The Biomedical Excellence for Safer Transfusion Collaborative

# Evaluation of Potential New Plasma Products Manufactured Following Storage at Room Temperature for up to 24 Hours

## Blood Products Advisory Committee
## May 16, 2012



**The Biomedical Excellence for Safer Transfusion (BEST) Collaborative** is an international research organization that works collaboratively to explore ways to improve transfusion-related services through standardization of analytic techniques, development of new procedures, systematic review of evidence, and execution of clinical and laboratory studies. We currently operate in teams covering 5 areas: Conventional Blood Components, Transfusion Safety, Clinical Studies, Cellular Therapy, and, our newest team, Donor Studies. We have 42 scientific members from 10 countries representing a diversity of interests and high levels of accomplishment. The supporting members of BEST span a broad range of the companies and blood suppliers engaged with blood collection, distribution and transfusion worldwide. We also have been pleased to have some participation from regulatory agencies such as FDA and the Paul Ehrlich Institute. BEST has published over 66 peer reviewed papers and has over 25 studies currently open. The results of our studies have been brought before BPAC several times, as exemplified in the presentation by two of our scientific members here today. As part of our mission, BEST believes it brings to the community thoughtful consideration to identify important questions in Transfusion Medicine, design and execute studies to address these questions, and provide critical thought and synthesis of the available evidence.

BEST is making comment on three areas relevant to the topic being covered today:

1. The evidence related to the safety and efficacy of plasma frozen following up to 24 hours of room temperature hold of either plasma collected by apheresis or from whole blood (a.k.a., PF24RT24),
2. The use of dichotomous acceptance rules by FDA, and
3. The FDA process of soliciting assistance in acquiring and processing data and evidence on this topic.

**PF24RT24 –** As we heard here today, PF24RT24 are recognized and have been widely used both safely and effectively for many years in Europe, most recently


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Canada, and in other countries such as Israel and Australia. There have been no reported concerns related to thromboembolic events from any of the hemovigilance systems within those countries. The laboratory data shown today also emphasize that the anticoagulant properties of Protein S in the total milieu of plasma is not affected by the range of activities presented by FDA (approximately 44 -161%).

Thawed plasma, while not a FDA licensed product, is recognized in their December 2009 Guidance for Industry (An Acceptable Circular of Information for the Use of Human Blood and Blood Components) as acceptable labeling for transfusable blood components with the indications of:

1. Management of preoperative or bleeding patients
2. Initial treatment in massive transfusion
3. Reversal of warfarin effects

We have heard evidence today that the 5 day hold of thawed PF24RT24, while Protein S levels decline, does not meaningfully change the functional contribution of the Protein S to plasma properties.

The link between solvent detergent (S/D) plasma and PF24RT24 is not established, and, as FDA acknowledges, has very different manufacturing methods as well as total coagulation factor profiles compared to PF24RT24. BEST believes this is a poor comparison and not an appropriate standard for which to judge thrombotic potential. The suggestion that the holding time prior to freezing of S/D plasma is causal to low Protein S and thrombotic events is at the lowest level of evidence and has not been subjected to a clinical trial. As acknowledged by FDA, S/D plasma distributed within Ireland and the UK has been prepared from plasma held up to 15 hours prior to freezing. Yet, no evidence has surfaced through the hemovigilance systems of a thromboembolic concern with its use in settings other than TTP. S/D plasma is recommended by the UK for the plasma exchange treatment of TTP. Increased thrombotic rates have not been reported with low molecular weight heparin and low dose aspirin thromboprophylaxis.

**Dichotomous Statistical Criteria –** Of late, the FDA has been quite fond of applying dichotomous acceptance criteria to continuous outcome data. BEST agrees that dichotomizing outcomes can be very useful when properly applied, for example, when a clinical outcome is clearly described such as death, recurrence of disease, or loss of organ function. As we are sure FDA would agree, a major loss in study power is observed when continuous data are dichotomized. Even beyond the aspect of power, there is the more serious issue of arbitrarily ascribing the threshold of success or failure as we have seen here with the assignment of factor activity greater than or less than 20% from control as a failure. BEST views this selection as arbitrary and generally at the whim of the FDA who have not presented adequate supporting rationale for this selection, sought a consensus of experts in the field in this area, or conducted a rigorous systematic review of the evidence.


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This analytical practice results in data presentations and descriptions using terms such as 'significant differences' and 'failures' with an unfounded negative implication. The use of this approach along with the discussion of 'significance', 'proportion of failures', 'statistical failures' and similar terminology is inciting and tends to bias the presentation of the data. BEST appreciates the difficulty of needing to pass judgment on products and processes, and that clear pass/fail criteria makes it much easier and cleaner for a reviewer. However, we are dealing with biological variation in the setting of relative performance with no clear linkage to a clinical outcome. Therefore, we encourage FDA to very critically and openly re-evaluate this practice.

As a corollary, FDA may direct that large clinical trials be conducted to determine these critical values. BEST agrees that in some situations this is the correct course of action and would support such trials. However, in the specific case of PF24RT24 and Protein S activities, we believe the experience of a large portion of the western world in transfusion medicine as well as the available laboratory outcomes provide sufficient evidence to move forward with PF24RT24 approval. We acknowledge that individual products and methods are reviewed by FDA on a broader scale with considerations in addition to Protein S activity.

**FDA Process –** Finally, BEST wishes to express disappointment with the FDA process in gathering evidence, data and opinions on the current topic. BEST met in general session less than one month ago. We were aware of the general concern of FDA, and wanted to bring our collective wisdom, experience and data to bear on the questions. However, we did not know the specific FDA issues even though the manufacturers A-D are members of BEST, and two of our scientific members were FDA invited speakers. In one room was gathered a large number of transfusion medicine and hematology experts with access to national and institutional data on PF24RT24, experience in the use of S/D plasma, and a desire to bring this information together in a helpful way. It was unfortunate we couldn't help more. It takes time to properly define the question, find and critique the evidence. BEST would like to find a way to work more productively with FDA as well as other regulatory groups in areas such as PF24RT24. Please be more open with the questions early in the process, and help us figure out how we can be part of the solution.

In summary for PF24RT24, BEST believes that the available data do not support holding up PF24RT24 approval based on the Protein S data presented. We would encourage the panel to recommend to FDA that there is no concern with the arbitrary 20% decline in Protein S levels and that there is no demonstrated clinical concern with the use of PF24RT24.

**Respectfully submitted,**

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