REVIEW MEMORANDUM

NDA 080041

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

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I. Background and Introduction

Currently in the United States platelets are stored in plasma for the shelf-life of the product. In the last 25 years alternate storage solutions with a range of plasma concentrations have been proposed. In 1995 Plasma Additive Solution (PAS) II was the first solution used in European blood centers to store pooled buffy coat platelet products. PAS II contains acetate as a nutrient for the platelets, citrate to prevent clumping and activation, and sodium chloride for osmolarity.

PAS III (InterSol®) is similar to PAS II with the addition of phosphate. The PAS III formulation is currently used in Europe as a processing solution in the pathogen inactivation process INTERCEPT Blood system for platelets (SPRITE studies). PAS III has also been approved in a number of European countries as a stand alone configuration (i.e. independent of pathogen reduction) for the storage of platelets in a fixed mixture ratio with plasma.

InterSol® is an isotonic solution composed of:

- Dibasic Sodium Phosphate Anhydrous, USP
- Monobasic Sodium Phosphate, Monohydrate, USP
- Sodium Citrate, Dihydrate, USP

- Sodium Acetate, Trihydrate, USP
- Sodium Chloride, USP
- Water for Injection, USP

It has no pharmacologic effect in vivo, it is used only for the storage of platelets in a volume ratio of InterSol/plasma of 65%/35%. Since all the ingredients of the solution were all previously independently approved by CDER, this NDA was not presented to the Blood Products Advisory Committee and this was based on the criteria of Section 918 of FDAAA.

In 2006 FDA approved Fenwal's IND -(b)(4)- submission which proposed a protocol to study the use of a 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 -(b)(4)- days (Fenwal Study "FCRP 0106, Amendment 1"). Prior to the IND submission FDA had held pre-IND meetings with the sponsor.

In September 2007 Fenwal submitted to FDA, in a pre-application package, recovery and survival data on their -(b)(4)- day platelets generated from IND -(b)(4)--. The data did not meet FDA criteria for either outcome. Subsequently Fenwal submitted an amendment to the original IND -(b)(4)- protocol to study 5-day platelets stored in 65% PASIII /35% plasma rather than -(b)(4)- day, and to study the effect of irradiation on 65% PASIII /35% plasma stored platelets (Fenwal Study "FCRP 0106, Amendment 2").

Since the receipt of the current submission on July 31 2008 FDA conducted an extensive interactive review process with the sponsor through faxes and teleconferences which culminated in a Complete Response letter dated April 6 2009. Subsequently FDA held additional communications with the sponsor to address the outstanding issues.

This review memo is focused on the clinical studies of the submission:

1) The platelet efficacy study for 5-day platelets stored in a mixture of 65% PASIII/35% plasma (volumes 2, 3, and 4).

2) Study to evaluate the effect of irradiation on platelets stored in 65% PASIII/35% plasma.

3) The validation study for use of the ---(b)(4)---------- on platelet stored in 65% PASIII/35% plasma (vol. 4).

4) Labeling (vol. 5).

FDA evaluation of this submission also included reviews on Chemistry, Manufacturing and Controls (CMC), Sterilization and packaging, toxicology, manufacturing inspection, BIMO, and Proprietary Name Review (PNR). These

sections were reviewed by appropriate FDA personnel and were determined to be adequate. The corresponding formal review memos are available on file.

II. Platelet efficacy studies for 5-day platelets stored in a mixture of 65% PAS III/35%plasma: AMENDMENTS 1 & 2

As mentioned above, Amendment 1 studies included data on the test platelets stored up to -(b)(4)- days, including data on 5-day. However this NDA seeks FDA approval only for 5-day platelets. Thus amendment 1 in this submission includes the in vitro results on 5 day platelets. In vivo data on 5 day platelets were conducted under amendment 2.

For efficacy studies the primary parameters are in vivo recovery, in vivo survival, and in vitro pH.

A. In vivo radiolabeling studies for 5-day test platelets

Using FDA standard on platelet radiolabeling (i.e. recovery and survival compared to a "fresh" platelet sample as control drawn and prepared on day of reinfusion of radiolabeled test samples, a.k.a. "Murphy standard) the 5-day test product showed successful results for both recovery and survival.
(FDA success criteria: 95% LCL of Test/Control ratio: > 66% for recovery and > 58% for survival).

