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Director, Division of Dockets Management, HFM-305
Food and Drug Administration,
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Dear Dr. Williams;

Thank you for the opportunity to comment on the Collection of Platelets by Automated Methods; Draft Guidance Docket No 2005D-0330. We support the Agency's desire to protect the safety of the donor and to standardize care throughout the blood collection industry. This draft guidance consolidates many important aspects of platelet collection; such as, implementation, validation, labeling, quality control and licensing steps. Bringing all of this information into one document should assist the community in executing the appropriate activities for collection of platelets by automated methods. Even though this guidance does not create legally binding requirements, the Agency should be aware that by common practice, establishments implement these recommendations as a rule. Often these guidance documents provide the framework to develop implementation plans, business work rules and compliance standards once implemented into standard operating procedures. Our attached comments, for the most part, seek clarification, or request scientific based data or peer reviewed references for review to assist industry in implementing the guidance. Our comments are in order as they are presented in the document.

Sincerely,

Harvey G. Klein, M.D.
Chief, Department of Transfusion Medicine

2005D-0330

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Donor Selection

We would like clarification to the guidance concerning testing donors prior to the first donation. In Section III.A., you state, "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:". It is not clear to us whether "Prior to the first donation" may be interpreted as a sample taken immediately prior to initiating the first platelet pheresis donation, or whether it could be a sample taken during the procedure using the "diversion pouch" attached to most apheresis disposable collection kits. In addition, it is not clear whether the test results must be evaluated prior to the start of the first donation procedure, or whether results may be evaluated during or after the procedure has been completed. Finally, it is not clear what is meant by "test ... for levels of the following laboratory values that are acceptable under the manufacturer's directions for use". Is the intent to test for the following analytes and evaluate results against acceptance criteria recommended by the apheresis machine manufacturer?

In the same section, you state, "If you cannot test before the first donation (for example, because the donor presents at a mobile collection site), you should evaluate the donor's WBC and platelet counts after the first collection. Please clarify whether the intent is to (1) evaluate a sample obtained prior to the first donation, but tested and evaluated against acceptance criteria at some future time, or (2) obtain a sample at the completion of the first procedure (post-donation) and use this specimen to test and evaluate the donor. We believe that the sample taken prior to rather than post donation most accurately reflects the donor's baseline WBC and platelet count, and should be the one used to assess the donor. Please provide wording to state more clearly that a pre-donation sample should always be obtained.

We suggest that you omit all mention of post-donation platelet counts (i.e., from a donor specimen obtained at the end of the collection procedure) as qualifying a donor for the next procedure. Our experience shows that there is never any reason to use a post-donation CBC platelet count for a decision tree analysis. Post-donation counts do not reflect the level of platelets in a donor, since they are acutely and substantially reduced by the actual procedure. Either the pre-donation count from the current donation, the one from the previous donation, or the mean of the last two pre-donation counts should be used to make decisions as to the safety of the procedure for the donor, or the targeted level of platelet yield that should be programmed into the device. Suggested re-wording: If you cannot obtain the results of the CBC test drawn before the first donation (for example, because the donor presents at a mobile collection site), you should evaluate the donor's pre-donation sample WBC and platelet counts after the completion of the first collection and make this data available for consideration prior to the next platelet donation.

In the same section, you state that one should not collect platelets from donors that have ingested certain drugs, i.e. "Aspirin (ASA)/ASA-containing drugs – 5 days from last dose (Ref. 10)". We do not believe that there is peer refereed, published data that suggests that a waiting period of 5 days is superior in restoring platelet function or survival than the current waiting period of 36 hours. The citation is to an abstract. A more reasonable approach may be a 72 hour waiting period in that it is generally accepted that ten percent of the total number of platelets is replaced each day. This would be a 30% replacement in unaffected platelets sufficient to obtain the desired outcome for the recipient based on many years of experience using this standard.

Also with Non-steroidal Anti-inflammatory Drugs (NSAIDS) – 3 days from last dose (Ref. 9). We do not find data to support the decision to move from a 24 hour waiting period to a 36 hour waiting period. This class of drugs has a relative short half life and the impact to platelet function is readily reversible. We have not found any reference to any negative recipient

outcomes from platelets obtained under the current waiting period for NSAIDs. Once again we do not believe that one center's operating procedure, as in reference 9, should be the basis for national policy.

