



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
New Orleans District Office
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Memorandum

Date December 27, 2005

From Brian S. Lynch, District Biologics Specialist, Montgomery, AL Resident Post

Subject Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff "Collection of Platelets by Automated Methods" Draft Guidance, Dated September 2005

To James W. Blakely, Supervisory Investigator, Jackson, MS Resident Post

As part of my duties as the District Biologics Specialist and to maintain my certification, I am required to review various Draft FDA Documents that provide guidance to the Blood and Plasma Industries and to the FDA Investigators who inspect the blood banks and plasmapheresis centers that make up the Blood and Plasma Industries. I have had serious concerns with the previous document that provided guidance to Blood Banks for the collection of platelets by automated methods. The Draft Guidance Document "Collection of Platelets by Automated Methods", dated September 2005, is an effort by CBER to revise and update the information in the "Revised Guideline for the Collection of Platelets, Pheresis", dated October 7, 1988, which was woefully outdated. Some of my concerns with the October 7, 1988 document, "Revised Guideline for the Collection of Platelets, Pheresis", were carried over to the new Draft Guidance Document, "Collection of Platelets by Automated Methods", dated September 2005. In addition, the review of the new Draft Guidance Document, "Collection of Platelets by Automated Methods", dated September 2005, revealed additional concerns.

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

The problems described below were noted during the review of Federal Register Document No. 2005D 0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, dated September 2005.

Section II B Definitions: Lacks a definition for Extracorporeal Cell Volume (ECV) for Red Blood Cells. The definition should include the ECV for Red Blood Cells in samples collected prior to the start of the automated procedure.

Section III B. 1. Donor Management - Platelet Count: Bullet #1. Most blood centers perform a pre-donation platelet count on first time plateletpheresis donors if possible. After the initial donation, process parameters are set using the pre-donation platelet count from last donation prior to the current donation or from a historical average provided the donor has enough donations that are current. If the donor has not donated in a while, the default platelet count of 150,000 specified by the manufacturer of automated equipment is used. Additionally, samples for required testing are collected prior to the start of the procedure rather than after the procedure is completed. This is done in case there is a problem during the procedure that results in the donor being disconnected before the procedure is completed. This way the blood bank has the required samples if the donor refuses to be re-stuck or does not have a suitable vein for collecting samples after being disconnected before the procedure is completed. This is done so that required testing can be performed if a suitable product for transfusion has been collected prior to the donor being disconnected before the procedure is completed.

Section III B. 2. Donor Management: Donation Frequency: Bullet #2 - This would cut pheresis platelet production by 20% to 30% nationwide. Are you sure you want to do this?

Section III B. 2. Donor Management – Donation Frequency: Bullets #3 - #5 are irrelevant as most blood banks that allow 24 donations per year will not schedule an allogeneic plateletpheresis donor for more than 2 donations per month with all donations at least 48 hours apart and no more than 2 donations in a seven day period. The donation frequency at some of the blood banks in the District is once every 28 days or a maximum of 13 donations per year which averages out to once a month for their best donors. If the donor is a dedicated donor for a specific recipient, the criteria listed in Section III. C. – Dedicated Donors are used.

Section III B. 3. Donor Management – RBC loss prior to collection of Platelets, Pheresis: Bullets #1 through #3 are irrelevant without an adequate definition of the ECV. The definition of the ECV shall include red blood cell volumes for all samples for all required testing collected just prior to the start of the procedure. Most blood banks collect whole blood samples for viral marker testing, pre-collection platelet counts, and all other required testing performed prior to the start of the plateletpheresis procedure from a sample port on the plateletpheresis collection set just prior to initiating the plateletpheresis procedure. Additionally, most blood banks use the ECV from the operator’s manual for the apheresis equipment used for plateletpheresis. I am familiar with Gambro/COBE Spectra Aphereis Instrument, Gambro/ COBE Trima Aphereis Instrument, and the Baxter Fenwal Amicus Cell Separator instrument used for plateletpheresis. No one in the area that I routinely inspect uses the Haemonetics instruments for plateletpheresis.

