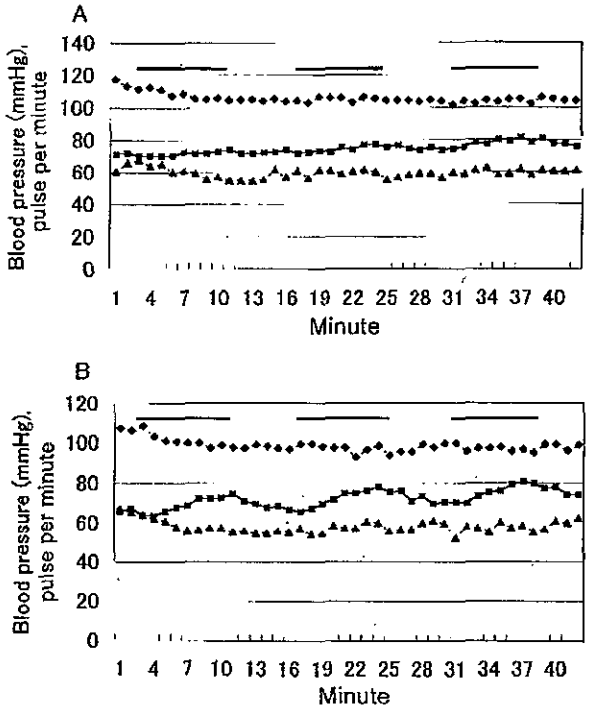

Fig. 5. Blood pressure and pulse rate measured every 1 minute during apheresis, averaging from five women donors whose pulse rate was stable (A) and increased (B) during blood withdrawal. (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

TABLE 2. CBV (mL) in donors showing stable pulse (type A) and fluctuating pulse rate (type B) during apheresis and in VVR donors*

Men	
Type A	4657.3 ± 284.3 (n = 20)
Type B	4347.1 ± 391.7 (n = 19)
VVR	4160.8 ± 458.6 (n = 2)
Women	
Type A	3819.1 ± 387.0 (n = 21)
Type B	3550.9 ± 341.1 (n = 41)
VVR	3535.6 ± 248.6 (n = 6)

* The differences of blood volume between type A and type B donors were statistically significant ($p < 0.05$) for both men and women donors. There was no difference in blood volume between VVR donors and type B donors.

blood (type B), as shown in Fig. 5B. The third was an irregular fluctuation without any clear relationship to blood withdrawal (type C, not shown). Types A, B, and C were shown in 31, 60, and 9 percent of women donors and 49, 46, and 5 percent of men donors, respectively. Women donors over 40 years old mostly (15 of 19) showed the type B fluctuating pattern, and there were only two each of donors showing types A and C, respectively. In contrast, in men donors over 40 years old, 40 percent were type B (6 of 15) and 60 percent were type A.

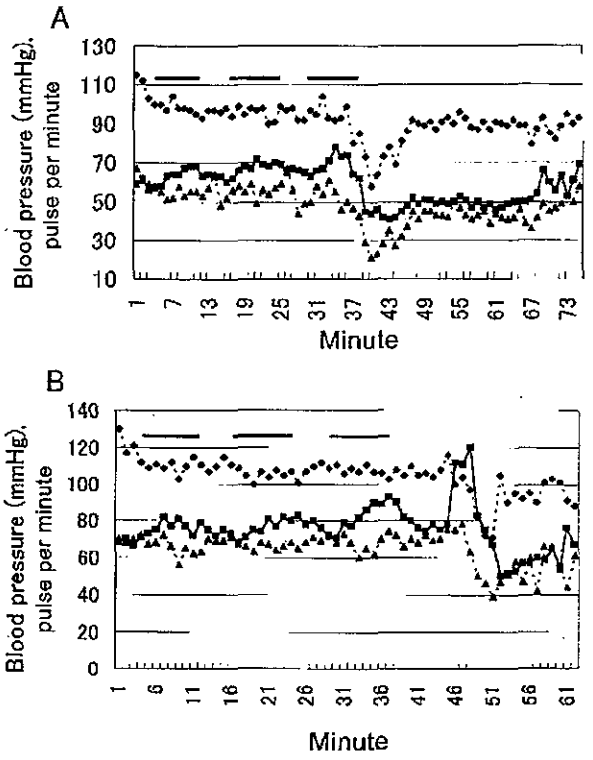

Fig. 6. (A) Blood pressure and pulse rate in a women donor (43 years old) who suffered from VVRs during the third cycle of blood withdrawal. VVRs were accompanied by tachycardia and lowered blood pressure, and then tachycardia was followed by prolonged bradycardia. The donor was laid down flat until recovery. (B) Another example of VVRs (a 20-year-old woman donor). VVRs occurred when she started to leave the bed and were accompanied by bradycardia and hypotension following transient tachycardia. Both donors showed an increase in pulse rate during blood withdrawal (indicated by horizontal bars). (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

The mean CBV of the donors showing pulse rate fluctuations (type B) was less (about 7%) than those showing stable pulse rate (type A) both for men and for women donors (Table 2), and their differences were significant ($p < 0.05$).