Donor Management

In Section III.B.1., you state, "For any collection facility that cannot perform a pre-donation platelet count (for example, a mobile collection site), you should use a platelet count as specified by the device manufacturer, or a post-donation count from a previous collection to set the target platelet yield." Please clarify the meaning of a "post-donation count in this context. Since it would be ill-advised to use a specimen collected at the end of the previous procedure to set a target, we assume that the intent is to use the results of a specimen collected at the start of the previous donation. If this is correct, suggested re-wording might include: "For any collection facility that obtains the sample for a pre-donation platelet count, but cannot perform the actual assay immediately, (for example, a mobile collection site or any other site that does not routinely evaluate the counts prior to the collection), you should use a platelet count as specified by the device manufacturer, or a pre-donation count from the previous collection, or the average of the donor's last two pre-donation platelet counts to set the target platelet yield.

In the same section you state that, "You should defer from donation donors whose platelet counts are less than 150,000/uL until a subsequent platelet count indicates that the donor's platelet count is at least 150,000/uL." This recommendation is not supported by published data. A review of reference 21 shows that all donors deferred for 2 months because one pre-count was <150k, and all donors deferred for 6 months because 2 pre-counts in one year were <150k, had returned their pre-count to > 150k on return visit after the deferral period was over. Not all donors returned – but the majority did (70-80%). Thus, if the donor is deferred for 2 to 6 months, as defined in the criteria in the paper, all should recover their counts. The FDA recommendation" above is NOT supported by published data. Each center should establish its own deferral criteria, and have written criteria in an SOP and then applied to donor management by trained personnel. There is NO need for a "reentry" platelet count to qualify the donor for subsequent donation after the deferral period is over any more than a re-entry hemoglobin determination would be needed for donors who fail 8 weeks earlier. The unusual donor who might begin a plateletpheresis procedure before the platelet count is available and is subsequently found to have a count <150,000 will have no ill effects and the unit will simply not meet criteria for use.

Donor Frequency

In Section III.B.2., you state that, "A donor should undergo no more than 24 Platelet, Pheresis collections in a 12-month period." These restriction criteria may have been prudent for donor safety based on early generation apheresis devices that collected large numbers of leukocytes. Improvements to collection devices and their efficiencies have reduced the number of donor lymphocytes in the final product. Current generation collection devices do not pose this risk. We do not feel that there is scientific data to support this restriction in the number of donations. Each attempt to donate platelets is being monitored with CBCs that include platelet and WBC counts as suggested in this guidance and the donor is determined to be eligible to donate at each subsequent visit based on this data. The use of real data to

determine eligibility should be used to protect donor safety rather than an arbitrary limit of 24 collections per year.

You also state that, "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. This statement should be deleted from the guidance. This logic and donor restriction is no longer valid and could be removed if the above arguments are accepted.

We do agree that there should be different days between the donation of single, double and triple platelet products. We agree with the proposed intervals in this section.

You also state that, "A post-donation platelet count should be performed after each collection." We find no justification for this. The efficiency of collection is directly related to the donor platelet count, making it highly unlikely that the donor's platelet levels could get down to dangerously low levels as a result of the collection procedure. Plateletpheresis donors do not have an increased incidence of clinical bleeding after donation. In many cases, platelet count will fall below the normal range [$<150k$], but will recover to normal levels within a few days. This transient decrease is without clinical relevance.

Medical Coverage

In Section III.D., you state that, "Under 21 CFR 640.22(c), the procedure for collection of Platelets, Pheresis, including the availability of medical care during the donation, must conform to the standards described in the biologics license application or supplement. 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). In case of an emergency, calling 911 may be used to obtain emergency medical care and transportation to another facility for further care, but we do not believe this is a sufficient substitute for an available physician as previously described."

