

Guidance for Industry

Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion

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GUIDANCE FOR INDUSTRY
PRE-STORAGE LEUKOCYTE REDUCTION OF WHOLE BLOOD
AND BLOOD COMPONENTS INTENDED FOR TRANSFUSION

This guidance document represents FDA's current thinking on the manufacture of pre-storage leukocyte reduced Whole Blood and blood components intended for transfusion. It does not confer any rights for or on any person and does not operate to bind the FDA or the public. An alternative approach may be used if it satisfies the requirement of the applicable statutes and regulations.

I. SCOPE OF RECOMMENDATIONS

This document describes Food and Drug Administration (FDA) recommendations regarding pre-storage leukocyte reduction of Whole Blood and blood components intended for transfusion, including products made by apheresis. This document provides information to assist licensed facilities in filing supplements to their biologics licenses to include leukocyte reduced products. It applies to Whole Blood, and to Red Blood Cells and Platelets, whether made from Whole Blood or by apheresis. This guidance document supersedes the FDA memorandum issued on May 29, 1996, entitled "Recommendations and Licensure Requirements for Leukocyte Reduced Blood Products."

II. PURPOSE AND RATIONALE FOR RECOMMENDATIONS

These recommendations update current Good Manufacturing Practices (cGMP) applicable to pre-storage leukocyte reduced Whole Blood and blood components for transfusion. Additionally, the Agency supports the use of leukocyte reduced blood and blood components and seeks to streamline the licensing procedure for leukocyte reduced blood products to assist blood establishments in making pre-storage leukocyte reduced blood products more widely available.

Although adverse transfusion reactions have been associated with leukocyte reduction by filtration [1,2], advances in blood cell separation technology enable the safe and substantial reduction of residual leukocytes. Such continuing improvements in technology have made it possible to provide purer Red Blood Cells and Platelets. The Agency believes that increased availability of pre-storage leukocyte reduced products will contribute to safety. The potential additional benefits of using leukocyte reduced blood products suggest that consideration should be given to making leukocyte reduced blood products more widely available.

FDA therefore is issuing recommendations for pre-storage leukocyte reduction of Whole Blood and blood components for transfusion, including recommendations for quality monitoring of the leukocyte reduction process. FDA believes that these manufacturing and quality assurance recommendations are consistent with current industry practices and standards.

III. BACKGROUND DISCUSSION

A. Changes Compared with the May 1996 Leukocyte Reduction Memorandum

In a May 29, 1996 memorandum, FDA issued recommendations on leukocyte reduction, a manufacturing step performed under controlled and monitored laboratory conditions. Leukocyte reduced components were to contain $\leq 5.0 \times 10^6$ residual white blood cells per blood component, with at least 85 percent retention of the original therapeutic cells. The memorandum was consistent with the outcome of a public workshop held in 1995 on that subject. This guidance is intended to update the manufacturing and quality assurance recommendations for pre-storage leukocyte reduction to further improve the purity, consistency, and safety of leukocyte reduced blood components. This guidance differs from the earlier May 1996 FDA memorandum in that it recommends the following:

- (1) to assure product safety and efficacy, the leukocyte reduced product should contain $\leq 1.0 \times 10^6$ residual white blood cells;
- (2) to use statistical methods for quality control testing in monitoring the leukocyte reduction process, to assure with 95% confidence that at least 95% of the products meet intended product specifications;
- (3) to increase the frequency of quality monitoring;
- (4) to reduce product loss by identifying repeated causes of filter failures;
- (5) to directly test every leukocyte reduced component intended to be used in lieu of cytomegalovirus (CMV) negative units for residual leukocytes;
- (6) to provide multiple licensing options to decrease reporting burden; and
- (7) to consider routine donor screening for sickle cell trait.

This guidance document presents FDA's current thinking on pre-storage leukocyte reduction of Whole Blood and blood components intended for transfusion. It was shaped in part by the discussions held at a FDA workshop entitled "Implementation of Universal Leukocyte Reduction" (December 10, 1999, Bethesda, Maryland), and the 66th meeting of the Blood Products Advisory Committee (BPAC; June 16, 2000; Silver Spring, Maryland).