The ECV for a single needle procedure on the Baxter Fenwal Amicus Cell Separator Instrument is not an issue as far as the ECV is concerned as the calculations for the ECV if the donor has completed the initial cycle is considered to be greater than 100 ml of red blood cells. The red blood cell ECV,

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

according to the Operator's Manual, is calculated as 64 ml for the residual volume in the collection set plus the hematocrit times the cycle volume after the first cycle is completed. If the first cycle is not completed, the ECV is calculated as the hematocrit times the cycle volume of whole blood collected during the first cycle. This is almost always greater than 100 ml for a single needle procedure. The standard operating procedures for these blood banks that use the Baxter Fenwal Amicus Cell Separator Instrument instruct the operator that the ECV for a single needle procedure on a Baxter Fenwal Amicus Cell Separator instrument is considered to be greater than 100 ml of red blood cells for a donor who has a cell loss during the preceding 8 weeks.

On the Gambro/COBE Spectra Apheresis Instrument, the red blood cell ECV for a single needle procedure in the operator's manual is listed as 93 ml for a single needle procedure based on a hematocrit of 40% and cycle volume of 232.5 ml of whole blood. All of the blood banks that I inspect use the ECV of 93 ml in the example in the Operator's Manual for the Gambro/COBE Spectra for determining the ECV irregardless of the donor's hematocrit. Note: If the donor has a hematocrit of 44% or greater, the red blood cell ECV is greater than 100 ml. The American Red Cross (ARC) Job Aid for estimating the red blood cell ECV and the red blood cell/plasma losses for the Gambro/COBE Spectra states that the estimates of plasma and red blood cell losses are based on a 40% donor hematocrit and successful reinfusion. The ARC Job Aid for the Gambro/COBE Spectra states the red blood cell/plasma losses include the plasma and red blood cells in the components, the disposable kit, and the sample tubes (60 ml). Note: The explanation in the American Red Cross Job Aid does not include the red blood cell ECV. The American Red Cross Job Aid for calculating the red blood cell losses for the Gambro/COBE Spectra Apheresis Instrument states to use 24 ml of red blood cells if the total sample volume of the sample tubes is less than 60 ml plus the 93 ml red blood cell ECV for a single needle plateletpheresis procedure if there is no rinseback/reinfusion to calculate the red blood cell loss. Thus the red blood cell loss for the Gambro/COBE Spectra Apheresis Instrument is calculated at 117 ml while the red blood cell ECV for the Gambro/COBE Spectra Apheresis Instrument is calculated at 93 ml based on the example in the owner's manual irregardless of the donor's hematocrit. All of the blood banks that I inspect perform their calculations for the red blood cell losses on the Gambro/COBE Spectra Apheresis Instrument using the red blood cell ECV of the samples plus the red blood cell ECV of the disposable kit for the no rinseback/reinfusion to calculate the red blood cell loss. The main difference is that all of the other blood banks that I inspect will automatically defer the donor for 8 weeks for a no rinseback/reinfusion on the Gambro/COBE Spectra Apheresis Instrument while the ARC will continue to bleed the plateletpheresis donor as long as the calculated red blood cell ECV for the plateletpheresis procedure is less than 100 ml. Thus a donor can donate whole blood or make a single red blood cell apheresis donation with platelets or plasma or both at the ARC and then donate platelets by plateletpheresis after 48 hours or platelets with concurrent plasma on the 28th day as long as the calculated red blood cell ECV is less than 100 ml which it is according to the way the red blood cell ECV is calculated by the ARC for a single needle plateletpheresis procedure on a Gambro COBE Spectra. There are no limitations in the procedures for the number of red blood cell losses due to no rinseback/reinfusion that can occur with or without a prior whole blood donation or a single red blood cell apheresis donation with platelets or plasma before the donor is deferred. I have written the ARC up for this several times. The ARC response is that until the definition in the guidance document is changed to include the red blood cell ECV of samples collected prior to the beginning of the procedure, they will continue to use the definition as it currently is written and will continue to bleed plateletpheresis until the definition is changed. I have explained to the ARC that guidance documents are not binding on the industry or to the FDA. However, the ARC Consent Decree Working Committee is reluctant to take action until the guidance document is changed.

