Summary Basis for Regulatory Action

Date: December 7, 2009

From: Salim A. Haddad, MD, Chair of the Review Committee

NDA#: BN080041/0

Applicant Name: Fenwal, Inc.

Date of Submission: July 31, 2008

PDUFA Goal Date: December 12, 2009

Proprietary Name/ Established Name: InterSol Solution/ Platelet Additive Solution 3

Indication: Storage of Amicus apheresis platelets in a mixture of 65% InterSol/35% plasma for up to 5 days

Recommended Action: Approval

Signatory Authorities Action:

Office Signatory Authority: Jay S. Epstein, MD, Director, OBRR _____

☐ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted	**Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date**
Clinical Review	Salim Haddad, CBER/OBRR/DH/LCH - Nov 24, 2009
Clinical Pharmacology Review	N/A
Statistical Review	Paul Hshieh and Tie-Hua Ng, CBER/OBE - Nov. 13, 2009
CMC Review	Ying Wang (Chemistry-CDER) - Nov. 9, 2009 Randa Melhem (Sterility/Container closure CBER/OCBQ/DMPQ)-Nov. 8, 2009
Pharmacology/ Toxicology Review	Jaro Vostal, CBER/OBRR/DH/LCH - Jan 29 2009, July 15 2009, July 27 2009, Nov 24 2009
Biomonitoring Review	Janet White, CBER/OCBQ - June 22, 2009
Establishment Inspection Report	Noreen Muniz, ORA - Feb. 23, 2009
Advisory Committee Transcript	N/A
Proprietary Name Review	Catherine Miller, OCBQ/DCM/APLB - Oct. 13, 2009

1. Introduction

This summary basis of regulatory action (SBRA) pertains to a new drug application for a novel platelet additive solution (PAS 3, InterSol® Solution) to be used for the storage of AMICUS apheresis platelets for up to 5 days in a container with a solution composed of 35% plasma/65% PAS 3.

This document will cover the disciplines of Chemistry Manufacturing and Controls (CMC), Toxicology, Clinical and Statistical aspects, Establishment inspection, Biomonitoring, and Proprietary name review.

2. Background

Up until the approval of this NDA platelets in the U.S. had been stored exclusively 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 3 (InterSol®) is similar to PAS II with the addition of phosphate. The PAS 3 formulation is currently used in Europe as a processing solution in the pathogen inactivation process INTERCEPT Blood system for platelets (SPRITE studies). PAS 3 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 has no pharmacologic effect in vivo; it is used only for the storage of platelets in a volume ratio of 65% InterSol/35% plasma.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The Chemistry, manufacturing and control (CMC) section of this application was reviewed by both CDER Office of New Drugs Quality Assessment as a consult review for all CMC sections except Sterilization and container closure, and by CBER/OCBQ/DMPQ for the Sterilization and container closure sections.

i. CMC (except Sterilization and container closure)

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

The chemical raw materials for InterSol solution are purchased from suppliers and are certified as USP compliant salts. All raw materials are sampled and tested to assure conformance to USP specifications per applicable monograph. The salt substances used as raw materials in InterSol solution are stored in tightly sealed containers as specified in the USP.

The Fenwal, Inc. facility at Maricao, Puerto Rico is designated as the manufacturing facility for InterSol solution drug product. Packaging, labeling and sterilization operations, as well as all quality control tests, are conducted at this facility.

Manufacturing process, process controls, filling and final assembly of the InterSol solution container are found satisfactory.

--(b)(4)--stability batches manufactured at the commercial site at the commercial scale were submitted. The stability data support the proposed ---(b)(4)- expiration date.

An interactive review process was conducted with the sponsor and was concluded to FDA's satisfaction.

ii. Sterilization and container closure integrity and sterility

The commercial container/closure system for InterSol Platelet Additive Solution is comprised of a PL 2411 --(b)(4)-- plastic container with a --(b)(4)-- co-extruded port --(b)(4)---------- Twist-off Protector (TOP) closure which ---(b)(4)---------- co-extruded port after the container has been filled.

--(b)(4)--- sterilization validation studies and qualification studies were performed to validate the 500 mL InterSol solution in the investigational configuration container.

The autoclave design, cycle parameters, and routine process control and validation procedures were in accordance with the current -----(b)(4)----------. Cycles were developed and validated to provide a minimum Sterility Assurance Level of at least -(b)(4)-

InterSol solution was sterilized in ---(b)(4)---------- in order to maintain the integrity of the –(b)(4)--------- assemblies. ----(b)(4)----------

----------(b)(4)----------The final product qualification study consisted of three parts: temperature distribution, heat penetration and biological challenge. Microbiological monitoring was established for production areas and for products components and process water. A spore suspension of ---*(b)(4)*---------- was used as the biological indicator (BI) challenge organism for sterilization processes for validations of all solution drug products manufactured at the Maricao, PR plant, including InterSol solution.

A licensed -(b)(4)- reagent was used to perform the -(b)(4)---- assay and the --(b)(4)---------- assay in their validation studies for the ----(b)(4)---------- assays for bacterial endotoxins.

