

II. New Standard For Platelet Evaluation

Issue Summary
Blood Products Advisory Committee
July 22-23, 2004

TOPIC II: NEW STANDARD FOR PLATELET EVALUATION

Issue: FDA seeks the advice of the Committee on a proposed new standard for the evaluation of platelet products using in vivo radiolabeling studies with comparison to a reference preparation of fresh platelets.

Background:

FDA is committed to development of a "Gold standard" for platelet product performance with a fixed standard to maintain platelet product quality over time. Such an approach would contribute to a less subjective regulatory review process, with common research protocols to minimize differences in methodology and to improve inter-laboratory compatibility. A standard of this nature would facilitate product development in a competitive, but fair environment.

General approach to platelet evaluation

New platelet products are continuously being developed and are always evaluated by FDA prior to their marketing. Products such as pathogen reduced platelets, 7-day storage platelets, cold stored platelets, platelets stored in new storage solutions, and platelet substitutes are very likely to reach FDA within months. These products will be evaluated for their safety and efficacy as has been done in the past. However, we are now proposing an alternate way of evaluating these products to make the process more standardized and to establish a standard of quality that will not change over time.

The general scheme in evaluating a platelet product consists initially of conducting **in vitro** testing to determine whether certain platelet biochemical pathways are intact and functional and whether platelets can respond to certain physiologic and artificial stimuli.

The next step is to evaluate whether the platelets have retained their **ability to participate in hemostasis**. Ideally, this would involve a clinical study in thrombocytopenic patients, the endpoint being either the prophylactic prevention of bleeding or the stoppage of bleeding in a therapeutic application. Such "bleeding" studies, however, are large and cost prohibitive. Thus, an alternate, and surrogate study design frequently used is the **survival of radiolabeled platelets in the circulation** of normal volunteers. This approach is based on the assumption that a healthy platelet that has remained in circulation will be able to participate in hemostasis. Thus the ability of a radiolabeled platelet to remain in circulation is a surrogate endpoint for platelet efficacy. Historically this surrogate endpoint has been accepted for most changes carried out on platelet collection and storage. However when the changes involve very novel methodologies that may alter basic platelet physiology with unpredictable and

unexpected effects on platelet performance (e.g. pathogen reduction technology) then a **full clinical bleeding trial** is required.

Current design of in vivo platelet radiolabeling trials

Two radioactive labels are available for tagging platelets: Chromium⁵¹ and Indium¹¹¹. When incubated with a platelet suspension, these compounds diffuse into intact cells and bind cytosolic proteins. The excess unbound radioactive compound is washed away after centrifugation. The radiolabeled cells can then be re-infused into the autologous donor. Serial blood samples from the donor are then drawn at various time points after the reinfusion, and the percentage of radiolabeled cells remaining in circulation compared to those infused is measured. Two indicators characterize the outcome of these studies: platelet *recovery* (platelet count extrapolated back to time 0 of reinfusion) and platelet *survival* in the circulation (point of intersection of survival curve with Y axis). Due to the known phenomenon of platelet sequestration, the initial recovery is close to 2/3 rather than 100% (1/3 of platelets sequestered in spleen). Under normal circumstances, the recovery varies between 45-66% while survival varies between 5 –7 days. There is considerable variability in the recovery and survival of platelet products among normal volunteers and among different laboratories performing these tests. Thus no minimum standards for platelet performance have been set. In general, recovery of less than 40% and survival of less than 3-4 days are considered poor performance.

The current approach to evaluation of a new (test) platelet product consists of a comparison between the performance of this new product with that of an established licensed product (control). Historically, FDA has allowed a 10%-20% difference between test and control, as such a difference is deemed not to be clinically significant. A study size of 20-24 healthy donors has been accepted as adequate to demonstrate a statistically significant difference between the two groups. The problem, however, with this current approach is that, with repeated application, a new lower standard can be set with each determination and over successive comparisons the quality of the accepted standard will decline.

Proposal for a New Platelet Standard:

Concept for a new standard

In the summer of 2002, CBER held a workshop on evaluation of blood products pathogen reduction methodologies with a section specifically addressing the efficacy of treated platelets. In that session, Dr Scott Murphy described the current testing paradigm as fostering a “quality inferiority creep” based on the notion presented in the previous paragraph. Dr. Murphy is one of the most recognized and respected authorities on platelet radiolabeling studies and has been publishing in this field for over 40 years. He proposed a new approach (later published in the January 2004 “Transfusion” Journal- see attached) that would set a quality standard for platelet radiolabeling studies. He suggested that instead of comparing the test platelets to an established licensed product, the comparison ought to be made with a “fresh” platelet specimen subsequently defined as drawn, prepared, labeled and infused on the same day of the reinfusion of the test

platelet product, with both products made from and infused into the same person. The test values for recovery and survival could then be expressed as a percentage of the control in the same subject. This strategy removes variability among donors and variability among laboratories, overcoming tendencies towards getting high or low results for recovery and survival. Dr Murphy recommended that the mean recovery be greater than two-thirds of fresh, and survival be greater than one half of fresh. The reason for lower criteria for survival was stated to be the known decrease in platelet survival in thrombocytopenic patients. In standard prophylactic transfusion, time to next transfusion is closer to 2 days. Accordingly, in real practice of platelet transfusion, survival seems less important than recovery.