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

The other piece of equipment used for plateletpheresis that I am familiar with is the Gambro/COBE Trima Apheresis Instrument which is used only by the ARC in the area that I currently cover. The red blood cell ECV for a single needle procedure in the operator’s manual for the Gambro/COBE Trima Apheresis Instrument is listed as 92 ml for a single needle procedure based on a hematocrit of 40% and cycle volume of 230 ml of whole blood. The American Red Cross (ARC) Job Aid for estimating the red blood cell ECV and red blood cell/plasma losses for the Gambro/COBE Trima Apheresis Instrument states that the estimates of plasma and red blood cell losses are based on a 40% donor hematocrit and successful reinfusion. The ARC Job Aid for the Gambro/COBE Trima Apheresis Instrument states the red blood cell/plasma losses include the plasma and red blood cells in the components, the disposable kit, and the sample tubes (60 ml). Note: The explanation in the American Red Cross Job Aid does not include the red blood cell ECV. The American Red Cross procedure for calculating the red blood cell losses for the Gambro/COBE Trima Apheresis Instrument states to use 24 ml of red blood cells if the total sample volume of the sample tubes is less than 60 ml plus the 95 ml red blood cell ECV for a single needle plateletpheresis procedure if there is no rinseback/reinfusion to calculate the red blood cell loss. Thus the cell loss for the Gambro/COBE Trima Apheresis Instrument is calculated at 119 ml while the red blood cell ECV for the Gambro/COBE Trima Apheresis Instrument is calculated at 92 ml based on the example in the owner’s manual irregardless of the donor’s hematocrit. For calculating the 95 ml red blood cell loss for the Gambro/COBE Trima Apheresis Instrument for a no rinseback/reinfusion, the calculation in the ARC procedure includes 92 ml for the red blood cell ECV for the disposable kit and the 3 ml of residual red blood cells in the tubing going to and from the disposable kit to the donor that is not included in the calculation of the ECV in the ARC Job Aid. Repeated inspections of ARC facilities in the area that I cover have shown that the ARC will continue to bleed the plateletpheresis donor as long as the calculated ECV for the plateletpheresis procedure is less than 100 ml. Thus a donor can donate whole blood or make a single red blood cell apheresis donation with platelets or plasma or both at the ARC and then donate platelets by plateletpheresis after 48 hours or platelets with concurrent plasma on the 28th day as long as the calculated red blood cell ECV is less than 100 ml which it is according to the way the red blood cell ECV is calculated by the ARC for a single needle plateletpheresis procedure on a Gambro/COBE Trima Apheresis Instrument. There are no limitations in the number of procedures with losses due to no rinseback/reinfusion that can occur with or without a prior whole blood donation or a single red blood cell apheresis donation with platelets or plasma before the donor is deferred. I have written the ARC up for this several times. The ARC response is that until the definition in the guidance document is changed to include the red blood cell ECV of samples collected prior to the beginning of the procedure, they will continue to use the definition as it is currently written and will continue to bleed plateletpheresis until the definition is changed. I have explained to the ARC that guidance documents are not binding on the industry or to the FDA. However, the ARC Consent Decree Working Committee is reluctant to take action until the guidance document is changed.

I do not have a problem with the ECV calculations for double needle procedures on the Baxter Fenwal Amicus or the Gambro/COBE Spectra. There is no double needle procedure approved for the Gambro/COBE Trima.