Sterility and ---(b)(4)------ level are part of the InterSol stability program. They are tested at release and then again at end of shelf-life.

In terms of final product release criteria, the sterilization cycle parameters are validated, and thus InterSol solution product will be parametrically released during commercial production.

Container closure and package integrity is in compliance with FDA Guidance.

Through the interactive process the sponsor addressed satisfactorily all issues raised by CBER/OCBQ/DMPQ reviewer.

b) CBER Lot Release

CBER lot release does not apply since each collected blood product is traditionally considered to be manufactured from a single product lot.

c) Facilities review/inspection

The inspected Fenwal manufacturing site was located in Maricao, Puerto Rico. It is FDA registered as a medical device and drug manufacturing establishment.
The Field Establishment Identifier (FEI) number is 2627511 and the inspection dates were Jan 21 to Feb 2, 2009.

The inspection disclosed two observations pertaining to:

1. Control procedures to monitor and validate performance:

    a. Failure to document -(b)(4)---filter validation exercises associated with the InterSol solution and all solutions manufactured on site.
    b. Failure to document and conduct evaluation of cleaning activities for the NDA solution.

2. SOPs not followed/documented: failure to document Clean in Place validation exercises.

Fenwal addressed item 1a by providing FDA with extractable data from the -----(b)(4)---filter which FDA found satisfactory. For item 1b Fenwal provided documentation which FDA inspector determined to be acceptable. Fenwal's response on item 2 was acceptable as well.

d) Environmental Assessment

No adverse impact is expected on animals, plants, humans, other organisms, or ecosystems.

4. Nonclinical Pharmacology/Toxicology

a) Toxicology studies of the InterSol solution itself were assessed and found acceptable.
b) Studies on the leachables/extractable materials from the container plastics were evaluated and found adequate.
c) Extractable/leachable data from the ---(b)(4)--------- filter at the Maricao manufacturing site were found satisfactory.

5. Clinical Pharmacology

N/A as the drug has no inherent pharmacological effect.

6. Clinical/ Statistical

a) Clinical Program

Prior to the submission of this NDA FDA had reviewed and approved the study protocols under IND -(b)(4)-.

Efficacy studies consisted of in vitro testing and in vivo radiolabeling studies.

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

In recovery and survival studies of radiolabeled platelets as compared to "fresh" radiolabeled control platelet samples drawn and prepared on day of reinfusion of test samples the 5-day test product showed successful results for both recovery and survival. Success criteria are Test/Control ratio: > 66% for recovery, and > 58% for survival. These criteria are satisfied if the upper limit of a two-sided 95% confidence interval of the mean percent recovery of (0.66 Control – Test) is < 0 and the upper limit of a two-sided 95% confidence of the mean percent survival of (0.58 Control –

Test) is < 0. For the test product the mean recovery ratio was 80% and the mean survival ratio was 71%.

2. In vitro results

All parameters, except for pH, were compared to a concurrent control (platelets stored in plasma). 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. A non-inferiority statistical approach was used to assess the 20% difference.

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): success criterion for pH is $\geq$ 6.2 for 95% of the products with 95% confidence.

   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. Of the remaining in vitro test parameters, three demonstrated an unaccounted for 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 compared to control platelets (116% vs. 22% increase).

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

   The ---(b)(4)---------- and in vitro parameter values cited above prompted some concern about the safety of the product. However a review of the available European hemovigilance data (Transfusion Clinique et Biologique 2007: 100-106; Transfusion Clinique et Biologique 2008: 289-293; French annual hemovigilance report 2008) and randomized studies (Transfusion 2000; 40:398-403; Blood 2006; 108:3210-3215) on the use of either InterSol or other similar platelet additive solutions for storage of platelets revealed no alarming findings that would preclude approval of the product. Nevertheless, post marketing studies were considered necessary to track adverse events in the recipient and ----(b)(4)---------- ----------

Conclusions:

Efficacy: Demonstrated by successful outcomes in the primary parameters of pH, in vivo recovery and in vivo survival.

Safety: Platelets stored in InterSol or other similar additive solutions and transfused to patients raised no undue safety concerns.

In order to further track adverse events in the recipients of Amicus platelets stored in 65% InterSol/ 35% plasma, Fenwal committed to conducting a controlled postmarketing study (PMR) pursuant to Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) and consistent with the July 2009 FDA Guidance "Postmarketing Studies and Clinical Trials—Implementation of Section 505 (o) of the FD&C Act." Adverse events, i.e. transfusion reactions, will be captured through active surveillance of the test and the control products. Transfusion reactions will be classified and compared by type (e.g. TRALI, febrile non-hemolytic transfusion reaction, allergic reaction, etc…). Fenwal will conduct the postmarketing requirement at select institutions that are currently transfusing AMICUS platelets in plasma and are planning to switch to AMICUS InterSol platelets.