The pulse rate data on VVRs were obtained from six women (20-43 years old) and two men donors (23 and 44 years old). They all showed the pulse rate fluctuations of the type B before the appearance of VVRs, as shown in two examples illustrated in Figs. 6A and 6B. The donors shown in Fig. 6 were kept in bed horizontally until they recovered, without medication. Typical VVRs were accompanied by marked bradycardia and periods of hypotension of various durations. The mean CBV of donors

who suffered from VVRs was similar to that of donors showing pulse fluctuations of type B both for men and for women (see Table 2).

DISCUSSION

The incidence of VVRs decreased with advancing age in the population of WB donors, both men and women donors, as previously reported.[2-4,6] A similar relationship was observed in men apheresis donors. However, no such a tendency was found in women apheresis donors. The VVR incidence of women apheresis donors was rather independent of age or even higher over 45 years old (see Fig. 1). This was not due to a high proportion of first-time donors in older women, because most donors over 45 years old were repeated donors.

The CBV was significantly (approx., 20%) less in women and it was also about 4 percent less ($p < 0.05$) in VVR donors than in healthy control donors. The VVR incidence tended to be higher with smaller CBV (see Figs. 3 and 4). It is possible in old donors that the actual CBV is less than that estimated solely from the height and weight determinations[7] and that the peripheral blood pool is small.[8] This may explain the larger effects of blood withdrawal in older donors. If stronger hypovolemia was a major factor in VVR incidence, it seems difficult to explain the difference in VVR incidence between WB and apheresis donors (see Figs. 1 and 3). Some other factors such as autonomic malfunction and hypocalcemia are more likely to be involved in higher VVR incidence in women, particularly older, apheresis donors.

A tachycardia was often observed during blood withdrawal without an associated change in arterial pressure. The ratio of the donors who showed such pulse rate fluctuations (type B) was higher in women than men and this difference was larger over 40 years of age. Furthermore, the VVR donors all showed type B fluctuations. Donors having smaller CBV have a tendency to produce tachycardia during apheresis (see Table 2). The increase in pulse rate usually became more marked with increasing cycles of blood withdrawal. This may have been due to an increased hypovolemia, because the extracorporeal blood volume increases with number of apheresis cycles. Tachycardia, without any significant changes in arterial blood pressure, has also been reported in response to a decreased venous return caused by lower-body negative pressure in humans[9,10] or by hemorrhage of up to 10 mL per kg blood in conscious dogs.[11] These responses are likely to be mediated by cardiopulmonary (low-pressure) baroreceptors, the sensitivity of which to hemorrhage is shown to be higher than those of carotid sinus (high-pressure) baroreceptors in dogs.[12] The mechanism causing the tachycardia during blood withdrawal is likely to be involved in triggering the patterns of VVRs by the circulatory control center.

In the apheresis, it is possible that the sensitivity of baroreceptor-mediated reflex is increased by a decrease in plasma Ca^{2+} concentration that is known to be caused by the supply of citrate during blood return.[12,13] This is probably one of the factors involved in the high VVR incidence in older women apheresis donors, whose VVR incidence is increased by repeating blood withdrawal and return. Not only the effects of blood withdrawal, but also the effects of citrate on the reflex mediated by cardiopulmonary baroreceptors would be stronger in the smaller CBV of old women donors. These factors may explain a high VVR incidence of elderly women donors and at later stage of apheresis.

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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Blood Applications, Office of Blood Research and Review at 301-827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2007

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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides you, blood establishments, and FDA staff with revised recommendations for the collection of Platelets by automated methods (plateletpheresis). This guidance is intended to help you ensure donor safety and the safety, purity, and potency of Platelets collected by an automated blood cell separator device. For the purpose of this document, Platelets collected by automated methods and resuspended in plasma will be referred to by the product name "Platelets, Pheresis." We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for manufacturing Platelets, Pheresis, and provide guidance on preparing a manufacturing supplement for Platelets, Pheresis under Title 21 Code of Federal Regulations 601.12
(21 CFR 601.12).

