



Puget Sound Blood Center

January 3, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2005D-0330
DRAFT Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods

To Whom It May Concern:

Please accept the following comments regarding the specified sections of this guidance:

Section III - Donor Selection and Management

A. Donor Selection:

1. A WBC is required prior to the first donation. No reason for this requirement is stated. If the concern is that repeated apheresis procedures might have a deleterious effect on the donor's white blood cell count, that concern is not addressed by this requirement as it is only determined prior to the first donation. If the concern is that donor's might have a disease that alters the white blood cell count and that facilities should know this so that the donor is deferred, it is inappropriate. White cell counts are not required for any other type of blood donation, and there are many tests that one could envision that might highlight donor abnormalities. We recommend that this requirement be deleted.
2. There is a requirement that if the platelet count cannot be determined prior to the first collection, it should be evaluated after the first collection. This is a curious requirement in that most facilities evaluate the donor's platelet count associated with all collections, not just the first one. It would be preferable to state the facilities have criteria for evaluating abnormalities in donor counts. Leave the specifics up to the facilities.
3. Deferral for aspirin-containing drugs is recommended to be 5 days. The current industry standard is 36 hours (AABB Standard 5.4.1a (8)), and no justification is provided for changing it. There are two articles in the literature that specifically address this issue. The first is Stuart MJ et al (Platelet Function of Recipients of Platelets from Donors Ingesting Aspirin. NEJM 1972;287:1105). In this study recipient bleeding times were measured after transfusion of platelets from donors who had or had not taken aspirin. If the donors had taken aspirin 36 hours before collection, the function of their transfused platelets was the same as that from donors who had not taken aspirin. This study is the one on which the 36 hour standard was based. Additionally, (Slichter and Harker, Brit J Haematology 1976; 34:403) showed that platelet dysfunction seen in donors who had taken aspirin was reversible in vivo in the transfusion recipients, as measured by the bleeding times, suggesting that donor screening for aspirin ingestion was probably unnecessary.

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The references cited in the Draft Guidance are not pertinent to this issue. They, and several others not cited, do not address the issue of donor aspirin ingestion. Rather they are focused on the duration of aspirin effect in patients about to undergo an invasive procedure.

Thus, we recommend that the deferral period for aspirin ingestion remain at the current 36 hours.

4. Deferral for ingestion of NSAIDs is recommended to be 5 days. NSAIDs are universally recognized to be reversible inhibitors of platelet function; that is, the dysfunction will reverse as soon as the platelets are infused. Therefore there should be no deferral associated with these drugs. This issue has been addressed many times by the AABB Standards Committee, and it was concluded that the appropriate answer was no deferral. The reference cited in the Draft Guidance is a website for military deferral rules. In addition to the fact that this is not a legitimate scientific reference, the reference was incorrectly cited—the suggested military deferral was for one day. Adding a deferral for NSAIDs would probably have quite a dramatic effect on the number of available donors because of the widespread use of these drugs. We recommend that deferral for NSAIDs be deleted.

B. Donor Management:

1. There is a requirement that a post-collection platelet count be performed in order to more accurately set the target parameters for the subsequent collection. We disagree that this is an appropriate use for the post-donation platelet count. It is well known that the donor's platelet count will drop 20-30% immediately after plateletpheresis and then return quite quickly to the baseline value. Unless the subsequent platelet collection is done very soon, the post-collection count is exactly the wrong value to be used to set the target parameters. Standard practice is to use the pre-count from the previous platelet collections, a much more accurate practice. In addition, with the baseline requirement for a platelet count of 150,000, there is essentially no chance that the post-donation count will be at dangerous levels. Therefore, we recommend that the requirement for a post-procedure platelet count be deleted.
2. Divided units cannot be collected from first time donors unless the pre-collection platelet count is available. This is an unnecessary restriction. If it turns out that the platelet count used to set the target is wrong, one will just end up with more or less in the product than one expected; there will be no damage to the donor. If the donor's count is lower, fewer platelets will be collected, but the chance that the donor's platelet count will be reduced to a dangerous level is vanishingly small. We recommend that this requirement be deleted.
3. There is a requirement that a divided collection be counted as two or three products for the purpose of the 24 per year limit. There are several problems with this requirement.