A complete statistical plan including hypothesis testing will be submitted with the final protocol as per the timelines outlined below:

Protocol Submission: Within 2 months after NDA approval and 510(k) clearance
Study Start: Within 3 months of acceptance by FDA of the final protocol
Final Report Submission: Within 17 months of initiation of the study

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3. Biomonitoring

The bioresearch monitoring inspections of the three clinical sites did not reveal problems that could impact the data submitted in the application.

b) Pediatrics

This application does not trigger PREA (21 U.S.C. 355c) requirements because it does not include new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration.

c) Other Special Populations

N/A

d) Overall Comparability Assessment

The drug substance is a collection of USP grade salts, all previously approved by CDER. Stability data, manufacturing process, process controls, filling and final assembly, and sterilization of the InterSol solution are found satisfactory. The preclinical data reveal no toxicological or biocompatibility concerns. Clinical data demonstrate the efficacy of platelets stored in InterSol. A few unusual in vitro findings however prompt FDA to require post marketing studies to assess adverse events in the recipients and ---------(b)(4)----------

7. Safety

Toxicology studies conducted on the PAS 3 solution itself and biocompatibility testing of the leachables/extractables plastic materials from its container bag were assessed and found acceptable. Evaluation of available European hemovigilance data (Transfusion Clinique et Biologique 2007: 100-106; Transfusion Clinique et Biologique 2008: 289-293; French annual hemovigilance report 2008) and randomized studies (Transfusion 2000;40:398-403; Blood 2006;108:3210-3215) on the use of either InterSol or other similar platelet additive solutions for the storage of platelets revealed no alarming safety issues.

8. Advisory Committee Meeting

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918]: REFERRAL TO ADVISORY COMMITTEE):

- All ingredients of the InterSol solution have been previously approved by CDER.

- The study design to evaluate efficacy of InterSol was adequate and the results of the study supports the storage of Amicus apheresis platelets in a mixture of 65% InterSol/35% plasma for up to 5 days.
- The use of InterSol as a stand-alone platelet additive solution has been approved in Europe since 2007. As a component of a pathogen reduction system for platelets InterSol has been in use in Europe since 2003. European hemovigilance data revealed no alarming safety issues.
- BPAC discussion of this application is unlikely to change the outcome of the review of this file from a regulatory standpoint.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

Final labeling of the package insert and directions for use reflects the experimental conditions and the outcome of the clinical studies.

A Proprietary Name Review was conducted by Advertising, Promotional, and Labeling Branch (APLB). APLB recommended that the proposed proprietary name, InterSol Solution, be found Acceptable with Concerns. The concern arose from similarity in pronunciation (Inpersol-irrigating solution for peritoneal dialysis) or spelling (Nutricel-Red cell preservative) or product characteristics (Adsol, Optisol, Nutricel- Red cell preservatives). The review team determined that the clinical concern is minimal.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The recommendation is for the approval of this NDA with 1) a post marketing requirement to conduct a controlled study to track the adverse events in the recipients and 2) ---------(b)(4)----------.

b) Risk/ Benefit Assessment

The clinical studies described above revealed that the levels of some in vitro parameters of the test product were significantly different from the control, namely CD 62, Extent of shape change (ESC), hypotonic shock response (HSR) and LDH release. The literature shows, in general, that in vitro parameters of platelets correlate poorly with their in vivo performance. Nevertheless the increase in CD62 which may

be indicative of platelet activation, along with the ----(b)(4)---------- of the collected product prompted FDA to require a post marketing study to follow any untoward effect on the test product.

Of all the in vitro parameters, ESC and HSR have shown the most correlation with in vivo performance. The low ESC and HSR values in this study were not unexpected as literature has shown that platelets stored in platelet additive solutions are associated with lower corrected count increment than platelets stored in plasma (Transfusion 2000; 40:398-403, Blood 2006; 108:3210-3215). However a Dutch study (Kerkhoffs J.L, Plenary Session Abstract Presentation AABB 2009, New Orleans) showed that while buffy coat platelets stored in InterSol have 10% lower CCI than plasma stored platelets, there was no difference in bleeding events between the two.

Increase in LDH release during platelet storage could theoretically be associated with platelet lysis. However the platelet count did not disproportionately decrease during storage in the clinical studies. Other studies have also shown that increase in LDH does not necessarily reflect platelet lysis (Infusion Therapy and Transfusion Medicine 2002; 29:193-198) or poor platelet quality (Transfusion 1997; 37:12-17).

Additionally, available European data on the use of InterSol or other similar platelet additive solutions for the storage of platelets raised no undue safety concerns (Transfusion Clinique et Biologique 2007: 100-106; Transfusion Clinique et Biologique 2008: 289-293; French annual hemovigilance report 2008; Transfusion 2000;40:398-403; Blood 2006;108:3210-3215).

c) Recommendation for Postmarketing Risk Management Activities

N/A

d) Recommendation for Postmarketing Activities.

The approval letter includes: 1) a post marketing requirement for the sponsor to conduct a controlled study to track the adverse event rate in the recipients; 2) -(b)(4)----------