

Subject: Written comments for docket number 2005D-0330, “Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods”

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Comment #1	Draft Guidance item: III. A. (page 5) <i>Prior to the first donation, test Platelets, Pheresis donors for levels of the following laboratory values that are acceptable under the manufacturer’s directions for use:</i> <ul style="list-style-type: none"> • <i>WBC count</i> • <i>Platelet count</i>
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We question the logic for requiring that a WBC count be performed on the first donation. A WBC count is not required for subsequent donations. Furthermore, FDA refers industry to follow “values that are acceptable under the manufacturer’s directions for use”. The manufacturer of our apheresis devices provides acceptable values for platelets but does not do so for WBC. We recommend that the WBC count requirement be eliminated.

Comment #2	Draft Guidance item: III. A. (page 5) <i>You should not collect Platelets, Pheresis from donors who have ingested...</i> <ul style="list-style-type: none"> • <i>Aspirin (ASA)/ASA-containing drugs – 5 days from last does</i>
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We see that this deferral period was established based on a single literature citation (Chest 2001 supplement). Does FDA have other data upon which this decision was made? If not, we recommend that the current deferral period of 48 hours (in use in the FDA-approved uniform donor history questionnaire) be continued until a more thorough evaluation of the affect of ASA on platelets can be completed.

Comment #3	Draft Guidance item: III. B. 2. (page 6) <ul style="list-style-type: none"> • <i>You should not collect more than 24 total Platelets, Pheresis components in a 12-month period</i>
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We have concerns with this requirement on two fronts:

Platelet component availability and patient safety: In our own setting, we have estimated that this limitation would result in an approximately 15% loss of platelet components produced. We have heard anecdotally that other hospital-based blood banks as well as independent blood centers have calculated similar or worse estimated losses in platelet component production. The FDA is quite aware that recruiting donors to maintain the platelet supply at its current marginally acceptable level is extremely challenging; we are not at all confident that nearly enough donors could be recruited to make up for the platelet losses that would occur should this proposal be formalized. Thus, we are fearful that the platelet supply will be severely inadequate to meet transfusion needs.

Industry experience in collecting more than 24 platelet components per year: The practice of collecting more than 24 platelet components per year from a donor has been safely performed in the blood bank industry for a number of years. We are not aware of reports of severe adverse events occurring in donors as a result of this practice. As requested by FDA we are submitting a retrospective study of donors in our center in regards to the effect of the numbers of platelet components collected on the donor’s platelet and WBC counts (see Appendix A). We have also submitted data from our center regarding the deferral of platelet donors due to low platelet counts (see Appendix B).

Recommendation: please refer to the “discussion” section of Appendix A

Comment #4	Draft Guidance item: III. B. 2. (page 6) <ul style="list-style-type: none"> • <i>The interval between collection of a double Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 7 days.</i> • <i>The interval between collection of a triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 14 days.</i>
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No literature references were cited for these requirements. Does FDA have evidence for proposing such donation intervals? We feel that current donor screening requirements (i.e. platelet count) and the apheresis technology that determines the maximum number of platelet components that can be safely collected based on the donor’s platelet count are adequate safeguards, and obviate the need for specific donation interval requirements for donors of double or triple platelet products. We recommend that the current donation interval requirement be retained.

Comment #5	Draft Guidance item: III. B. 2. (page 6) <ul style="list-style-type: none"> • <i>A post-donation platelet count should be performed after each collection</i>
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We feel that the pre-donation platelet count serves as a safety measure for the donor. In addition, today’s apheresis technology is capable of warning of and/or not allowing platelet collections that will result in the donor having a post-donation platelet count estimate of less than 100,000/μL. The collection of a post-donation platelet count also presents labor intensive and logistical problems that may be a deterrent to donation (e.g. added red blood cell loss for donors; possible extra venipuncture). We recommend that this requirement be removed.