This guidance applies only to the following Platelets, Pheresis components:

- Platelets, Pheresis (single, double, and triple collections);
- Platelets, Pheresis Leukocytes Reduced (single, double, and triple collections); and
- Platelets, Pheresis or Platelets, Pheresis Leukocytes Reduced collected concurrently with Plasma, Red Blood Cells (RBCs), and/or Source Plasma.[1]

This guidance replaces FDA's "Revised Guideline for the Collection of Platelets, Pheresis" dated October 1988. Also, this guidance finalizes the draft guidance, "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods" dated September 2005.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

[1] This guidance does not apply to plateletpheresis components collected concurrently during apheresis granulocyte collection procedures or plasma reduced apheresis platelets, which are not currently licensed products, or to platelets prepared from plasmapheresis as described in 21 CFR 640.22(b).

The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

If you have any questions about the effect of any portion of this guidance on a regulatory requirement, contact the Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review, Division of Blood Applications, at 301-827-3524.

II. DISCUSSION

A. Background

Plateletpheresis is the routine collection of platelets using an automated blood cell separator device, which results in the product Platelets, Pheresis manufactured from a high yield of platelets from a single donor. Transfusion of Platelets, Pheresis is effective for treating patients with platelet related insufficiencies, while limiting the recipient's exposure to platelets from multiple donors. In recent years, many improvements have been made in automated blood cell separator device technology, platelet storage stability, and blood cell counting methods, including:

- collection process efficiency;
- storage container characteristics; and
- accuracy of methods for determining a donor's pre-donation platelet count and component yields.

Automated blood cell separator devices are now capable of various plateletpheresis collection procedures including but not limited to the following:

- collection of double and triple platelet components obtained during a single procedure;
- use of in-process leukocyte reduction (Ref. 1);
- collection of concurrent plasma components (Ref. 2); and
- collection of concurrent RBC components (Ref. 3).

This document includes the following recommendations:

- Published research indicates that there is poor recovery of viable platelets stored at a pH of less than 6.2 (Refs. 4 and 5). Therefore, your process validation and quality control (QC) testing for Platelets, Pheresis should assure a pH at or above 6.2, to rule out a pH less than 6.2 on the date the product is issued or on the date the product expires (outdates). Note that we recommend that you adopt a stricter pH standard than that currently specified in 21 CFR 640.25(b)(2).
- You should include additional deferral criteria for donors of Platelets, Pheresis who have taken certain medications (see section III.A.) (Refs. 6, 7, and 8).

- To protect the safety of the donor, seven days should elapse after collection of a double or triple Platelets, Pheresis before the donor is eligible to donate Platelets, Pheresis again. In addition, first-time donors without a pre-donation platelet count should not undergo collection of a triple Platelets, Pheresis.
- Because of similarities between plateletpheresis and Source Plasma donation, you should follow the donor weight provisions for Source Plasma donors under 21 CFR 640.63(c)(6) (see Section III.A.).
- QC testing, as prescribed in 21 CFR 640.25(b)(1) through (3) requires that, each month, four units prepared from different donors be tested at the end of the storage period for platelet count, pH of not less than 6.0 when measured at the storage temperature of the unit, and volume. In addition, 21 CFR 211.160(b) requires that laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

We also note that bacterial contamination of blood components and associated transfusion risks is a continuing problem (Refs. 9 and 10). Bacterial contamination testing is a necessary part of process validation and quality assurance monitoring for Platelets, Pheresis.

B. Definitions

For purposes of the terms used in this guidance, the following definitions apply:

Actual platelet yield – The total platelet yield in the component, calculated by multiplying the platelet count of the sample times the volume of the component (platelet count x component volume = actual platelet yield).

Apheresis – Automated blood collection in which a device continuously or intermittently removes a small volume of whole blood, separates the components, collects certain components, and returns to the donor the uncollected remainder.

Automated blood cell separator – A device that uses a centrifugal or filtration separation principle to automatically withdraw whole blood from a donor, separate the whole blood into blood components, and return to the donor the remainder of the whole blood and blood components. The automated blood cell separator device is intended for routine collection of blood and blood components for transfusion or further manufacturing use.

Bacterial contamination testing – Testing conducted to determine whether a product contains viable contaminating bacteria.

Component – A part of a single donor's blood, such as platelets, separated from whole blood by physical or mechanical means. For Platelets, Pheresis, a component is a

transfusable product that may result from a single collection (resulting in one component), a double collection (resulting in two Platelets, Pheresis components), or a triple collection (resulting in three Platelets, Pheresis components).