B. Benefits of Pre-Storage Leukocyte Reduction

In current medical practice, leukocyte reduced Whole Blood and blood components have been shown to be beneficial [3-7]:

- (1) to reduce immunization to leukocyte antigens that may complicate care of patients who undergo transplantation or chronic transfusion therapy (e.g. patients with aplastic anemia or hematologic malignancies);
- (2) to reduce transmission of CMV to patients at increased risk of CMV disease (e.g. chemotherapy recipients for whom severe neutropenia is

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- expected, recipients of hematopoietic progenitor cell replacement therapy, CMV seronegative recipients of CMV seronegative solid organ grafts, and low birth weight premature infants); and
- (3) to reduce recurrent febrile, non-hemolytic transfusion reaction (FNHTR)(e.g. patients with history of two or more febrile reactions to transfusion).

Based on the identified benefits, FDA believes that leukocyte reduced products should be provided to patients with these defined indications, and that pre-storage leukocyte reduced products should be provided in preference to bedside filtered blood products based on evidence of their superior quality and safety.

Limited data suggest that leukocyte reduction may have additional, more general benefits by avoidance of immunomodulatory effects, and as a safeguard against transmission of known and as yet undiscovered leukocyte associated pathogens. The known and potential benefits of leukocyte reduction were discussed by FDA's Blood Products Advisory Committee (BPAC) at its public meeting in September 1998. At that meeting, a majority of the voting committee members found that the benefit-to-risk ratio associated with leukocyte reduction is sufficient to justify the universal leukocyte reduction of transfusion blood components, irrespective of the theoretical considerations for transfusion-transmitted Creutzfeldt-Jakob disease (CJD). Consistent with the advice of the BPAC, FDA is providing guidance to streamline the procedures for licensure of leukocyte reduced products in order to assist the industry in making these products more widely available. FDA supports the increased use of leukocyte reduced blood.

C. Potential Benefits of Pre-Storage Leukocyte Reduction

Leukocyte reduction has been reported to reduce FNHTR, human leukocyte antigen (HLA) alloimmunization, and CMV transmission [3-7]. In addition, a growing list of potential, but not established, benefits of leukocyte reduction includes reduction of:

- (1) transfusion-associated immunomodulation [11];
- (2) bacterial overgrowth [3, 12];
- (3) viral reactivation [3, 12];
- (4) reperfusion injury following cardiopulmonary bypass [12];
- (5) red blood cell and platelet storage lesions [13]; and
- (6) the theoretical risk of transfusion-transmitted CJD and new variant CJD (nvCJD) [14].

At present, leukocyte reduction is not considered appropriate for the prevention of transfusion-associated graft-versus-host disease (TA-GVHD) owing to the availability of irradiation as the definitive and preferred method against this serious adverse transfusion outcome [15]. In addition to eliminating the potential for precipitous

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hypotension, pre-storage leukocyte reduction allows the leukocyte reduction process to be monitored under controlled conditions that assure product purity, consistency, and safety.

D. Safety Concerns Related to Bedside Filtration

Bedside filtration remains available as a leukocyte reduction method to physicians prescribing transfusion therapy. As a post-storage procedure, however, bedside filtration has been associated with precipitous hypotension in the transfusion recipient, an infrequent yet serious adverse effect not clearly associated with pre-storage leukocyte reduction [8]. Patients on medications that inhibit the angiotensin converting enzyme (ACE inhibitors) appear to be particularly susceptible. Also, it is recognized that bedside filtration may fail to adequately remove leukocytes due to uncontrolled filtration times and temperature. Therefore, pre-storage leukocyte reduction is generally preferable to bedside filtration [8-10].

E. Potential for Leukocyte Reduction to Decrease the Theoretical Risk of nvCJD

Limited scientific data have suggested the possibility that leukocyte reduction may be a useful precautionary measure against the theoretical risk of transfusion-transmitted nvCJD [14]. Over the last two years, some international blood authorities have implemented or are seriously considering the implementation of the regulatory requirement to leukocyte reduce all Red Blood Cells and Platelets intended for transfusion (universal leukocyte reduction, ULR), as well as plasma for further manufacturing in some cases. Countries implementing these requirements include the United Kingdom, Ireland, France, Germany, Austria, Portugal, and Canada. However, FDA's Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) advised on June 2, 2000, that current scientific data are inadequate to affirm the effectiveness of leukocyte reduction in significantly reducing the infectivity of CJD and nvCJD in blood components.

