

Blood Products Advisory Committee  
March 13, 2003  
Gaithersburg MD

Summary for Topic II: Discussion on Extension of the storage period for pooled platelets.

Issue: What approach should FDA take to scientific validation of a possible extension of the storage period for pooled platelets?

Background:

The dual objectives of improving bacteriological safety and making more efficient use of platelet inventories would be better served if random donor platelets could be pooled prior to storage and tested only once for bacterial contamination, combined with an extension of dating from 5 to 7 days. However, the FDA's current regulations state that a platelet pool must be transfused within 4 hours of pooling. The storage period for pooled platelets has been only 4 hours mainly because of the concerns about accelerated bacterial growth. The growth of the bacteria may be increased when the contaminated unit of random donor platelets is combined with a pool of 5-6 other random donor platelets that would provide a larger volume of media for growth (1). In addition, there have been theoretical concerns about interactions of leukocytes from different donors with each other (mixed lymphocyte reaction) that could increase the rate of adverse reactions to platelet transfusions, and damage the platelets as well (2,3). The efficacy of the platelets stored under these conditions has not been investigated thoroughly in the US.

In Europe, platelet pooling and storage up to 5 days has been incorporated into routine clinical practice (4-8). There is a difference between European and US platelet processing and that is the use of buffy coat platelets. In Europe platelets are prepared by immediate cooling of whole blood with butane-1,4 diol cooling plates to 22 C and stored for 4-22 hours. The whole blood is then subjected to a hard spin and separated into plasma, buffy coat and red cells. The buffy coats are allowed to rest for 2 hours and then 5 ABO-compatible buffy coats are pooled into a single container via a sterile connecting device with 1 unit of plasma from one for the donors. The pool is subjected to a light spin and the platelet rich plasma is filtered through a leukocyte reduction filter into a final platelet pool storage bag. Several European countries allow storage of the platelet pools for up to 7 days while some countries have a 5 day storage limit. Screening for bacterial contamination is required.

In US the whole blood collected and stored at room temperature for up to 8 hours. Platelet rich plasma is prepared by a light spin and separated into a separate storage bag. Platelet concentrate is prepared by a hard spin of the platelet rich plasma. Platelet-poor plasma is then removed but enough plasma is left behind to resuspend the platelet concentrate for storage of up to 5 days. Platelet pools can be made up to 5 days later by

combining 4-6 units but must be transfused within 4 hours. Leukoreduction can be done on individual units or pooled products up to 72 hours after collection.

The FDA historical concerns for pre-storage pooling of random donor platelets focused on the issues of a) potential adverse events and decreased platelet clinical performance associated with the pooling process and b) increased bacterial proliferation in contaminated pools. The European experience with pre-storage pooled platelets may be sufficient to demonstrate that the concept of long term storage of pooled platelets is viable. However, differences in the way platelets are prepared in Europe and in the US may be significant enough not to allow the extrapolation of the European experience with buffy coat platelets to platelets prepared by the PRP method. For example, the PRP platelets may have more severe collection damage due to the hard spin and resuspension and thus may not store as well as buffy coat platelets. There are several options that could be recommended to evaluate the clinical performance of buffy coat pooled platelets and PRP pooled platelets. One would be to incorporate the buffy coat method for all pre-storage pooling as is done in Europe. The identical storage conditions and storage bags used in Europe could then be approved in the US based on data obtained in Europe. Another option would be to compare the clinical performance of platelets collected by the buffy coat and PRP method in a clinical study. The storage conditions and storage bags for the PRP platelets could then be approved in the US based on this study. A yet another option, which the FDA currently favors, would be to evaluate clinical performance of PRP platelets in a clinical trial to compare pre-storage pooled platelets against platelets pooled within 4 hours of transfusion.

The issue of detecting bacterial contamination in PRP pooled platelets and buffy coat pooled platelets is similar. The European experience with bacterial detection devices may be sufficient for the US market if the platelet collection and storage conditions are reproduced in the US. On the other hand application of these devices to PRP platelets may need a field trial similar in design to what the BPAC concurred with in December 2002 for apheresis platelets.

