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INTERNAL MEMORANDUM

DATE: Feb 21, 2012

FROM: Jan Simak, Ph.D.
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TO: Nisha Jain, MD

CBER Safety WG

SUBJECT: **Justification of PMR for CBER safety WG**

Submission type: NDA

BN 090067

Product Name: Isoplate Solution in the 500 mL EXCEL Container

Applicant/Manufacturing Site: B. Braun Medical Inc., Irvine, CA

Conclusion and Recommendation:

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 identified concerns meet one of the criteria of a PMR: “To identify an unexpected serious risk when available data indicates the potential for a serious risk”

Therefore we are requesting a post marketing requirement: To track the adverse events in the recipients of Isoplate platelets and compare them to a control. The study should have the same design as the PMR study for Intersol product.

Background:

Platelets are procured from donors either by preparation from a whole blood donation or through an automated apheresis procedure. This submission pertains only to platelets collected by Trima Accel system (Terumo). The NDA approval is dependent on 510(k) clearance of Trima Accel system for the collection of hyperconcentrated platelets.

Currently in the U.S. platelets, after their collection, are stored in the plasma of donors or in a newly approved platelet additive solutions (PAS) from Fenwal (BN080041). In Europe platelets are stored in a mixture of plasma and PAS. Potential benefits of the partial replacement of plasma with PAS are as follows:

- Increased availability of plasma for other uses (transfusion, fractionation)
- Reduction of adverse events associated with plasma administration (TRALI, allergies, NHTR, etc,...).

The benefit of reduction of adverse events associated with plasma administration has not been demonstrated in independent clinical studies and is very unlikely when PAS is used to replace just 65% of plasma, like in the case of the Isoplate.

The Isoplate Solution is identical to the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) an FDA approved sterile, nonpyrogenic intravenous injection packaged in B. Braun's EXCEL® Container and approved, as of September 29, 1989 (ANDA 19-696), for the following indication: For use in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent. Composition of Isoplate is different from Intersol.

ISOPLATE (B.BRAUN) PAS Composition

Each 100 mL contains:

| | |
|---|---------------|
| Dibasic Sodium Phosphate, Heptahydrate, USP | 12 mg |
| Monobasic Potassium Phosphate, NF | 0.82 mg |
| Sodium Acetate, Trihydrate, USP | 370 mg |
| Sodium Chloride, USP | 530 mg |
| Potassium Chloride, USP | 37 mg |
| Magnesium Chloride, Hexahydrate, USP | 30 mg |
| Sodium Gluconate, USP | 50 mg |
| Water for injection | qs |
| NaOH, Glacial Acetic Acid | pH adjustment |

INTER SOL (Fenwal) PAS Composition

Each 100 mL contains:

| | |
|--|--------|
| Dibasic Sodium Phosphate, Anhydrous, USP | 305 mg |
| Monobasic Sodium Phosphate, Monohydrate, USP | 93 mg |
| Sodium Citrate, Dihydrate, USP | 318 mg |
| Sodium Acetate, Trihydrate, USP | 442 mg |
| Sodium Chloride, USP | 452 mg |
| Water for Injection, USP | qs |

Review of the submission:

A multidisciplinary review determined that the submission is approvable. The reason for addressing CBER SWG is our request to consider a post marketing requirement for this submission related to results of *in vitro* testing of Isoplate stored platelets.

As a background platelets are evaluated through *in vitro* and *in vivo* studies conducted at the end of proposed storage period.

In vivo studies are considered the gold standard in term of assessing the quality of the product. They consist of radiolabeling the product, injecting them into volunteers and assessing the circulation of the platelets. The test product (i.e. platelets stored in Isoplate) passed FDA criteria for assessing circulation.

In vitro studies bench-top studies consist of measuring pH as well as other parameters which examine different aspects of platelet metabolism.

- pH, among all the *in vitro* tests, is considered a primary endpoint because it has a well-defined acceptance criterion: $\text{pH} \geq 6.2$.

- The other parameters have no well defined absolute 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. Some correlate better than others. Therefore these parameters are compared to a concurrent control (platelets stored in plasma) and FDA traditionally looks for an difference of no more than 20% between test and control for each of the parameters.

The *in vitro* Isoplate stored platelet quality study met the primary endpoint of $\text{pH} > 6.2$, but failed in one secondary endpoint, the surface P-selectin expression, which is more than 20% higher in the test group ($22 \pm 15.4\%$) compared to control ($15.1 \pm 9.1\%$). We believe that high P-selectin expression ($> 20\%$ higher compared to control) on 5 day Isoplate stored platelets is a significant finding that may have clinical consequences.

Similar finding of elevated P-selectin expression were observed in the Intersol stored platelets and PMR was issued for the Intersol product.

To assure clinical safety of the product, a postmarket study focused on platelet transfusion adverse events should be required in the same extent as required for Intersol.

Additional reason for PMR is a lack of clinical safety data for PAS stored platelets since the Isoplate will be the second approved PAS in the U.S. Composition of the Isoplate is different from Intersol and the PMR study of Intersol did not start yet.

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 identified concerns meet one of the criteria of a PMR: “To identify an unexpected serious risk when available data indicates the potential for a serious risk”

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