- Recovery ratio at 5 days: successful [mean recovery ratio: 80%; 95% LCL of test/control > 66%]
- Survival ratio at 5 days successful [mean survival ratio: 71%; 95% LCL test/control >58%].

B. In vitro results

For in vitro testing the **control** consisted of an apheresis platelet product collected from the same donor (paired control) and stored in **100% plasma.**

a. pH (primary parameter): FDA success criterion for pH is $\geq$ 6.2

All 70 test product samples had pH at 5 days $\geq$ 6.9 (range 6.9-7.5) with a mean of 7.2.

b. Out of the remaining in vitro test parameters three exceeded a 20% relative difference between test and control at 5 days:

- CD62 at 5 days (marker of activation): Test 11.3% ± 5.8; Control 8.1% ± 5.0
- Hypotonic shock response at 5 days: Test 52.8% ± 9.1; Control 67.3% ± 9.5
- Extent of shape change at 5 days: Test 13.3% ± 6.8; Control 23.3% ± 4.7.
- Additionally, test platelets showed higher LDH release during 5-day storage than control platelets (116% vs. 22% increase).

C. Test and Control Product ---b(4)------

The ---b(4)-------- in the collected products leading to the discard of the product was respectively 6.9% and 5.05% for test (PASIII/plasma) and control (plasma) products. The --b(4)-------- was 1.25% in 2003 for platelets collected in 100% plasma using the same apheresis device.

D. Safety of the drug

Toxicology of the PAS III solution itself and of its container bag was assessed and was found acceptable. Evaluation of available data from Europe on patients transfused with platelets stored in InterSol/plasma revealed no concerning safety issues.

E. Additional studies

Results of a recently concluded Dutch study comparing buffy-coat platelets stored in plasma vs. InterSol/plasma revealed that platelet corrected count increments (CCI) associated with InterSol/plasma were about 10% lower than in plasma however there was no significant difference in bleeding.

FDA assessment of the 5-day results:

The study passed the primary parameters which have defined acceptance criteria i.e. in vitro pH, in vivo recovery and in vivo survival.

In vitro parameters other than pH have no well-defined absolute FDA acceptance criteria. The reason is that while these parameters are useful in characterizing the product, a strict correlation between their values and the ultimate quality of the product has not been clearly established in the literature[1]. Some correlate better than others. Therefore these parameters are compared to a concurrent control (platelets stored in plasma) and a relative difference of less than 20% between test and control for each of these parameters is deemed not clinically relevant. A difference of > 20% in some in vitro parameters may be clinically meaningful.
Out of 10 parameters 4 parameters compared unfavorably to the control: CD62 which is a marker of activation of platelets, Extent of shape change and Hypotonic shock response which measure the physiologic response of platelets placed under stress. Lactate dehydrogenase release was also increased in the test platelets. Based on the literature the significance of these findings is unclear[1] but all were against the InterSol.

This issue was discussed at the August 4 2009 CBER Blood meeting and in a subsequent meeting with OBRR leadership (Drs Jay Epstein and Ginette Michaud on August 27 2009). The review of the available safety data in the submission and in the lierature[3,4] and on the use in Europe of InterSol as a platelet storage solution in combination with plasma revealed no undue concerns. However considering the limited safety data, the unusual results of some in vitro parameters, and that InterSol would be the first such solution in the U.S. FDA requested a post marketing evaluation of the test product to characterize further its safety profile.

The post marketing evaluation was discussed at the CBER Safety Working Group CBER SWG) on October 8, 2009 which determined that adverse events in the recipient will be tracked in a post marketing requirement (PMR) based on section 901 of FDAAA and the July 2009 FDA Guidance "Postmarketing Studies and Clinical Trials—Implementation of Section 505 (o) of the FD&C Act". The relevant criterion to mandate the PMR was FDA concern "to identify an unexpected serious risk when available data indicates the potential for a serious risk".
CBER SWG also determined that a post marketing commitment (PMC) would --b(4)---------- in the collected as this does not constitute a safety issue. Concurrence by CDER SWAT team was obtained.

The sponsor was informed and accepted FDA's decision regarding the post market studies. The sponsor committed in a Nov 12 2009 communication to FDA to conducting a study that would address FDA's concerns regarding the adverse event rate in the recipient and the --b(4)---------- the collected product.