#### Proposed plan for validation of extended storage of pooled platelets:

##### Clinical performance of platelets

Because of the possible concerns, FDA believes that the safety and efficacy of the platelets stored under pooled conditions in a particular storage bag needs to be demonstrated. In vitro studies can be done to evaluate the pre-storage pooled platelets and the extent of the mixed lymphocyte reaction in the pooled product. The critical study will be a transfusion of the pooled platelets into thrombocytopenic patients to assess the clinical performance of the platelets. A comparison of platelets pooled at the time of transfusion with platelets pooled pre-storage can be done. Each manufacturer will need to validate their storage bag for its ability to store pooled PRP platelet products. The general approach to validation of the storage containers and bacterial detection is outlined below:

Storage containers need to be validated for storing platelet pools for 5 or 7 days with supporting in vitro tests and by clinical studies that evaluate platelet performance. The clinical study would involve a comparison between transfusions of platelet pools formed pre-storage or formed 4 hours prior to transfusion. The primary endpoint would be corrected count index (CCI) in a thrombocytopenic patient population. A less than 20 % difference between results in the two arms would be considered as equivalent.

#### Bacterial detection

The extension of the storage of pooled platelets will require a bacterial detection device that has been validated to detect bacterially contaminated platelet pools in clinical practice. The current detection devices (Pall BDS and BioMerieux Bact T Alert) have been cleared by the FDA for quality control of platelet products (leukoreduced apheresis and single random donor units) (9,10). It is our current thinking that to obtain FDA clearance for a screening device for release of products for transfusion, a field trial will need to be performed that demonstrates that the device can predict if a unit, sampled early in the storage period and declared negative, will remain “culture negative” to the end of storage. This approach was presented to the BPAC on December 2002 and the committee agreed with the general concept although details of these studies were left up to the interested sponsors. The general approach to validation of the bacterial detection devices is outlined below:

Bacterial contamination screening methods and devices need to be validated with in vitro tests and with a “field trial” that evaluates their ability detect contaminated platelet pools in actual clinical practice. A field trial would sample actual platelet pools at two time points to confirm the initial sample results. The study would need to be large enough to assure with 95% confidence that both cultures agree 95% of the time. Such trial may require a large number of units screened due to the low rate of contamination (~1/2000 units).

#### Questions to the committee:

- 1) Please comment on the FDA proposed plan for validating an extension of the storage time for pooled platelets?
  - a) In vitro validation of the storage containers
  - b) Controls and clinical end-points for demonstration of clinical efficacy
  - c) Validation of the bacterial detection system
  
- 2) Please comment on the applicability of the European experience with pre-storage platelet pooling of buffy coat platelets to the FDA proposed criteria for approval of pre-storage pooled PRP platelets.

3) Please comment on the following bacterial detection validation issues:

- a) How useful is the bacterial detection data on buffy coat platelets collected in Europe to validation of bacterial detection devices for PRP platelet pools?
- b) If bacterial detection devices are validated for single PRP-prepared random donor platelet units do they need to be re-validated in PRP platelet pools?
- c) If bacterial detection devices are validated for leukoreduced platelet products do they need to be re-validated for non-leukoreduced platelet products?

References:

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3) Moroff et al. Storage of pools of six and eight platelet concentrates. *Transfusion* 33; 374-378, 1993

4) Boomgaard et al. In vitro evaluation of platelet concentrates, prepared from pooled buffy coats, stored for 8 days after filtration. *Transfusion* 34;311-316, 1994

5) Wildt-Eggen et al. Evaluation of storage conditions of platelet concentrates prepared from pooled buffy coats. *Vox Sang.* 70;11-15, 1996

6) Van der Meer et al. WBC-reduced platelet concentrates from pooled buffy coats in additive solution; an evaluation of in vitro and in vivo measures. *Transfusion* 41;917-922, 2001

7) Van der Meer et al. Leucoreduced platelet concentrates in additive solution: an evaluation of filters and additives solutions. *Vox Sang.* 81;102-107

8) Krailadsiri et al. Platelet storage lesion of WBC-reduced, pooled, buffy coat-derived platelet concentrates prepared in three in-process filter/storage bag combinations. *Transfusion* 41;243-250, 2001

9) Brecher et al. Evaluation of an automated culture system for detecting bacterial contamination of platelets: an analysis with 15 contaminating organisms. *Transfusion* 41;477-482, 2001

10) McDonald et al. Evaluation of the BacT/Alert automated blood culture system for detecting bacteria and measuring their growth kinetics in leucodepleted and non-leucodepleted platelet concentrates. *Vox Sang.* 81;154-160, 2001