Concurrent component – When a blood component, such as Platelets, is being collected during an apheresis procedure, a concurrent component is a different blood component (i.e., Plasma, RBCs) collected at the same time.

Dedicated donation – Platelets, Pheresis donated for a specific recipient.

Devices cleared or approved – Describes a device that has been cleared or approved by FDA pursuant to a 510(k) Premarket Notification (cleared device) or Premarket Approval Application (approved device). (See Title 21, United States Code, section 360c; Federal Food, Drug, and Cosmetic Act (FDCA), section 515 – Premarket Approval; and, FDCA, section 510(k)).

Donation frequency – Interval between a donor's collection procedures.

Process validation – Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Qualification – A part of process validation that establishes confidence that a manufacturing device is capable of operating consistently (equipment installation qualification) and can be performed effectively and reproducibly (process performance qualification), and that the finished product meets all of the release requirements for functionality and safety (product performance qualification).

Residual White Blood Cell (WBC) count – The number of WBCs remaining in a Leukocytes Reduced component, calculated by multiplying the WBC count from a sample of the component times the volume of the component. In this document:

- references to residual WBC count testing apply when the Platelets, Pheresis will be labeled as Leukocytes Reduced.
- references to percent platelet retention apply to leukocyte reduction by filtration, provided there is access to a pre-filtration sample.

Rolling 12-month period – Continual assessment of a donor over a 12-month period. This is not a set 12-month period (i.e., calendar year).

Target platelet yield – The intended platelet yield programmed into an automated blood cell separator device, which may be based on the donor's platelet count and other factors.

Tolerance values – Minimum and maximum values (i.e., container volume; platelet concentration) described by the manufacturer as being acceptable. These values may also be described as specifications.

Weight/volume conversion – The total weight of the component minus the tare weight of the empty container divided by the specific gravity of the component equals volume of the component.

III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection

Under 21 CFR 640.21(c), plateletpheresis donors must meet donor suitability criteria described in the biologics license application or supplement. These typically conform to donor suitability requirements (21 CFR 640.3) and recommendations applicable to donors of Whole Blood. In addition, we recommend:

- donor weight of at least 110 pounds (currently required for Source Plasma donors under 21 CFR 640.63(c)(6))
- Prior to the first donation, collect a sample for a platelet count.
- If you cannot test a sample for a platelet count prior to the first donation (for example, because the donor presents at a mobile collection site), you should collect a pre-donation sample and evaluate the donor's platelet count after the first collection.

You should not collect Platelets, Pheresis from donors who have ingested platelet inhibitory drugs recently enough to adversely affect platelet function in the product, or the safety of the donor. These recommendations include, but may not be limited to:

- Aspirin (ASA)/ASA-containing drugs/Feldene – two full medication free days prior to donation (Refs. 6 and 7)
- Plavix (Clopidogrel) and Ticlid (Ticlopidine) – 14 full medication free days prior to donation (Ref. 8).

When the drugs listed in this section are taken for a specific medical condition, donors should not discontinue taking drugs prescribed or recommended by their physicians in order to be eligible[2] to donate Platelets, Pheresis. However, we do not necessarily recommend deferral of such donors for all blood products, if the donors are in good health, and establishments may make eligibility determinations for donations of other products.

[2] We are using the terms "eligible" and "eligibility" in this guidance to refer to the donor suitability requirements described in 21 CFR 640.3 and 640.21(c).

B. Donor Management

1. Platelet Count

- You should collect a pre-donation sample from the donor for a platelet count. The device operator should enter that platelet count, or the one obtained immediately following initiation of the collection procedure, to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. These steps should be consistent with the automated blood cell separator device manufacturer's directions for use.

- For any collection facility that cannot test a pre-donation sample for a platelet count (for example, a mobile collection site), you may use an average of previous historic platelet counts (as specified by the device manufacturer), or a default platelet count (either as recommended by the automated blood cell separator device manufacturer, or determined by using blood center specific values), to set the target platelet yield. You should not collect a triple Platelets, Pheresis from first-time donors who do not have a pre-donation platelet count available either prior to or immediately following initiation of the collection procedure. Concurrent components may be drawn if the donor meets eligibility requirements for those components.

- You should defer from donation donors whose platelet counts are less than 150,000 platelets/uL until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least 150,000 platelets/uL.