This guidance does not protect donor safety. If a donor has a life-threatening event or a cardiorespiratory arrest, the arrival of a physician 15 minutes later will not help. An alternative would be to have a qualified, medical professional licensed to administer drugs on site and immediately available (i.e. within less than one minute) at all times. A physician should be available by phone or page within five minutes. The only donor death directly attributable to plateletpheresis donation in the past 20 years was due to severe anaphylaxis, with respiratory arrest, occurring within 10 minutes of the start of a plateletpheresis procedure. The reaction was documented to be due to sensitization to ethylene oxide (very high titer IgE anti-ETO in donor's serum). Collectors should have an SOP to address the possibility of anaphylaxis.

Information Provided to the Donor

In section IV., you state "Information about potential side effects ... include anticoagulant effects (tingling and/or nausea), hypovolemia (decreased blood volume), and fainting." We suggested that you add allergic reactions as a possible side effect.

In the same section you state that we should include "A statement that the long-term effects of repeated plateletpheresis on the donor's platelet and leukocyte count is not understood." We suggest that the statement also include that no sustained clinical harm has ever been documented.

Target Platelet Yield :

In Section V., you state that:

To assure that each component obtained from a multiple collection of Platelets, Pheresis results in an actual platelet yield of at least 3.0×10^{11} platelets, you should use the following targets. When collecting:

- Double components, the device's target platelet yield setting be at least 6.5×10^{11} .
- Triple components, the device's target platelet yield setting be at least 10.0×10^{11} .

Since the most effective target yield settings may be device dependent, we recommend that this section be modified to state that target value should be set to a value that is consistent with the manufacturer's recommendation and has been validated to consistently produce double platelet products with a minimum of 3.0×10^{11} in each labeled component, or triple platelet products with a minimum of 3.0×10^{11} in each labeled component.

Process Validation

In Section VI., you state that for each device intended for the routine collection of Platelets, Pheresis must be cleared by FDA for this purpose (see 21 CFR 864.9245). You should conduct Process Validation for each device used in your establishment prior to implementing routine collections.

To say that you should conduct process validation for each device used could be misinterpreted. This should be clarified to state that you should conduct Process Validation for each TYPE of device.

Validation Protocol

In Section VI., you state that "the validation protocol should include at least the following: ... Residual WBC count for the collection (if leukocyte reduced) and percent recovery." It is not clear how percent recovery would be calculated for collections that are leukocyte reduced by apheresis. If this is intended to apply only to plateletpheresis products leukocyte reduced by filtration after collection, please qualify the requirement. The requirement for calculation of percent recovery is also stated under the heading of "Product Performance Qualification".

Product Performance Qualification (Component Collection)

In Section VI.B., you state that we should "Test a minimum of 60 consecutive single (30 for double and 20 for triple) collections for each type of automated blood cell separator..." We believe that the minimum number should be the same, regardless of whether you are targeting single, double or triple collections. It is the collection process itself that is being validated, and the number of collection events is the same in all three cases. If only 20 collections are required to validate triples, then only 20 collections should be required to validate singles.

You state that we should perform bacterial contamination testing on 500 collections with 0 failures. We do not find this reasonable as it is not statistically based and is inconsistent with references cited in this document that there will be 1 initially positive in 1550 collections, with 1 in 5000 confirmed positive collections. An expectation of zero events is unreasonable. In addition, it may not be possible to determine if a contamination was related to donor issues or to the collection process itself. The intent of validation is to evaluate performance of the collection procedure in a closed system. Bacterial contamination testing of finished products may not be an effective means of validating this aspect of the collection process. Since it is a closed system, perhaps it would be more efficient to evaluate phlebotomist skin prep technique independently of product performance qualification. Another possible source of contamination is in sampling, and this can also be evaluated independently since it is a user technique issue. We assume that sterility in the manufacturing of the bag itself has been validated by the manufacturer and reviewed by FDA as part of device approval. Finally, bacterial contamination testing is performed on each finished product. Since it is done as an end-product test, it may not be important to include in validation, particularly if staff competency in sterile technique is assessed.

You also state, that we should include all devices the initial product performance qualification and additional devices of the same model be included in monthly QC testing only. This should be clarified. We think the intent was for the data to be collected equally from all devices of each type. The collections should be equally distributed to obtain the "n" desired but not that each device have the full number of data points collected from each individual instrument.