The FDA agreed with the concept of Dr. Murphy's proposed testing standard and has taken steps to develop this approach. In order to elucidate the details of putting this new concept into practice, a workshop titled "Workshop on Use of Radiolabeled Platelets for Assessment of In Vivo Viability of Platelet Products" took place on May 3rd on the NIH Campus in Bethesda, Maryland. FDA believes that the new approach will establish a uniform standard for platelet products similar to what has been used for red cells for several decades. In particular, it will be useful in the near future because a number of novel platelet products that are being developed have the potential to severely damage platelets during processing (pathogen reduction).

Discussion at the May 3 workshop

The goal of the workshop was to orient the transfusion community towards a new approach for assessing the quality of platelet products via radiolabeling studies in healthy volunteers and to obtain the opinions of experts in the field.

The rationale and merits of the novel approach were discussed at the workshop, along with appropriate study protocols for comparing platelet products to the standard. Preliminary data using the new approach were presented. An Expert Panel discussion at the end of the workshop concurred with Dr Murphy's acceptance criteria of 66% and 50% for recovery and survival ratios. Note, however, that FDA advocates 66% for both parameters. The stated reason for a lower criterion for platelet survival is that in thrombocytopenic patients platelet have significantly decreased survival because a large portion of the cells goes to support endothelial cells and are removed from circulation. Since the platelets are removed due to reasons other than an acquired "storage" lesion it was argued that platelet survival was not as critical parameter to evaluate in platelet products and thus could be relaxed. The counter argument voiced by the FDA is that the radiolabeling studies are performed in healthy volunteers who are not thrombocytopenic and that any decrease of platelet performance in survival would be reflective of a storage- or collection-induced damage. It is not clear whether increased clearance due to storage damage and increased clearance mechanism in thrombocytopenic patients would be additive in the patients and thus FDA would prefer to maintain the higher standard (0.66 ratio of test /fresh) for platelet survival in healthy donors.

Questions for the Committee:

1. Do committee members agree that a standard comparing in vivo recovery and survival of a reference preparation of fresh autologous platelets to stored platelets in the same individual would represent a useful scientific advancement in platelet efficacy evaluations?
2. If FDA were to adopt a standard as described in 1. using in-vivo radiolabeling studies conducted in healthy autologous donors, would the following criteria be appropriate?
 - a) Recovery 66% or higher
 - b) Survival 66% or greater
 - c)
3. Please comment on any alternative proposals.

**Statement of
The American Association of Blood Banks
Before the Blood Products Advisory Committee**

July 22, 2004

New Standard for Platelet Evaluation

**Presented by M. Allene Carr-Greer, MT(ASCP)SBB
Deputy Director, Regulatory Affairs**

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

AABB wishes to commend the Food and Drug Administration for its review of techniques currently employed for evaluation of novel platelet products. The current recommendation, as described in the 1999 *draft* "Guidance for Industry For Platelet Testing and Evaluation of Platelet Substitute Products," does not include a minimum performance standard that the novel platelet product must achieve. Rather, the new platelet product is compared to an already licensed product and is expected to meet the same performance level, "plus or minus." Over time, this process, could lead to licensure of inferior products.

The "Workshop on Use of Radiolabeled Platelets for Assessment of In Vivo Viability of Platelet Products," held at the National Institutes of Health on May 3, 2004, focused a group of experts on several important issues. These included establishment of a minimum performance standard for platelet products in radiolabeling studies and a discussion on the appropriate study protocol for comparing platelet products to the standard. While there was agreement that today's platelet products do not show any sign of "creeping inferiority," there was also widespread agreement that a "gold standard" should be developed whereby novel platelet products are compared to fresh autologous platelets in a healthy donor. Consensus was reached on a minimum performance standard for percent recovery and viability for platelet products in radiolabeling studies. Agreement was also reached that a standard protocol for the radiolabeling studies should be developed.

Uniform protocols and fixed standards will result in sustained platelet product quality over as well as a more uniform and less subjective regulatory review process. AABB encourages FDA to move forward with recommendations ensuring that the highest quality platelet products are available for patient transfusion.