III B. 4. Total volume losses per collection procedure: I think it would be better to use an annual volume loss (12 month cumulative loss) of 14,400 ml for the large donors (24 donations times 600 ml) who weigh greater than 175 lbs. and 12,000 ml. for small donors (24 donations times 500 ml) who weigh 175 lbs. or less. In the last 20 years, I have never seen a donor who donated 24 times in a single year including directed donors for specific recipients or a donor who exceeded the annual volumes listed above. However, I have routinely seen donation volumes that have exceeded the recommended 600 ml

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

limit for a large donor and the 500 ml limit for a small donor. None of the equipment that I am familiar with have volume limits based on donor size. There are minimum and maximum platelet concentrations per ml of plasma and minimum plasma volumes for a given platelet count but no preset volumes based on donor size. There are machine parameters that can be set for the volume of whole blood to process based on donor platelet counts and donor size and the type of products to be processed.

The draft document does not adequately address red blood cell losses or deferral periods. The draft document fails to list a 12 month cumulative red blood cell loss that would prevent the donor from donating if the donor exceeded the maximum red blood cell loss for a 12 month period in less than the 12 month cumulative period. The draft document fails to address deferral periods for multiple red blood cells losses occurring in an 8 week period. An example would be a donor who donates whole blood or makes a plateletpheresis donation with a concurrent red blood cell donation that may or may not include concurrent plasma that is followed in 48 hours (2 days) later by a PP (plateletpheresis only donation) or 28 days later by a P2 (plateletpheresis with concurrent plasma) collected by a single needle procedure on a Gambro/COBE Spectra Apheresis Instrument or on a Gambro/COBE Trima Apheresis Instrument with a no rinseback/reinfusion where the calculated red blood cell loss including red blood cell volume of the samples collected prior to the procedure is greater than 100 ml. Using a documented ARC scenario, the donor could donate platelets with concurrent red blood cells on a Gambro/COBE Trima Apheresis Instrument with a red blood cell loss of 254 ml (200 ml for the red blood cells, 30 ml red blood cells for the residual in the kit, and 24 ml of red blood cells for samples collected prior to the initiation of the procedure). The donor could then donate plateletpheresis using a single needle procedure within 2 days (48 hours) or plateletpheresis with concurrent plasma 28 days later according to ARC donation interval table on a Gambro/COBE Trima Apheresis Instrument or a Gambro/COBE Spectra Apheresis Instrument because the calculated ECV for both instruments is less than 100 ml of red blood cells. If the donor experienced problems during the donation and the donor’s red blood cells were not returned, i.e. no rinseback or no reinfusion of red blood cells. The donor would lose an additional 119 ml of red blood cells if the donor donated on Gambro/COBE Trima Apheresis Instrument or an additional 117 ml of red blood cells if the donor donated on a Gambro/COBE Spectra Apheresis Instrument. The donor would then be able to donate plateletpheresis only in 2 days (48 hours) or plateletpheresis with concurrent plasma 28 days later based on the current ARC definition of red blood cell ECV. By this time, the donor would have lost at least 370 ml of red blood cells. This is equivalent to a double red blood cell donation. In the actual records observed and written-up, the donor donated platelets with concurrent red blood cells and plasma on a Gambro/COBE Trima Apheresis Instrument on 05/01/04. The red blood cell loss for the procedure was recorded as 254 ml and the plasma loss for the procedure was 650 ml. The donor returned on 05/08/04 for a PP (plateletpheresis) procedure that was performed on a Gambro/COBE Trima Apheresis Instrument. The procedure was 71 minutes in length. No product was collected. The procedure was QNS and the outcome was No rinseback. The red blood cell loss was listed as 119 ml and the plasma loss as 148 ml on the Trima Apheresis Procedure Record and on the Apheresis Donor Continuous Record for the donor in question. The donor’s total red blood cell loss for the time period 05/01-08/2004 was 373 ml. The donor returned on 06/24/08 and made a P2 (plateletpheresis with concurrent plasma) donation on a Gambro/COBE Trima. The only reason that the donor did not return before 06/24/04 was that the donor exceeded the ARC red blood cell 12 month cumulative cell loss of 1540 ml after the donation on 05/08/04. According to ARC Donor Interval Table, the donor would have been deferred from all donations for a sixteen week period if the donor had made a double red blood cell donation by apheresis or had attempted a double red blood cell donation where the first unit was collected and there was a no rinseback/reinfusion during the collection of the second unit. The red blood cell loss by the donor described above was equivalent to a double red blood cell donation where the first

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

unit was collected and there was a no rinseback/reinfusion during the collection of the second unit. The only difference was that the losses occurred over an 8 day period rather than a single day. Documentation will be provided upon request.