F. Referral to Advisory Committee

Referral to the Advisory Committee was waived based on sec. 918 of FDAAA which states that, 'prior to the approval of a drug no active ingredient of which has been approved in any other application under this section or section 351 of the PHS Act, the Secretary shall refer such drug to FDA Advisory Committee'. All ingredients of the InterSol solution have been previously approved by CDER.

III. Study to evaluate the effect of irradiation on platelets stored in 35% plasma/65% PASIII (Amendment 2)

Amendment 2 recruited 50 donors and yielded 43 procedures with all products collected in 65% PASIII/35% plasma, 18 of which were double collections, and 25 single collections. The 18 paired products were used to study the effect of irradiation on platelets stored in 65% PASIII/35% plasma.

In previous discussions FDA had indicated to the sponsor that in order to obtain a claim for irradiated products both in vitro and in vivo data need to be conducted and meet FDA criteria. The sponsor indicated that they were seeking no claim and that they would be conducting only in vitro studies. Therefore it was mutually agreed that labeling would include the results of the in vitro study without a claim and a

statement that in vivo studies were not conducted and that in vitro studies are not indicative of in vivo performance.

Except for LDH and extent of shape change (ESC) in vitro testing results of the irradiated product closely mirrored that of the control. The range of platelet yield for test product was mainly between 2.5 $x10^{11}$ and 3.5 x 10^{11} platelets, with one product < 2.5 x 10^{11} and two > 3.5 x 10^{11} platelets.

IV. The validation study for use of the ---(b)(4)---------- on platelet stored in 65% PASIII/35% plasma

A traditional bacterial spiking study was conducted with -(b)(4)- bacterial organisms using ---(b)(4)----- aerobic and anaerobic -(b)(4)-. The detection and sensitivity of ---(b)(4)---------- in InterSol was comparable to that in plasma. Additionally, FDA requested from the sponsor a comparative bacterial growth study in InterSol/plasma vs. plasma. Using organisms selected based on clinical reports of bacterial contamination paired apheresis platelets were spiked with low CFU/ml (-(b)(4)--CFU/ml). The spiked units were sampled every -(b)(4)- hours ---(b)(4)------- and CFUs were plotted against time. -(b)(4)- parameters were compared between InterSol/plasma and plasma: lag time, doubling time, maximum CFU concentration, time to maximum concentration. The results showed that:

- Lag time shorter for InterSol/plasma
- Doubling time: small statistical difference between plasma and Intersol/plasma in favor of plasma
- Max concentration and Time to max concentration: no statistical difference
- At -(b)(4)- hours bacterial concentration -(b)(4)- logs higher in InterSol/plasma than in plasma.

Based on these results bacterial detection in InterSol/plasma stored platelets was determined to be adequate and may compare favorably to 100% plasma storage.

V. Labeling

Labeling changes were made at FDA's request to reflect the study outcomes.

VI. Summary and Conclusion

This is a New Drug Application from Fenwal to gain approval for a new (first in US) platelet additive solution (PAS III or InterSol®) for the storage of Amicus-derived apheresis platelets in a mixture of 65% PAS III/35% plasma for up to 5 days. The sponsor submitted studies which met FDA criteria demonstrating the efficacy of these platelets at end of 5-day storage. Additionally the sponsor showed that the ---(b)(4)--------- device, which was previously cleared for detecting bacteria in platelets stored in plasma, similarly detects bacteria in a mixture of 65% PAS III/35% plaasma. The sponsor agreed to a post marketing requirement to track the transfusion reaction rate in the recipients and to a post marketing commitment --b(4)----------

---------- in the collected product. FDA review of the other disciplines in the submission was equally satisfactory.
Based on the above I recommend approval of this NDA.

References

1. Rinder HM, Smith BR. In vitro evaluation of stored platelets: Is there hope for predicting posttransfusion platelet survival and function? Transfusion 2003;43:2-6.
2. Workshop on Use of Radiolabeled Platelets for Asessment of In Vivo Viability of Platelet Products, accessed at www.fda.gov/downloads/BiologicsBloodVaccines/Newsevents/WorkshopsMeetingsConferences/TranscriptsMinutes/UCM054447 , p 29/357.
3. Andreu G et al. “Introduction of platelet additive solutions in transfusion practice”. Transfusion Clinique et Biologique 2007: 100-106.
4. Rebibo D, et al. Introduction of platelet additive solution in platelets: towards a decrease in transfusion reactions. Transfusion Clinique et Biologique 2008: 289-293.