Comment #6	Draft Guidance item: III. D. (page 7) <p><i>“...a physician should be present on the premises during collection of Platelets, Pheresis...”</i></p>
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Although this does not present a problem in our hospital-based center we have concerns that this requirement could have an impact on the collection of platelet products at independent blood centers. We rely on a supply of platelets from these centers for a significant number of products used for our patients. We are also concerned with the application of this requirement to mobile, off-site blood drives at which Platelets, Pheresis may be collected. It would seem that access to emergency services personnel (e.g. paramedics or nearby Emergency Room), in combination with CPR-certified collections staff, are adequate safety measures for platelet donors. We recommend that this requirement be removed.

Comment #7	Draft Guidance item: IV. (page 8) <p><i>“...You should provide Platelets, Pheresis donors with...the following information specific to platelet collection”</i></p> <ul style="list-style-type: none"> • <i>A description of the number of Whole Blood, apheresis Red Blood Cells or plateletpheresis collection procedures and/or components that may be collected per year and the donation interval for each.</i>
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This information is not straight forward for all donors and can become very complex depending on many variables. Some examples are:

- Donation intervals for apheresis red blood cells depends on whether you make a single or double unit donation
- Donation interval for plateletpheresis after whole blood donation depends on the extracorporeal red cell volume of the apheresis instrument to be used
- Donation interval for plateletpheresis after apheresis red blood cell donation is different depending on whether you did: single or double red cell donation; single red cell donation only; or single red cell donation with platelets

- Donation interval variations exist depending on red cell loss during incomplete apheresis red blood cell procedures
- Donation interval exceptions are allowed for dedicated donors supporting a specific patient or donors of products of special value to a specific patient (e.g. HLA) on a case-by-case basis
- Donation interval variations exist depending on the donor's cumulative red blood cell loss record for various combinations of whole blood and apheresis procedures and outcomes (i.e. complete vs. incomplete procedures)

Due to the complexity of the numerous scenarios that dictate donation intervals (and the resulting number of allowable donations per year), this information is best addressed with the individual donor, as needed, on a case-by-case basis rather than providing a standard description to donors as this item implies. We recommend that this requirement be removed.

Comment #8	Draft Guidance item: V. B. (page 8) <i>“...you should use the following targets. When collecting:</i> <ul style="list-style-type: none"> • <i>Double components, the device’s target platelet yield setting be at least 6.5×10^{11}</i> • <i>Triple components, the device’s target platelet yield setting be at least 10.0×10^{11}</i>
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Target platelet yield settings are specific to use of the device at each center due to a number of variables that include operators, type of cell counters in use, type of apheresis devices in use etc. We feel the target platelet yield settings should be set according to the manufacturer’s recommendations and the facility’s in-process experience/results in plateletpheresis collections.

Comment #9	Draft Guidance item: V. C. (page 8) <i>During the course of the apheresis collection procedure, you should visually inspect separated plasma for hemolysis.</i>
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This is not practical in using today's continuous flow apheresis instruments, especially in single needle procedures where there is constant switching by the instrument between draw from and return to the donor (approximately every minute). The FDA statement "...evaluation (prior to re-infusion to the donor)..." implies that we evaluate the plasma prior to each return cycle.

Comment #10	Draft Guidance item: VII. C. 2. (page 19) <i>...laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures. One example of a scientifically sound statistical sampling plan is the use of scan statistics (see Appendix A). However, other statistical plans may also be appropriate. Statistical plans should:</i> <ul style="list-style-type: none"> • <i>Use an alpha of 0.05 and a power of $\geq 80\%$</i> • <i>Detect a $>5\%$ non-conformance rate</i>
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Use of the suggested scientifically sound plans (or alternatives) is a novel approach and may have merit in our industry. However, prior to making such plans a requirement we would like to suggest that these types of plans be implemented on a pilot study basis at a number of collection centers that are representative of our industry (e.g. large and small, independent and hospital-based). Should the methods in the pilot study be effective and found to contribute to increased quality and safety of products produced, then a defensible case could perhaps be made for recommending such QC monitoring plans.

Comment #11	Draft Guidance item: VII. F. (page 21) <i>Rates of bacterial contamination of plateletpheresis should be monitored, and rates that exceed 1:3000 (Ref. 7) should be considered potentially non-conforming, and an investigation be initiated.</i>
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The approach to bacterial testing is not standardized in the US, because some facilities use aerobic testing whereas others have implemented both aerobic and anaerobic assays. Thus, consistent baseline data on bacterial detection rates are not yet available. This recommendation is premature, and we suggest it be deleted until further, more mature data are available.