F. Potential for Reducing Other Leukocyte-Associated Infections

The potential to reduce infection by pathogens that are primarily white blood cell associated may extend beyond CMV [6,7] to include other known and unknown agents potentially transmitted by white blood cells [14].

IV. MANUFACTURING RECOMMENDATIONS

All pre-storage leukocyte reduced blood components must be manufactured in accordance with cGMP [21 CFR Parts 210-211, 600-680]. Leukocyte reduction filters are typically component-specific; a filter intended for one component type should not be used with other

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component types [16]. When leukocyte reduction is performed according to cGMP and without breaching closure, the expiration date of the component remains unchanged. If a filter is attached to a blood container using aseptic technique but without an FDA-cleared sterile tubing connection device (STCD), the container is considered an open system. Leukocyte reduced Whole Blood and Red Blood Cells prepared in an open system and stored at 1 - 6 °C have an expiration of 24 hours. Platelet units that are entered, pooled and filtered have an expiration of 4 hours [21 CFR 606.122]. Currently, Pooled Platelets, regardless of their method of preparation and processing have an expiration of 4 hours. All blood components including those leukocyte reduced prior to storage should be administered through a standard blood filter designed to remove clots and/or microaggregates that form during blood storage [16,17].

A. Methods and Blood Components

Whole Blood and blood components intended for transfusion may be leukocyte reduced prior to storage using any of the following closed system methods:

- (1) filtration through an in-line filter integral to the blood collection set;
- (2) filtration through a filter system attached to a blood component container using an FDA-cleared STCD [18];
- (3) direct leukocyte reduction, simultaneous with Platelets, Pheresis collection, using automated cytopheresis without filtration.

Leukocyte reduced blood components are listed in Table 1, along with corresponding product specifications (maximum residual leukocyte content, minimum amount of therapeutic product) and applicable leukocyte reduction methods. Investigations should be performed on leukocyte reduced blood products that fail to retain at least 85% of the original therapeutic component.

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Table 1: Blood Components and Leukocyte Reduction Methods
(LR = Leukocytes Reduced; STCD = Sterile Tubing Connecting Device)

Blood Components	Recommended Maximum Residual Leukocyte Content	Recommended Minimum Therapeutic Product Post Filtration	Applicable Methods
Whole Blood, LR	1.0×10^6	160 ml ¹ [16] red blood cells	STCD-filtration; In-line filtration
Red Blood Cells, LR	1.0×10^6	160 ml ¹ [16] red blood cells	STCD-filtration; In-line filtration Preparation from Whole Blood, L.R.
Platelets, Pheresis, LR	1.0×10^6	3.0×10^{11} platelets	Automated Plateletpheresis; STCD-filtration; In-line filtration Automated plateletpheresis
Platelets, LR	1.6×10^5	5.5×10^{10} platelets	STCD-filtration; In-line filtration

¹ A unit of Platelets derived from Whole Blood is infrequently leukocyte reduced. For an adult transfusion recipient, multiple units of Platelets (4-6) are pooled into a single platelet dose. The total dose (4-6 units) should contain $\leq 1.0 \times 10^6$ residual leukocytes. In order to preserve product shelf life, multiple units of Platelets are typically pooled after storage and prior to filtration, rather than filtering individually prior to pooling.

Although plasma components, when manufactured under cGMP, may have a residual leukocyte content of less than 1.0×10^6 per unit, data to support the recognition of such products has not been submitted for CBER review and approval. Currently accepted and validated cell counting procedures may need to be modified for plasma products. Plasma components (including Fresh Frozen Plasma and Cryoprecipitated Antihemophilic Factor) may be labeled "Leukocytes Reduced" provided that manufacturing process validation and quality monitoring as described in Sections D and E includes these components.