First, it is not necessary. Counting each collection as a single collection has been the practice for years at blood collection facilities, and there is no evidence that frequent platelet donors experience any clinically meaningful decrements in their platelet counts. For those individual donors who might drop their platelet counts below acceptable levels, current safeguards (determining a platelet count at each donation) are more than adequate to protect these donors.

Second, it would adversely impact the platelet supply. At the Puget Sound Blood Center in 2004, 178 donors donated platelets at least twelve times. These donors accounted for 3048 donations and 4811 transfusion products. If donor had been limited to 24 transfusion products, we would have lost 946 products, amounting to approximately 6.3% of our total plateletpheresis production.

Third, keeping track of the number of donations for each rolling twelve month period is hard enough when one counts collections; it will be very difficult if one has to count the divided units as two or three collections. It would also seem strange to count a 6.1×10^{11} collection as two products and a 5.9×10^{11} collection as one product.

We recommend that the current practice not be changed and that the 24 per year limit apply to collections, not transfusion doses.

4. There is a requirement that the total volume of blood components retained per collection be no more than 500ml (or 600ml for donors weighing 175 pounds or greater). Since some collection devices have specifically been approved by the FDA for collection volumes greater than these amounts, we recommend that the requirement be to follow the manufacturer's rules for the specific collection device.
5. General Comment: Many of the proposed requirements seem to stem from the concern that under current practices there may be clinically important donor safety issues for frequent platelet donors or for donors whose platelet count might be less than 150,000. We have looked at some of our own experience in this regard.
 - A review of Puget Sound Blood Center data from 1/1/2000 to present and including 69,662 collections, resulted in the following information: There were 17 collections in which the pre-collection platelet count (for which the result was only available post-collection) turned out to be $<150,000$ and in which one could make a semi-plausible argument that the count was down because of previous collections (e.g. the previous collection was within four weeks of the index case). Six of 17 donors did not return. Eleven donors did return and continued to donate with platelet counts above 150,000. Thus, this issue occurred 0.02% of the time; even so, there were no apparent adverse effects on the donors. Additionally, there were 178 collections in which the pre-donation platelet count was $<150,000$, including 29 first time donors, 134 donors whose platelet counts were generally in the 150-180,000 range (and who occasionally dipped below 150,000), and 15 donors whose drop to $<150,000$ could not be explained by excessive previous collections (last collection > 6 months previously). All collections cited above are approximately 0.2% of total collections reviewed. In summary, we occasionally collect donors with platelet counts $<150,000$, with no apparent adverse effects on their health.
 - We reviewed the records of donors who had undergone at least 40 collections from 1/1/2000 to the present. The average number of collections was 67. Overall these donors were responsible for 12,867 collections and 20,168 transfusion products. The mean platelet count for the first and final collection was 255,000 and 252,000, respectively. The mean ratio of the final to the baseline platelet count was 0.9999.
 - On the basis of the above data, we recommend retaining the present intervals between collections from Platelets, Pheresis donors, including those donating double and triple platelet collections.

D. Medical Coverage:

1. There is a requirement that a physician be on the premises during any plateletpheresis procedure. We believe this requirement is problematic and unworkable for several reasons.

First, it is not necessary. Platelet collection is not a dangerous procedure. It has been shown to be much safer than whole blood collection (see McLeod et al, *Transfusion* 1998; 38:938). Most facilities in this country collect platelets in a variety of locations, many of which are far distant from their headquarters. They have done so for years without adverse consequences.

Second, although the FDA states that emergency response personnel do not provide the same level of safety as would a blood center physician, we respectfully disagree. These emergency response teams,

which can reach any donor facility within 5-10 minutes, are highly trained in dealing with cardiopulmonary emergencies and unstable patients, much more so than the average blood center physician. In our facility, if both the blood center physician and an emergency response team were at the scene, the blood center physician would step aside and leave the situation to the experts.

Finally, institution of such a rule would for the most part result in the cessation of plateletpheresis procedures around the country. At the Puget Sound Blood Center, collections would decrease by 89%, dropping from 15,500 to 1,700 per year.

Blood centers currently have adequate safeguards in place to protect the safety of the donor. These usually involve the rapid availability of the blood center physician by phone as well as the rapid availability of an emergency response team. We strongly recommend that the FDA accept these current practices as adequate.