Comment #12	Draft Guidance item: Appendix A (page 30) <i>We recommend that you define a plan for the random selection of 10% of your annual collections to be tested.</i>
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It is not clear whether “annual collections” is the number of collection procedures performed or the actual number of Platelets, Pheresis components produced. Please clarify this point.

Summary:

We would like to thank the FDA for providing us the opportunity to submit comments on this draft guidance. We fully support the FDA’s desire to protect the safety of our donors, provide standardization for the collection of Platelets, Pheresis, and address the numerous questions that have arisen in our industry since the last guideline was published in 1988. Being a hospital-based collection center, we are also acutely aware of the potential impact changes such as these may have on the availability of platelet products for our patients. While we fully support every endeavor for improving product quality and donor safety, this must be done in a manner that will not have a negative impact on the availability of platelet products and jeopardize the safety of the patients we serve.

APPENDIX A: Retrospective Study of the Effect of Plateletpheresis Donation on the Pre-Donation White Blood Cell and Platelet Counts in Two Groups of Donors

Abstract:

In order to determine whether the donation of > 24 platelet units per year has a deleterious effect on donor WBC or platelet counts, we undertook a retrospective study to compare these parameters among donors who had donated more than 24 units per year and those who donated 24 or fewer plateletpheresis units per year. The data showed essentially no difference between the two groups for change in WBC counts and a small but clinically insignificant difference for change in PLT counts. In Appendix B we also compared the deferral rates for low platelet counts among first time and frequent donors and found that not only were the rates similar, but the deferral rate for donors of more than 24 plateletpheresis units/year was significantly less than first-time and other frequent donors; deferrals for low platelet counts totaled 1.1% among more than 24,400 donations.

Background:

Today's apheresis technology allows for the collection of multiple Platelets, Pheresis products in a single plateletpheresis collection procedure. Current FDA requirements limit plateletpheresis collections to twenty-four procedures per year, without limitation to the number of products collected during each procedure. FDA is proposing a limitation of twenty-four Platelets, Pheresis products per year. The proposed limitation is based on FDA's concern that collection exceeding this limit may have a detrimental effect on the donor's circulating white blood cell (WBC) and platelet (PLT) counts. This retrospective study was performed to determine the effect of plateletpheresis donation on WBC and PLT counts in donors donating more than twenty-four Platelets, Pheresis products per year (test group) relative to donors donating less than or equal to twenty-four Platelets, Pheresis products per year (control group).

Study Design and Methods:

Individuals who had made plateletpheresis donations at our facility in at least four of the preceding five years were divided into two groups. One group consisted of donors who had donated more than twenty-four Platelets, Pheresis products in one or more years of the study period, and another group consisted of donors who had donated less than or equal to twenty-four Platelets, Pheresis products per year during the study period. In order to compare the two groups equally, a standardized Platelets, Pheresis product was defined as containing 3.3×10^{11} platelets. The number of products donated by each donor per calendar year was then determined by taking the sum of the actual platelet yields for each donation, divided by the standardized measure of 3.3×10^{11} platelets per product. Records of pre-donation WBC and PLT counts of the two groups of study donors were reviewed over time. For WBC counts, data was available and reviewed for three years 2001, 2002, and 2003. For PLT counts, data for almost five years (2001 through 2005 year-to-date) was reviewed.

Selection of Study Donors:

Records of donation appointment histories in our electronic donor scheduling system were reviewed to identify donors who had made platelet donations in at least four of the last five years. The appointment disposition field in our scheduling system indicates whether the donor made single or multiple product donations. Based on these criteria, donors were randomly selected into the two groups, consisting of twenty-five donors in each group.