2. Donation Frequency

To protect the safety of the donor:

- a donor should undergo no more than 24 Platelet, Pheresis collections in a rolling 12-month period.
- the interval between each collection of Platelets, Pheresis should be at least two days with no more than two procedures in a seven-day period.
- the interval between collection of a double or triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least seven days.
- the automated blood cell separator device should be set with a post-donation platelet count target of no less than 100,000 platelets/uL.

3. RBC Loss Prior to a Collection of Platelets, Pheresis

To protect the donor from significant RBC loss, we recommend that:

- you not allow a donor who has donated a unit of Whole Blood, a single unit of Red Blood Cells by apheresis, or a single unit of Red Blood Cells by apheresis concurrent with Platelets, Pheresis or Plasma in the previous 8

weeks to donate Platelets, Pheresis, unless the extracorporeal red blood cell volume during the Platelets, Pheresis collection is expected to be less than 100 mL (Ref 3).

- you not perform any collection procedure on a donor who has donated two units of Red Blood Cells by apheresis within the previous 16 weeks (Ref. 3).

4. Total Plasma Volume Loss Per Collection Procedure

The total plasma volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should not exceed:

- 500 mL (600 mL for donors weighing 175 lbs or greater), or
- the volume described in the labeling for the automated blood cell separator device (this volume may be more or less than the 500 mL or 600 mL volume stated in the above bullet).

IV. INFORMATION PROVIDED TO THE DONOR

Under 21 CFR 640.22(c), the collection procedure must be as described in the biologics license application or supplement. As part of the collection procedure, Platelets, Pheresis donors should receive information about the collection procedure and its associated risks. You should provide Platelets, Pheresis donors with the same information that is provided to a Whole Blood donor[3], plus the following information specific to the platelet collection:

- a description of the procedure for collection of Platelets, Pheresis and its associated risks.
- information about potential side effects of the procedure including possible effects as a result of solutions and/or treatment to reduce side effects such as treatment with a calcium replacement. Examples of side effects include anticoagulant effects (tingling and/or nausea), hypovolemia (decreased blood volume), fainting, and any other side effect as described by the automated blood cell separator device manufacturer.
- information indicating that there are limitations to the number and types of components that can be donated per year.

V. COMPONENT COLLECTION

Improvements in collection of Platelets, Pheresis have enabled blood establishments to obtain from a single collection procedure one, two, or three Platelets, Pheresis component(s) (and concurrent collection of Plasma, Source Plasma and/or RBC components).

[3] Refer to FDA regulations and guidance developed by FDA on this topic and available on the FDA website. http://www.fda.gov/cber/blood/bldpubs.htm

Under 21 CFR 640.22(c), the collection procedure must be as described in the biologics license application or supplement. In addition, the phlebotomy must be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue (21 CFR 640.22(d)). A sterile connecting device may be used as described in the manufacturer's directions for the apheresis collection set. The automated blood cell separator device must perform in the manner for which it was designed (21 CFR 606.60(a)). Accordingly, your collection procedures should be consistent with the Operator's Manual, directions for use, and/or manufacturer's specifications. Specifications identified by the manufacturer may include, but not be limited to, the donor's platelet count, weight, height or hematocrit; the minimum/maximum volume of the storage container; platelet concentration per uL in the storage container, or actual platelet yield. In addition, supplies and reagents must be used in a manner consistent with instructions provided by the manufacturer (21 CFR 606.65(e)).

VI. VALIDATION OF THE COLLECTION PROCESS

The Current Good Manufacturing Practice (CGMP) regulations described in 21 CFR Parts 210 and 211 contain the minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing or holding of a drug to assure that the drug meets the requirements of the FDCA as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess (21 CFR 210.1(a)). These CGMP regulations also apply to Whole Blood and blood components (21 CFR 210.2(a), 211.1(b)) and supplement the CGMP regulations for blood and blood components contained in 21 CFR Part 606. As an element of CGMP, process validation "establishes documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics" (Ref. 11).[4] We recommend that establishing documentation of process validation include, but not be limited to, validation protocol development, installation qualification, process operator performance qualification, and product performance component qualification (Ref. 11).

Each device intended for the routine collection of Platelets, Pheresis must be cleared or approved by FDA for this purpose (see 21 CFR 864.9245). You should conduct validation of the collection process using each type of device used in your establishment prior to implementing routine collections.

In addition, your validation efforts should include the following manufacturing steps:

- cell counting
- pH measurement: we recommend that a pH meter or gas analyzer be routinely used rather than pH (nitrazine) paper.
- component weighing

[4] The requirement for process control is set forth in general terms in 21 CFR 211.100.