



Mississippi Valley Regional
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Tuesday, December 27, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration 1448 5 DEC 30 P1:41
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket number 2005D-0330, Guidance For Industry And FDA
Review Staff: *Collection of Platelets by Automated Methods*

To the Docket Officer:

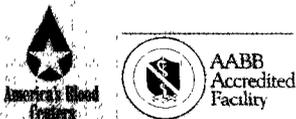
Thank you for the opportunity to comment on the above referenced document. I am representing the Mississippi Valley Regional Blood Center, a licensed blood collection facility in Davenport, IA that collects and distributes more than 10,000 apheresis platelet units to its system hospitals and to blood centers and hospitals nationwide.

This draft document is a comprehensive revision of the prior guidance. It will provoke much discussion. America's Blood Centers, the association of independent FDA licensed community blood centers, will be submitting detailed technical comments on all aspects of the draft that I wholly endorse.

My apheresis personnel and I have three major concerns about the impact of this document, regarding new limits on the number of components allowed to be collected, requirements for on-site physician consultation for donor emergencies, and what appear to be arbitrary deferral periods after use of nonsteroidal anti-inflammatory drugs that I will detail in this letter. The first two have the potential to severely restrict the availability of plateletpheresis components, the third a modest impact, and from my standpoint as a transfusing clinician, to adversely affect the care of patients.

III.B.2 on page 6: You should collect no more than 24 total Platelets, Pheresis components in a 12-month period. Two components collected from a double collection of Platelets, Pheresis and three components collected from a triple collection of Platelets, Pheresis would be counted as two components and three components respectively.

In 2004, we made 1.45 platelets per apheresis donations across our entire donor base, and the minimum estimate at that rate, using the proposed 24 components standard for collection loss is 12.5% at a time of increasing demand. This is a minimum estimate because we specifically recruit for frequent apheresis those donors



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most consistently able to produce multiple products per donation, and would therefore disproportionately restrict production from our most frequent donors. As apheresis technology becomes more efficient, this proportion will only increase. We are manually reviewing our collection records to establish a more realistic estimate, and preliminary calculations put the real loss between 30 and 40% of collections. The result of this requirement will be to markedly reduce the available supply of platelets, pheresis for clinical use, which I am confident is not the intention of the agency.

The reference cited by FDA says, "Conclusions: Regular plateletpheresis donors develop sustained decreases in platelet count. **However, clinically significant thrombocytopenia is unusual** when rigorous ongoing review and prudent deferral policies are established and followed." (Emphasis added). In this light, what is FDA attempting to improve with the tight restriction on collection of this critical product? Better donor protection will be afforded by leaving the 24 donations per year criterion intact, not limiting the number of components allowed to be produced, but increasing the minimum interdonation interval to 10-14 days to allow more platelet recovery with no impact on supply. Routine donor platelet counts provide a self-adjusting governor on the frequency of apheresis and depth of thrombocytopenia that donors will sustain. They offer adequate donor protection in my view.

A related, if less crucial, issue is then raised regarding consent of the donor.

IV. third bullet on page 8. *A statement that the long-term effects of repeated plateletpheresis on the donor's platelet and leukocyte count is not understood.*

I suppose this is strictly true, however, the available evidence and approaching 20 years of experience suggests there is no long-term adverse effect, and I would inquire as to the need for this highly qualified and, for some, disconcerting language. My suggestion is that, if any language is required, it should be along the lines of "*Your platelet counts will be followed while you continue to donate and we will respond appropriately by reducing the frequency of donation if there is any sustained decrease.*"

III.D on page 7: We believe that a physician should be present on the premises during the collection of Platelets, Pheresis to ensure that necessary medical treatment be available to the donor in a timely fashion. We interpret "present on the premises" to include a qualified physician able to arrive at the premises within 15 minutes (Ref. 11).

This requirement, referenced from a *proposed (but never final)* guidance dated 1985, is not reasonable for several reasons. No evidence is cited that (blood center) physicians can respond more effectively to emergencies occurring during plateletpheresis than the nurses and technicians with extensive training and, most important, extensive experience managing the common urgent reactions. Fifteen minutes is, under any circumstance, a wholly arbitrary time limit that far exceeds the allowable interval before irreversible brain injury occurs in the worst-case scenarios of ventricular fibrillation and asystolic cardiopulmonary arrest. I cannot locate literature through the National Library of Medicine that suggests outcomes are improved by attendance of non-specialist (i.e. not emergency, cardiology, critical care) physicians at out-of-hospital cardiac arrest.

