs. $H_1 : \mu_t - 0.8\mu_c > 0$ (2)

FDA response: No. The acceptance criteria have been stated clearly and should be based on

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the lower limit of the 95% two-sided confidence interval for $u_t - 0.8u_c$ (or u_t / u_c).

2. Testing null hypotheses can be done using either one- or two-sided Type I error. Fenwal believes that the in vitro parameters should be tested using a two-sided Type I error, because the direction (lower or upper confidence limit) is not clearly defined for all assays. Does FDA agree that this is the appropriate analysis?

FDA response: See above.

3. The null hypotheses can be tested using a two-sample test or a paired test. In FCRP-0106 Amendment 1, because these are were two separate collections Fenwal believes the analysis should be based on a two-sample (independent) test. In FCRP-0106 Amendment 2, the Test (gamma irradiated) and Control (non-gamma irradiated) groups were obtained during one collection, therefore, Fenwal believes the analysis should be paired. Does the FDA agree with these methods of statistical testing?

FDA response: Yes.

4. The FDA has requested additional analyses on biochemical (not including pH) and functional parameters from FCRP-0106 Amendment 1 and Amendment 2 gamma irradiated versus non-gamma irradiated. Fenwal believes that these parameters should be only analyzed using the end of storage values for the Test and Control. Does FDA agree with this interpretation?

FDA response: Yes.

5. In regards to the 20% analysis of Test versus Control, in FCRP-0106 Amendment 1 the platelet products were obtained in two separate collections. The acceptance criteria for evaluability of the "paired" products did not take into consideration that this analysis would be conducted since it was not specified in the protocol. Since the Test product was collected in an additive solution and contains only 35% plasma Fenwal believes that glucose and bicarbonate should not be included in the 20% analysis for Amendment 1. Does the FDA agreement with these omissions for analysis?

FDA response: Yes

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6. Testing null hypotheses can be done using either parametric confidence intervals based on the mean or non-parametric confidence intervals based on the median. Fenwal believes that the biochemical and functional parameters from FCRP-0106 Amendment 1 and Amendment 2 should be tested using non-parametric confidence intervals based on the median due to small sample sizes, type of testing, and distributional properties. The studies FCRP-0106 Amendment 1 and FCRP-0106 Amendment 2 were not statistically powered to detect the desired effect of 20% for any given parameter (i.e., no multiplicity adjustment) because these parameters were collected only to ascertain supplemental information. These parameters are neither primary nor secondary endpoints. Does FDA agree that this is the appropriate analysis?

FDA response: The sample size of more than 30 in each group should be large enough to use parametric confidence intervals. However, the nonparametric confidence intervals are also acceptable but please provide us the detailed formulae.

Amendment 3 (12_23_2008).

2. **On page 53 of 287, the non-parametric method was used to compute the lower 95/95% tolerance limit of pH, please provide the formula for this calculation.**

The steps by which the non-parametric lower 95/95% tolerance limit for pH was calculated is provided in **Attachment 2**.

FDA response: The steps to compute lower limit of 95/95% tolerance limit for pH with non-parametric approach has been reviewed (Amendment 003, attachment2), however, please 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 and pH data.

Please provide a response at your earliest convenience, preferably by COB Thursday 12-Feb-2009. We appreciate your assistance regarding this matter. If you have any questions, please feel free to contact Heather Erdman at 301.827.6182.

Thanks,
Heather Erdman, RAC
Regulatory Project Manager
FDA/CBER/DBA/OBRR/RPMB

Information provided by: Transmitted by H. Erdman Date _____

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