B. Standard Operating Procedures

Written standard operating procedures (SOP) for leukocyte reduction must be maintained [21 CFR 606.100(b)]. The SOPs should identify:

- (1) the blood products to be leukocyte reduced;
- (2) blood product specifications;

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- (3) leukocyte reduction methods;
- (4) leukocyte reduction equipment and its manufacturer;
- (5) the labeling and disposition of products failing to meet product specifications;
- (6) the methods for identifying donor specific repeated process failures.

In addition, the following aspects of the leukocyte reduction processes should be described in sufficient detail to ensure manufacturing consistency.

1. Leukocyte Reduction Equipment

FDA regulations require that equipment used in the collection or processing of blood and blood components “shall perform in the manner for which it was designed.” [21 CFR 606.60(a)]. An establishment must maintain written SOPs for all steps in the collection and processing of blood and blood components [21 CFR 606.100(b)]. Accordingly, an establishment must incorporate the device manufacturer’s instructions for use into its SOPs. Regulations further require establishments to maintain records “concurrently with the performance of each significant step in the collection [and] processing of blood and blood components.” [21 CFR 606.160(a)(1)].

The SOP should indicate that the leukocyte reduction equipment (blood collection sets, filters, or apheresis machines) is either cleared or approved for its intended use by CBER. Filters intended for bedside filtration should not be used for pre-storage leukocyte reduction. The SOP should accurately incorporate the equipment manufacturer’s instructions for use.

2. Leukocyte Reduction Procedures

FDA recommends that the SOP describe at least the following:

- (1) the time interval, according to the filter manufacturers’ directions for use, but no more than 72 hours, within which leukocyte reduction is to be performed following blood collection;
- (2) the temperatures at which leukocyte reduction is to be performed;
- (3) the use of an FDA-cleared STCD according to FDA-cleared instructions for use [18]; and
- (4) the time interval, within which filtration should be completed after beginning filtration [19,20].

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3. Process Validation and Quality Monitoring

The SOP should include procedures for process validation and quality monitoring. Each leukocyte reduction process should be validated initially and monitored periodically to detect process failures that may compromise blood product quality (See Sections D and E).

4. Investigation of Process Failure

The SOP should describe how leukocyte reduction process failure is to be investigated and resolved. Process failure may be apparent during manufacturing or may be detected through quality control testing. The SOP should address the disposition of blood units manufactured during a potential or confirmed unstable process (See Sections D and E).

A blood component that requires a filtration time longer than the time interval specified in the manufacturer's directions for use may be released for transfusion use as leukocyte reduced only if direct quality control testing of that unit confirms acceptable product specifications. Products that fail to meet the processing specifications in the manufacturer's directions for use or that fail to meet product specifications should be thoroughly investigated. For example, products from an individual donor may repeatedly have extended filtration times. Additional investigation including manufacturing record review should be conducted to determine if the unit could have been detected earlier in the manufacturing process.

Leukocyte reduction by filtration often fails for Whole Blood or Red Blood Cells collected from donors with sickle cell trait [21-28]. Routine donor screening for sickle cell trait or use of a validated alternative method should be considered for all donors. Such testing should reduce the number of products lost to filter failures. To address process failures, the SOP should include testing the blood unit for sickle cell trait when process failure is apparent, either at filtration or at quality control testing. Typically, process failure will be apparent during filtration and further investigation may detect the donor with sickle cell trait. Rarely, sickle cell trait units may be detected at quality control testing. Additional investigation including manufacturing record review should be conducted to determine if the unit could have been detected earlier in the manufacturing process. In either instance, leukocyte reduction procedures need not be revised, but the blood unit should not be released for transfusion unless directly tested and found acceptable.

C. Product Labeling

The *Circular of Information for the Use of Human Blood and Blood Components (The Circular)* describes in detail the indications, contraindications, side effects, hazards, dosage, and administration of leukocyte reduced products [16]. The

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Circular is periodically revised by the blood industry subject to FDA review and acceptance. The container label must follow a format accepted by FDA [21 CFR 606.121]. Table 2 lists the proper names of the major leukocyte reduced blood products, followed by the corresponding International Society of Blood Transfusion (ISBT) Code 128 name [29]. Until ISBT Code 128 terminology is adopted, product labels should include the name of the appropriate anticoagulant storage solution as modifiers (e.g., CPDA-1 Whole Blood, Leukocytes Reduced). Product modifications (e.g., Irradiated, Frozen) should be indicated after the phrase "Leukocytes Reduced." The phrases "Leukocytes Removed," "Leukocyte Poor," "Leukocytes Depleted," and other similar terms should not be used in product labeling.