Later in the same section you state that product performance qualification should be completed for each automated blood cell separator used in your establishment. This statement conflicts with the previous bullet. PQ on each separator does not equal incorporating a new device into the QC plan. We think the intent was that performance qualification should be performed on each type of device for platelet collection.

Later in the same section you state that we should perform bacterial contamination testing using a CBER cleared or approved bacterial detection system specifically labeled for testing of plateletpheresis components (Refs. 16, 17, 18, and 19), used in the manner for which it was cleared or approved. This should be clarified to be consistent with FDA policy that equipment may be used for non-approved uses if it has been validated to work as intended in the facility.

QUALITY ASSURANCE (QA) AND MONITORING, Standard Operating Procedures (SOPs) and Record Keeping, Adverse reactions:

We think this section should also state that there should be an SOP for medically competent staff should be trained to administer drugs from a written or verbal order.

pH measurement:

In Section VII, you state, "Accurate pH measurement is time dependent, and samples should be tested within 1 hour of sampling.

Please provide a peer reviewed reference that supports that pH should be done within an hour. Suggest that you add wording to provide for the use of other validated testing schemes.

Component Storage and Shipping

You state that when sterile docking, "You should use containers from the same manufacturer." We recommend that you should follow the recommendations of the sterile docking device manufacturer, and validate the device for the intended use.

Donor Monitoring

Platelet counts

You recommend that one should notify the Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL.

We recommend that you omit this entire sentence. We have previously noted that we do not see any usefulness for a post collection count. The cited Lazarus paper proposes an algorithm to allow donor to attempt donation again without testing a qualifying sample prior to donation.

QC monitoring

You state that you interpret testing "at the end of allowable storage period" to include testing at the time of issue. However, in the section on QC protocol, you state that the facility should "Allow for testing at the maximum allowable storage time for the container system used (or representing the dating period). 21 CFR 640.25(b) specifies that QC testing be performed at the end of the storage period. Components that expire or are returned to the collection facility may be used for QC. We interpret "at the end of the storage period", to include testing within 12 hours of expiration." These interpretations appear to be in conflict with each other.

You recommend that as part of your QC protocol you should include testing of components collected on each individual automated blood cell separator device. This should be clarified so that one can determine if the intent is to test from each individual device or from each type of device. Please clarify if platelets from every instrument should be selected at each QC interval.

Please explain the value of performing platelet count again at the end of storage. Please provide references to show that platelet counts performed on products that are 5 days old will be accurate.

You also recommend that we test for percent component retention. We cannot determine a scientific reason to do this for apheresis platelets that are leukoreduced by the action of the instrument. The only time retention may be an issue is if an in lab filter is used. Please clarify your intent.

You also recommend that we calculate the volume of the component on day of QC testing. Please clarify if your intent is that the volume be calculated before or after final QC samples are taken from the product. Please provide rationale for only re-determining the product volume as this is only logical if the intent is to re-calculate the product content after all samples are collected to ensure there is still a minimum platelet concentration 3.0×10^{11} per the product label.

You also state that the acceptance criteria should ensure that the percent component recovery should be $\geq 85\%$ or per the manufacturer's specifications. This seems to be the requirement for leukoreduced red cell components but doesn't seem to apply to apheresis platelet components.

Quality System Audits

You state that we should audit records of component bacterial contamination testing, and rates that exceed 1:3000 (Ref. 7) should be considered potentially non-conforming, and an investigation be initiated. This seems to be inconsistent with process validation requirement of 0 defects in 500. Please clarify which threshold we should use to determine the acceptability level to deem the process in control.

Changes Being effected in 30 Days (CBE-30) Supplement: Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (21 CFR 601.12(c)).

You state that Upgrades provided by the manufacturer to your cleared apheresis device should be reported to the agency as a CBE-30. Please define or clarify upgrades so that we can readily determine if this applies to software only or also to other elements such as disposables that do not alter the previously validated final product or result in products that make additional manufacturing claims or data or information management systems that do not have direct impact on the final product.