Section I - Information Provided to the Donor

1. There is a requirement for a statement that long term effects of repeated plateletpheresis on the donor's platelet and leukocyte count is not understood. Since there has now been 20-30 years experience in plateletpheresis with no apparent adverse effects on donors, this statement is unduly alarming. We suggest that this requirement be deleted or, at a minimum, revised to say that there is no known long term adverse effect of frequent platelet donation.
2. There is a requirement that the donor be informed of the various donation intervals allowed for various blood components. This is not a practical suggestion. These intervals are so complicated that blood center computer systems are required to calculate them. It would not be possible to relay these complicated algorithms to donors in any meaningful way.

Section VI. - Process Validation

B. Validation Protocol

1. It is unclear whether retrospective validation of Platelets, Pheresis collection processes is required in facilities with established programs and ongoing quality assurance monitoring programs that demonstrate processes are in control. If it is, we consider it to be an undue burden and recommend deleting the requirement.
2. Minimum /maximum values are required for Target platelet yield. This requirement is inappropriate and should be deleted. The target platelet yields will vary between instruments used and the particular collection algorithms of the various facilities. They are not measured values. These values should be set only for attributes of the collected components, not the settings on the machines used to obtain them.
3. For leukocyte reduced products, determination of percent recovery is only applicable if the leukocyte reduction is performed by filtration after production of the initial product. If leukoreduction is performed as an integral part of a centrifugal apheresis procedure, percent recovery is a meaningless concept. This requirement should be reworded to reflect this.

D. Product Performance Qualification

1. Platelet yield: The number 3×10^{11} was originally meant to indicate the number of platelets that could reasonably be obtained by an apheresis procedure, the achievement of which meant that the process was being done properly. FDA regulations state that 75% of collections should achieve this level; AABB Standards say that 90% should achieve this level. Although in recent years some have enshrined 3×10^{11} as a "minimum" yield, there is no medical justification for this position. The dose of platelets required by a patient varies widely, depending on the patient's underlying condition, body weight, platelet count, anticipated hemostatic challenges, response to a given dose of platelets, etc. The appropriate dose may be 2×10^{11} in some patients, 8×10^{11} in others. It is thus unreasonable, both from a medical and from a production point of view, to consider 3.0×10^{11} an acceptable platelet yield and 2.9×10^{11} an unacceptable platelet yield. In fact there is a growing consensus that the appropriate platelet dose for prophylactic transfusion (i.e. to a non-bleeding patient with a low platelet count) may be substantially less than 3.0×10^{11} . There is currently a NHLBI sponsored national multi-center randomized controlled trial underway to determine the optimal dosing strategy.

From a manufacturing quality point of view, the optimal situation might be to produce a product with minimal variation in dose (e.g. all products contain between 3.4 and 3.6×10^{11} platelets), not just a minimal dose, as suggested by these guidelines. As an analogy, a tablet of amoxicillin is not specified to contain at least 250mg of the drug (in which case 500mg would be acceptable); rather it must contain 250 +/- x mg.

For any targeted platelet yield, there will be a mean actual yield, usually close to the targeted yield, with a bell shaped curve of yields surrounding the mean. This is unavoidable given the normal biologic variation in the donors. There is variation in platelet counts as well as in aggregation and separation characteristics of the platelets. Thus there is currently no way to achieve the precision of the amoxicillin tablet discussed above. In our facility, if we set the target yield at 3.5×10^{11} , about 20% of the collections will fall below 3.0×10^{11} . If we set it at 5.0, about 1% will fall below 3.0×10^{11} . Mandating that no product fall below 3×10^{11} does not improve quality (i.e. it does not increase the predictability of the yield); it just sets the mean collection at a higher level. Forcing the higher target does three things. First, it decreases the number of donors who can participate---those with lower platelet counts or less available time to spend donating. Second, in the era of divided units, it actually decreases quality (predictability of the dose). It will force facilities to attempt to collect sufficient platelets to divide the units for all donors (since they have to set the targets so high anyway). If they reach the goal, the resultant products contain about 3×10^{11} platelets. If they don't, the resultant undivided product will contain 5.5 - 6×10^{11} platelets, about twice as much. We thus have a binary distribution of dose in the same product. Third, as stated above, it somewhat flies in the face of much current medical thinking that lower platelet doses (even lower than 3.0×10^{11}) may be more appropriate.