Table 2: Component Names for Container Labels

Proper Name	ISBT 128 Name
Whole Blood Leukocytes Reduced	WHOLE BLOOD LEUKOCYTE REDUCED
Red Blood Cells Leukocytes Reduced	RED BLOOD CELLS LEUKOCYTES REDUCED
	APHERESIS RED BLOOD CELLS LEUKOCYTES REDUCED
Platelets, Pheresis Leukocytes Reduced	APHERESIS PLATELETS LEUKOCYTES REDUCED
Platelets Leukocytes Reduced	PLATELETS LEUKOCYTES REDUCED

D. Process Validation

Process validation requirements for finished pharmaceuticals [21 CFR 210, 211] apply to the manufacture of leukocyte reduced blood and blood components, and the use of leukocyte reduction equipment, respectively. "The Guideline on General Principles of Process Validation" provides general direction in this area [30].

Under 21 CFR 210/211, manufacturers must prepare a written validation protocol which specifies the procedures and tests to be conducted and the data to be collected that will provide a high degree of assurance that each leukocyte reduction process will consistently produce a product meeting its predetermined specifications and quality

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characteristics. Elements incorporated into a leukocyte reduction validation process, should include but not be limited to:

- (1) blood collection times, platelet content, plasma content;
- (2) intrinsic donor characteristics (e.g. sickle cell trait) and initial blood collection;
- (3) equipment quality and proper handling and use;
- (4) operating procedure (e.g., storage time between blood collection and filtration; filtration time, pressure, and temperature; equipment priming).

Each leukocyte reduction process should be tested initially in sufficient detail to establish process stability and acceptable process performance. Following successful validation, each leukocyte reduction process should be tested at least weekly to detect a potential unstable manufacturing process that may compromise blood product quality.

E. Quality Monitoring

1. Quality Monitoring Program

A facility should establish and follow a statistical monitoring plan that assures, at 95% confidence level, that more than 95% of the units intended to be labeled as leukocyte reduced meet product specifications [31,32]. One example of a plan that satisfies these goals and is acceptable to FDA without prior FDA review is presented below.

Statistical plan

Initially, a facility tests 60 consecutive units for each of the following major process variations:

- (1) filtration of Whole Blood;
- (2) filtration of Red Blood Cells;
- (3) filtration of Platelets;
- (4) filtration of Platelets, Pheresis
- (5) direct collection of leukocyte reduced Platelets, Pheresis

Testing 60 consecutive units for each process will assure compliance if all of the products meet the product specifications. Additional testing will be important if a failure is identified.

Using more than one variation of filter, SOP (e.g. different temperature) or apheresis instrument increases the total number of process variations which would require initial validation and weekly evaluation; quality control testing should be

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performed separately for each of the 4 major leukocyte reduction process variations. A blood center should determine its monthly production rate for each type of product and leukocyte reduction process. The minimum number of products tested for each type of product and process should be 20 per month. This will enable a specific number of products to be tested every week. Testing of 5 units per week for each leukocyte reduction process should allow early detection of an unstable process thus averting potentially costly product retrievals. If all testing is acceptable, the facility assures at 95% confidence, on a floating three month basis, that more than 95% of the blood units manufactured meet product specifications. The testing of 60 units (with all units acceptable) should be repeated whenever an unacceptable unit is identified or a leukocyte reduction process is significantly changed.

2. Sample Collection and Quality Control Testing

Blood samples should be collected, processed, and tested within 24 hours of leukocyte reduction. Sampling procedures should include thorough mixing of blood and the use of freshly filled tubing segments. Sample testing should be performed using validated procedures at a registered blood center or at a laboratory certified by the Health Care Financing Administration (HCFA) for testing leukocyte reduced blood products. The following methods may be used in enumerating low numbers of residual leukocytes and in calculating product recovery.