Section VI. D. Performance Criteria: The criteria listed for the performance qualification exceed the capabilities of the apheresis instruments currently in use. The average failure rate for the leukoreduced plateletpheresis products is 5%. This is usually due to poor phlebotomy technique and not to machine error or to elevated donor white blood cell counts. However, approximately one (1) out of five (5) leukoreduction failures can not be attributed to any known factors. All of the blood facilities that I inspect that collect leukoreduced plateletpheresis products perform platelet counts and residual white blood cell counts on 100% of the leukoreduced plateletpheresis products collected. If a leukoreduced plateletpheresis product fails the residual white blood cell count, the product can be sold as a non leukoreduced plateletpheresis product which is a licensed product that was on the market for a number of years before leukoreduced plateletpheresis products became available either as a part of the collection process or by post collection filtration.

The actual platelet yield criteria can not be met for basically the same reasons listed above. Bad phlebotomy techniques can result in a poor platelet yield. Technician error in setting the collection parameters on the instrument can also result in a poor platelet yield. All of the blood banks that I inspect set collection parameters for the instrument using the historical average of the pre-collection platelet count of the three donations prior to the current donation if available. This can result in a low platelet yield if the donor has a significant drop in his or her platelet count since the last donation as most blood banks do not have the capability to perform pre-donation platelet counts at the fixed donor sites where most of the plateletpheresis products are collected.

On page #11, the information in the two sub-bullets under the first bullet under the statement “You should use the following collection performance qualification criteria:” are contradictory.

Last but not least, bacterial contamination testing criteria are a mute point since all blood banks are performing 100% bacterial testing of all plateletpheresis products collected. To get 500 plateletpheresis products from a single instrument would take a minimum of 4 months if the facility averaged 125 collections per month per instrument. My busiest facility averages 75 plateletpheresis procedures per instrument per month while most average between 40 and 50 plateletpheresis procedures per instrument per month if they can keep the instruments in service. Some instruments get used more use than others and some instruments are more dependable than others. Most of my facilities keep at least one instrument for back-up should an instrument on the floor go out of service for an extended time period. The largest issue that I see with bacterial contamination testing is false positive test results. The bacterial contamination systems approved for use do not detect the presence of bacteria but measure oxygen/carbon dioxide concentrations or turbidity to determine the presence of bacteria. Approximately 80% of the positive test results that I have seen in the blood banks that I inspect are false positives even on the systems that reportedly detect the presence of bacteria by turbidity. Additionally, none of the systems currently in use will detect the presence of anaerobes.

The real problem with bacterial contamination involves the pooling of random donor platelets in hospital blood banks that operate as transfusion facilities that are exempt from inspection. The FDA has no control over these facilities nor do we want control over these facilities. None of the blood banks in my

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

area currently manufacture random donor platelets but some of the blood banks import random donor platelets from other blood banks for distribution. According to 13th Edition of the AABB Technical Manual, the estimated risk/unit transfused for bacterial contamination of plateletpheresis is 1:19,500 (page 603) while the estimated risk/unit transfused for bacterial contamination of random donor pooled platelets is 1:1,700 (page 623).

Section VII B. 3. Red Blood Cell Losses: See pages #2 - #5 above.


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DISTRIBUTION LIST

Federal Register Document No. 2005D-0330, CBER 200436, Technical Review of Guidance for Industry and FDA Review Staff “Collection of Platelets by Automated Methods” Draft Guidance, Dated September 2005, 12/27/05, BSL

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