Materials and Methods:

Records of the donors in both groups were obtained and the results of pre-donation WBC count, pre-donation PLT count, and platelet product final yield for each donation entered into an MS Excel spreadsheet by calendar year. Each month of the calendar year had two result entry fields to accommodate up to twenty-four donations per year. Each donation made was entered into the monthly field that most closely correlated

with the actual donation date. For each calendar year, the median WBC and PLT counts were determined and the total number of products donated was calculated based on the sum of the actual platelet yields for each donation, divided by a standardized measure of 3.3×10^{11} platelets per product. The change in median WBC and PLT counts between the first year and last year in the study period were determined for each donor. Finally, this change in counts was compared between the two study groups.

Results:

The five-year cumulative totals for both groups of donors resulted in an average of 2.3 products donated per donation in the test group and 1.3 products donated per donation in the control group (Table 1).

Table 1. Five-Year Cumulative Totals

Group	# Donations	Median	Range	# Products	Median	Range
Test (n = 25)	1482	54	36 - 102	3388	128	71 - 244
Control (n = 25)	795	27	9 - 95	1025	36	10 - 106

The percent change in median pre-donation PLT count between the first year and last year in the study period was as follows for the two groups:

- Test: 7% decrease in PLT count (R = -23% to 11%)
- Control: 1% decrease in PLT count (R = -26% to 11%)

For the test group, twenty-two donors had median PLT counts for the entire five-year study period and three donors had counts over a four-year period. For the control group, nineteen donors had counts for the entire five-year study period and six donors had counts over a four-year period.

The percent change in median pre-donation WBC count between the first year and last year in the study period was as follows for the two groups:

- Test: 7% decrease in WBC count (R = -21% to 2%)
- Control: 9% decrease in WBC count (R = -24% to 14%)

For the test group, twenty-two donors had median WBC counts for the entire three-year study period and three donors had counts over a two-year period. For the control group, all donors had counts over the entire three-year study period.

Discussion:

Our experience and data suggests that donors who donate more than twenty-four Platelets, Pheresis products per year (averaging 3.3×10^{11} platelets per product), do not appear to suffer a clinically significant adverse effect on their circulating WBC and PLT counts.

In addition to this evidence, both current and proposed FDA guidelines require monitoring of platelet donors over time. Current FDA guidelines suggest that “The accumulated laboratory data for donors should be monitored by qualified personnel and reviewed every four months by a licensed physician.” Proposed FDA guidelines suggest “You should review a donor’s records before each donation to monitor the donor’s ability to recover his/her baseline platelet count.”

We feel that these donor monitoring measures, combined with the evidence we present in our study, support the continued practice of collecting multiple Platelets, Pheresis products for each donation made, up to a maximum of twenty-four donations per year, rather than the proposed limitation to twenty-four products per year. We realize the numbers of donors in our study is small and performed without baseline WBC and PLT count data. However, the results support our experience and observations over the years that these procedures can be safely performed under current donor screening criteria and ongoing monitoring. We would be supportive of an effort to further investigate this issue in controlled prospective studies if necessary.

APPENDIX B: Incidence of Donor Deferral for Low Platelet Counts in Plateletpheresis Donors

Donor deferrals for low platelet counts (less than 150,000/ μ L) in Platelets, Pheresis donors were reviewed for all donation attempts over a four-year period covering 2001 through 2004. There were 240 deferrals for low platelet count out of 21,420 donations made during this time period. The 240 deferrals involved a total of 192 donors. Records of appointment disposition for these donors were reviewed and deferrals further stratified as follows:

- 51% (n = 98) First-time donors
- 47% (n = 90) Repeat donor donating less than or equal to 24 products per year
- 2% (n = 4) Repeat donor donating more than 24 products per year

Of note is that deferrals for low platelet counts were essentially similar for first-time and repeat donors of \leq 24 products/year. Deferrals for low platelet counts were strikingly lower among donors of $>$ 24 platelet units per year, compared to donors in the other two categories.

We feel the very low number of deferrals seen in donors donating more than 24 products per year is further evidence to support the continued practice of allowing plateletpheresis donors to donate more than 24 products per year. In addition, the very low percentage of deferrals for low platelet counts – 1.1 % of 24,420 donations – supports our belief that more prescriptive testing will not offer meaningful enhancements to donor safety.