Manual methods using a Nageotte counting chamber and Turk's staining solution (alone or in conjunction with a recommended red blood cell lysing reagent and/or centrifugation) may be adequately sensitive and reliable for counting leukocytes at less than 0.5-1.0 cells/uL [33-36, 40]. Automated methods using FDA-cleared instrumentation compares favorably in sensitivity, precision, reliability, and efficiency to the manual Nageotte chamber method but may lose sensitivity if sample dilutions are necessary [37-40]. Product content may be calculated simply by multiplying product volume in mL (net weight of blood unit in grams divided by the specific gravity correction factor) by cell concentration (hematocrit or platelet count per mL)[31].

3. Expected Results and Actions

Results from weekly process testing should provide data that demonstrate with 95% confidence level that more than 95% of blood units contain $\leq 1.0 \times 10^6$ residual leukocytes per unit (or $\leq 1.6 \times 10^5$ residual leukocytes for single units of Platelets derived from Whole Blood). (This standard is met on an ongoing three-month basis as long as zero failures are encountered on quality control testing of at least 5 units per week for each product and process variation.) Leukocyte

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reduced units also should meet the standards for minimum product content specified in Table 1. Additionally, filtration should result in at least 85% therapeutic product recovery. (Failure to recover at least 85% of the therapeutic product does not render a given product unsuitable, however, this failure should trigger an investigation of the filtration process.)

4. Unexpected Results and Actions

The frequency and the extent of process control testing failure may be helpful in investigating process stability. Operating near the minimum process standard (i.e., 95% confidence that more than 95% of units will meet product specifications) may require frequent process investigations. Upon identification of a unit that does not meet intended leukocyte reduced product specifications, the identified blood unit could be released for transfusion without a change in the expiration date, provided:

- (1) the container closure has not been breached;
- (2) the label accurately reflects the content of therapeutic cells and residual leukocytes (e.g., "Low Volume", "other than standard content", and/or NOT labeled "Leukocytes Reduced"); and
- (3) the container is labeled, "Do Not Leukocyte Reduce."

The effect of repeated filtration, including bedside filtration, on the safety and efficacy of blood components has not been established.

When an unacceptable unit is detected, the minimum process standard (more than 95% of units acceptable, at the 95% confidence level) is no longer assured. Investigation should be conducted and corrective actions should be taken if needed [40]. Technical advice may be sought from the manufacturer of the leukocyte reduction equipment (filter or apheresis machine). The investigation with or without corrective actions should be documented. The leukocyte reduction process should be revalidated using 60 consecutive units after the correction of a process deficiency [31]. If a process deficiency is found, all units affected by the deficiency should be identified. For the units that remain under facility control, direct quality control testing should be performed to the extent possible for each unit, and the container label should be corrected as needed. If direct testing cannot be performed due to age of the product, (e.g., accurate white blood cell counts can no longer be obtained) the container label should be corrected so that the product is no longer labeled as "Leukocytes Reduced." For the units that have been released, consignees should be notified within 24 hours.

Users of the leukocyte reduction equipment should report equipment failures to the equipment manufacturer who must review, investigate, and follow up the complaint [21 CFR 211.198 and 820.198]. If a leukocyte reduction process has

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been confirmed to be deficient, manufacturers of the leukocyte reduced blood products should inform the consignees of the previously distributed, potentially unsuitable blood units [21 CFR 7.49] within 24 hours. Results of the process investigation and follow up consultation on product safety and efficacy should be provided as soon as possible. Licensed manufacturers of leukocyte reduced blood products must notify FDA of biologic product deviations in the manufacture of such products [21 CFR 600.14 and 606.171]. All unlicensed manufacturers must report manufacturing biologic product deviations to FDA [21 CFR 606.171].

5. Technical Training and Performance Evaluation of Operating Personnel

Control over operational variables must be maintained through initial and continued staff training in conjunction with routine staff participation in leukocyte reduction and periodic staff performance assessment [21 CFR 606.20 (b)].

Training should include the following:

- (1) equipment use and maintenance;
- (2) clinical consequences of blood units that do not meet product specifications;
- (3) collection, preparation, storage, and stability of quality control samples;
- (4) SOP for leukocyte reduction, product labeling, and quality monitoring.