All of our nursing personnel are certified and regularly recertified in basic life support techniques in accordance with American Heart Association standards. Equipment used in advanced life support (medications, airways, ventilation equipment and defibrillators) is not maintained at our donation sites. This is because response times for EMTs, experts in advanced life support, are <5 minutes in communities where we perform apheresis. The EMTs who arrive are far more highly skilled than I, as well as most of the non-specialist physicians I have worked with as a clinician for 30 years. Whom would you rather have provide resuscitation to yourself or a loved one, an EMT or paramedic with extensive training and current experience, or a blood center physician, often a pathologist, who has not performed an urgent resuscitation or certified in advance cardiac life support since before his or her residency or fellowship (if at all)?

During repeated FDA inspections of our facilities over many years, the requirement in the 1988 *Revised Guideline for Collection of Platelets, Pheresis...*

“A qualified physician who is familiar with the procedure should be available to attend the donor within 15 minutes when a pheresis procedure is being performed and should be available for consultation and management of donor adverse reactions.”

...has never been interpreted or enforced by field personnel to require a physician's **physical** attendance of the donor. As a blood center medical director for twenty years, I have never been called to attend a donor with a severe reaction who my nurses have not appropriately evaluated and treated before my arrival. In no case have I contributed materially to a donor's basic support, beyond my responsibility to assist in the development and revision of SOPs and to be available by telephone. Is the FDA aware of information suggesting otherwise, that the physical attendance of a physician is associated with improved outcomes after a serious reaction?

Second, this requirement would flatly close three of our four collection sites representing 40-50% of collections that are remote from the main center where I keep my office. It would restrict the hours during which collections could occur at the main center to those when I am in town and on site. Perhaps we would lose 25-30% of collections from our main site produced when I am absent. This kind of impact cannot have been anticipated by the agency during drafting of this document.

III.a. on page 5 of the guidance states, “You should not collect Platelets, Pheresis from donors who have ingested drugs that adversely affect platelet function. These include, but may not be limited to:

- *Aspirin (ASA)/ASA-containing drugs – 5 days from last dose (Ref. 10)*
- *Non-steroidal Anti-inflammatory Drugs (NSAIDs) – 3 days from last dose (Ref. 9)*

I am puzzled by the citation of the Armed Services Blood Program Office medication deferral guideline (Ref. 9) as authority for an FDA guidance document. The ASBPO list is neither the product of a peer-reviewed publication, a national committee of experts charged with this function, nor a recognized standard setting organization. In addition, there were no public hearings or other broad input in the decision making process by

which the list was developed and deferral times established. No data are provided to validate the 3-day deferral for NSAID use, and it is possible this is unnecessarily long.

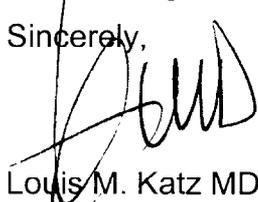
While ASA produces irreversible platelet inhibition, the other NSAIDs do not. There are data demonstrating normal platelet function at ≤ 24 hours after the last dose of a weeklong course of 600 mg TID of ibuprofen (Goldenberg et al. *Ann Intern Med.* 2005;142:506-509). I am also interested in what evidence exists suggesting that platelets from non-ASA NSAID treated donors, transfused to appropriate thrombocytopenic patients, after at least 24-48 hours of storage during testing and before use, are associated with any hemostatic defect or decrement in effectiveness for treatment or prevention of hemorrhage. I have attempted, and failed, through the National Library of Medicine database to find such evidence. It is plausible that metabolism of the drugs and reversal of any hemostatic defect continues during storage and after infusion, and it would be preferable that FDA encourages study of this issue before adopting arbitrary deferrals.

In a survey of 112 plateletpheresis donors at my center, 2 would discontinue donation. 21 take NSAIDs other than ASA, occasionally to fairly regularly, and would need to be reminded in advance of their appointments to hold the medication or use acetaminophen. 41 use NSAIDs, but believe they would remember to stop or substitute an acceptable alternative, and 48 do not use NSAIDs. The adoption of this guidance, is likely achievable, but would require careful review and amendment of recruitment and scheduling SOPs. It would result in a substantial number of new on-site deferrals, and donor loss among those who have taken the medications or forgotten to discontinue them, absent evidence from FDA that it would improve the regulated product.

In summary, the above comments are offered to protect the adequacy of the platelet supply. Absent evidence that current limits on the number of procedures or components produced, or that current approaches to availability of physician consultation for donor emergencies are having an adverse effect on donors, and with many years of experience and some data that they are not, it is inappropriate for FDA to impose new limits. The proposals in the draft will significantly restrict the availability of platelets, pheresis. An arbitrary deferral for NSAID use is not evidence-based and should be further studied with appropriate techniques before being mandated.

Comments you will receive from America's Blood Centers will more fully address some of the highly technical quality control issues discussed in the draft guidance. I am participating in their drafting and endorse them.

Sincerely,



Louis M. Katz MD
Executive Vice President, Medical Affairs

Electronic Copy: Sharyn Orton PhD.