The purpose of the above discussion is to suggest that the precision attached to the lower limit of the dose distribution (95% confidence that 95% of products contain at least 3.0×10^{11} platelets) is excessive and really accomplishes nothing medically or in the way of quality. It merely says that everybody has to collect more platelets from the donors. We do not believe this is the best approach and suggest that the current system works fine.

2. pH: Although the pH limits themselves are not unreasonable, the allowed variation is. Mandating a zero failure rate will guarantee failure. pH failures do occur rarely and do not imply a failure in the process. The AABB Standard for 90% to be above 6.2 is reasonable. A requirement that 95% be above 6.2 with 95% confidence is excessive and requires too many measurements. The manufacturer's platelet storage bags approved by the FDA had higher pH failure rates. It is not reasonable for the FDA to hold blood centers to a higher standard than the bags that the FDA has approved.

Section VII. - Quality Assurance (QA) and Monitoring

A. Standard Operating Procedures and Record Keeping

1. Providing the actual platelet yield from each collection of Platelets, Pheresis to the transfusion facility. Although we understand the intent, we consider this requirement to be an undue burden on blood center staff. We feel that the current practice of making the yields available to the transfusion facility (if they ask) and providing general information about product content is appropriate. As a practical matter, the patient's physicians are going to pay no attention to this information even if provided. It is also noted that similar information is not required for whole blood platelets, red cell components, or plasma components. We recommend retaining current requirements for product labeling.
2. The requirement that the actual platelet content be placed on the label if the yield is $< 3.0 \times 10^{11}$ should be deleted. First, as indicated above, nobody is going to pay any attention to it. Second it doesn't seem reasonable to require it for a yield of 2.9×10^{11} and not for 3.1×10^{11} .

B. Donor Monitoring

Review of donor's ability to recover baseline platelet count. We do not feel that whether or not the donor's platelet count is at least as high as his first platelet count is the relevant information. What's important is whether it's at least 150,000. Current practice is to review donor information to ensure that the donor is eligible. This should suffice. We recommend deleting this requirement.

C. Component Testing

1. Residual WBC counts should not be required for units that will not be labeled as leukocytes reduced. We recommend that this requirement be reworded to so indicate.
2. With reference to QC testing, please clarify that the platelet yield of a component, determined at the conclusion of manufacturing, can be used for QC monitoring and that the sample obtained at the end of the storage period for pH testing on the same unit does not need to be tested a second time for platelet yield.
3. Requirement that QC be done on platelets collected from each individual apheresis machine. We believe this is an unreasonable requirement since all machines have been validated and are operated by the same personnel using the same SOPs. To keep track of each machine that happens to be in use during each time period would greatly complicate the QC task for no apparent reason. We recommend that this requirement be deleted.
4. The suggested statistical approach seems excessive, requiring that 10% of the total production undergo QC testing. It must be true that the fraction of production needed for QC depends on the total production numbers. It also must be true that the number of samples required for QC depends on the variance of the results and the difference between the results and required results. For example, the number of units QC'd for residual leukocytes, where the mean values are an order of magnitude below the required cutoff, surely is less than that for platelet yield. We recommend that these statistical issues be further discussed at a FDA sponsored workshop.

F. Quality System Audits

1. Is the FDA's intent in listing specific audit details to mandate audit practices?
2. It is stated that bacterial contamination rates greater than 1:3000 should be considered non-conforming. We feel that this is too prescriptive. Positive rates of 1:3000-1:5000 are the norm when only aerobic testing is performed. Whether addition of anaerobic testing would increase the positive rate to the "non-conforming" category is not known. Also the 1:3000 value is too close to the acceptable rate. With small numbers, one additional positive might falsely place a facility in the category of having a problem. We recommend stating that facilities should monitor results investigate positive results without prescribing specific levels.

Section X.- Reporting Changes to an Approved Biologics License Application (BLA)

Part B refers to the use of a CBE-30 to submit a request to implement (1) upgrades provided by the manufacturer to your cleared apheresis device and (3) implementation of a new collection facility under an approved Comparability Protocol. We recommend that these two issues continue to be reported in accordance with the July 2001 Guidance – Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture.

Thank you for the opportunity to share our comments regarding this draft guidance.

Sincerely,



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Executive Vice President, Medical Division
Medical Director