F. Quality Assurance and Manufacturing Records

A quality assurance unit should provide oversight of product manufacturing. All manufacturing records should be reviewed and approved by the quality assurance unit. Manufacturing records must be maintained and reviewed as part of quality assurance [21 CFR 606.160 and 21 CFR 211.192]. Process validation, quality monitoring, routine production, special investigation, corrective action, and repeat process validation should be performed according to previously established center SOP. Records of the performance of these procedures should be sufficiently detailed to facilitate process control. At minimum, the following identifying information should be included:

- (1) responsible personnel;
- (2) relevant dates and times;
- (3) leukocyte reduction equipment (filter, apheresis machine, or apheresis soft goods), together with lot numbers, receipt dates, product inserts, and equipment validation data;
- (4) validation data for each leukocyte count method used;
- (5) validation data for each leukocyte reduction process.

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V. REGISTRATION AND LICENSURE

Pursuant to 21 CFR Part 607, an establishment that routinely manufactures leukocyte reduced blood products must register with the FDA within 5 days of initiating this activity and annually thereafter using Form FDA 2830. An establishment that distributes these products in interstate commerce also must be licensed for each leukocyte reduced blood product, in accordance with Section 351 of the Public Health Service Act.

A licensed facility that changes its Whole Blood manufacturing procedures to include leukocyte reduction in accordance with all recommendations contained in Section IV may supplement its biologics license to include leukocyte reduction by submitting the following as changes being effected in 30 days (CBE-30) [21 CFR 601.12 (c)(5)]:

- (1) Form FDA 356h, indicating the submission as CBE-30;
- (2) product labeling for each product;
- (3) quality control data from the initial validation of each leukocyte reduction process;
- (4) evidence of quality assurance oversight, including review and approval of manufacturing records by a quality assurance unit;
- (5) a statement that the facility is following this guidance.

Licensing of leukocyte reduction is facility-specific; an applicant should submit a separate request for each facility. As a CBE-30 license application supplement, interstate product distribution may begin 30 days after FDA's receipt of the supplement filing unless notification is received from FDA that a prior approval supplement is required.

A licensed facility that seeks to manufacture leukocyte reduced blood using automated apheresis procedures (21 CFR 640.21-23) or using alternatives to the recommendations contained in Section IV should submit an application as a prior approval supplement (PAS) [21 CFR 601.12 (b)]. The PAS should describe each alternative method in sufficient detail for a meaningful FDA review.

An applicant seeking licensure for multiple facilities may submit as a PAS a comparability protocol (CP) [21 CFR 601.12 (e)] which describes elements common to all facilities. When FDA approves the CP, the applicant may then submit facility-specific data as CBE-30 in accordance with the approved CP. Each of these licensing options is further described in Table 3:

- (1) a PAS which describes apheresis methods or alternatives to this guidance;
- (2) a PAS for a CP which describes identical processing at multiple facilities;
- (3) a CBE-30 supplement when leukocyte reduction is performed by filtration after manual collection in accordance with all recommendations contained in Section IV.

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Table 3: License Application Contents and Alternatives
(PAS = prior approval supplement; CBE-30 = changes being effected in 30 days)

Submission Elements	PAS Apheresis or Alternative to Guidance	Comparability Protocol		CBE-30 Manual Collection and Follows Guidance
		Protocol (PAS)	Data (CBE-30)	
Form FDA 356h as cover (additional cover letter optional)	X	X	X	X
Listing, leukocyte reduced products Product specifications	X	X		
Standard operating procedures (leukocyte reduction)	X	X		
Form FDA 2567 Product labels including <i>Circular</i>	X	X	X	X
Description of process validation Quality monitoring plan	X	X		
Quality control data (initial process validation)	X		X	X
Evidence of quality assurance oversight, manufacturing and records	X		X	X
Protocol and rationale (for multiple facilities)		X		

A. Apheresis Procedures: Prior Approval Supplements (PAS)

If apheresis procedures are used, the procedures for collection and processing shall be as described in a biologics license application or a supplement to a biologic license application (21 CFR 640.21-23). The license application should be organized in a manner similar to Section IV to facilitate rapid evaluation. Applications should be submitted as a PAS. Interstate product distribution may not begin until the PAS submission has been reviewed and approved by FDA.

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B. Alternatives: Prior Approval Supplement (PAS)

The recommendations in Section IV are intended to serve as factors FDA considers acceptable in evaluating a license application for leukoreduction of Whole Blood and blood components. Alternatives may be acceptable if adequately supported and deemed to provide public health protection equivalent to or more stringent than FDA recommendations. The license application should be organized in a manner similar to Section IV to facilitate rapid evaluation. Alternative proposals should be submitted as a PAS. Interstate product distribution may not begin until the PAS submission has been reviewed and approved by FDA.

C. Alternatives: Comparability Protocol (CP) for Multiple Facilities

For multiple facilities under the direction and control of the same applicant, a CP may be submitted to consolidate reporting. The CP itself should be submitted as a PAS.

The submission should include the following:

- (1) indicate which information is common to all facilities;
- (2) provide the rationale for expecting the components manufactured at different facilities to be comparable;
- (3) provide a plan (protocol) for performing quality control testing; and
- (4) the criteria for evaluating the test results, to confirm that manufacturing at a particular facility is acceptable and comparable.

When approved, the CP allows facility-specific information to be described as CBE-30. As with CBE-30 reporting of manufacturing in accordance with FDA recommendations, interstate distribution of products manufactured at a facility covered under the CP may begin 30 days after FDA's receipt of the CBE-30 filing from that facility prior to approval, unless FDA indicates that a PAS should be filed or denies approval of the CP.

D. Review Divisions within FDA

Two divisions within the FDA review biologics license applications for leukocyte reduction in the manufacture of Whole Blood and blood components. Questions about licensing and specific review questions about leukocyte reduction of Whole Blood or Red Blood Cells should be directed to the Division of Blood Applications (DBA); specific review questions regarding leukocyte reduction of Platelets or Platelets, Pheresis should be directed to the Division of Hematology (DH). Questions may be directed also to the Office of Communications, Training, and Manufacturers Assistance (OCTMA) as an initial general point of contact. All registration forms

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(Form FDA 2830) and licensure applications/supplements should be submitted to the Director, Center for Biologics Evaluation and Research (CBER). Table 4 presents FDA contact information regarding leukocyte reduction.

Table 4: FDA Contact Information

Submissions: <ul style="list-style-type: none">• Registrations• License Applications	Director, Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.
General questions	Director, OCTMA, HFM-40, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-2000; Fax (301) 827-3843.
Review Questions: <ul style="list-style-type: none">• Licensing• Red Blood Cells• Whole Blood• Platelets• Platelets, Pheresis	Director, Division of Blood Applications, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-3543; Fax (301) 827-3534.

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VI. GLOSSARY

applicant: Any person or entity who has submitted an application to manufacture a product subject to licensure under Section 351 of the Public Health Service Act [42 USC 262].

container closure: The seal of a final product container which assures product sterility.

current good manufacturing practice (cGMP): Methods used in, and the facilities or controls used for, the manufacture, processing, packing or holding of a drug including, but not limited to, blood components, to assure that such product meets the requirements of the Federal Food, Drug and Cosmetic Act as to their safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess [21 CFR 210.1]

leukocyte reduction equipment: Equipment used during blood manufacturing to reduce the leukocyte content in accordance with established product specifications. The equipment is typically 510(k)-cleared by CBER (pre-storage leukocyte reduction filters and apheresis machines) but may also be approved as a new drug (blood collection sets with integral in-line filters) owing to the anticoagulant/storage solution component of the equipment.

process validation: Establishing confidence and documenting evidence that a specific process consistently functions within established limits towards manufacturing of products that meet predefined specifications.

quality assurance (QA) program: An organization's comprehensive system for manufacturing safe, effective, and quality products according to regulatory standards. This program includes preventing, detecting, and correcting deficiencies that may compromise product quality.

quality assurance (QA) unit: One or more individuals designated by, and reporting directly to, management with defined authority and responsibility to assure that all quality assurance policies are carried out in the organization.

quality monitoring; quality control (QC) testing: As a component of a quality assurance program, the direct monitoring of products or activities to confirm that product manufacturing is in accordance with intended product specifications.

sterile tubing connection device (STCD): A device used to sterilely join blood tubing or segments without breaching container closure.

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