

A CONCEPT PAPER ON Pre-storage Leukocyte Reduction of Transfusion Blood Components

Introduction

This concept paper has been developed by FDA to serve as the basis for a public discussion of the issues associated with pre-storage leukocyte reduction of blood components intended for transfusion use. The public discussion may facilitate the development of an FDA guidance document as well as regulations on pre-storage leukocyte reduction of transfusion blood components.

Leukocyte Reduction Issues

Under current FDA regulations, leukocyte reduction of transfusion blood components is not required. In addressing leukocyte reduction, FDA issued recommendations in a blood memorandum on May 29, 1996, defining leukocyte reduction as a blood manufacturing step that (1) reduces leukocytes content to 5.0×10^6 residual cells, and (2) is performed under controlled and monitored laboratory conditions (current Good Manufacturing Practice, "cGMP"). The memorandum was written in accordance with the outcome of a public workshop held in 1995 on the same subject.

Since 1995, many national blood authorities outside of the United States have introduced leukocyte reduction as a routine step in the manufacturing of blood and blood components. In the United States, FDA's Blood Products Advisory Committee (BPAC) stated in September 1998 that leukocyte reduction as a routine step is advisable from a scientific basis, irrespective of effectiveness against CJD. Subsequently, on June 2, 2000, FDA's Transmissible Spongiform Encephalopathies Advisory Committee did not affirm the effectiveness of leukocyte reduction in significantly reducing the infectivity of CJD and nvCJD in blood components, due to inadequacy of the available scientific data.

Requiring implementation of universal or routine leukocyte reduction in the United States remains controversial. The associated cost of approximately 300 to 500 million dollars annually may weaken the transfusion delivery system on a national scale. Still, the Public Health Service Advisory Committee recommended in April 2000 that assurance of adequate public health funding should be pursued in support of safely implementing leukocyte reduction as a routine blood manufacturing step.

The 1996 FDA Memorandum on Leukocyte Reduction

In 1995, FDA sponsored a workshop to publicly discuss the regulation of leukocyte reduction. The participants strongly supported FDA's not approving specific indications for using leukocyte reduced blood components, as such an approach was seen as potentially interfering with medical practice. As a result, the 1996 memorandum currently in effect outlines manufacturing recommendations only, and remains silent on the indications for using leukocyte reduced blood components. The specific recommendations in the memorandum have become outdated over the last 5 years, and FDA is considering appropriate revisions to the existing guidance.

Benefits of Leukocyte Reduction

Leukocyte reduced blood components are used most commonly today in the United States for three indications. These include: (1) to eliminate recurrent febrile non-hemolytic transfusion reaction, (2) to reduce the incidence of HLA alloimmunization of the transfusion recipient that may contribute to the patient's potential refractory state against platelet transfusions, and (3) to reduce the incidence of transfusion-transmitted cytomegalovirus infection under relevant clinical situations. A growing list of controversial indications with variable but without definitive support in the literature include the potential reduction of: (a) transfusion-related immune suppression, (b) cell storage lesion, (c) bacterial overgrowth, (d) viral reactivation, (e) transfusion-related acute lung injury, and (f) reperfusion injury after a cardiopulmonary bypass procedure.

Leukocytes in a unit of Whole Blood or non-leukocyte blood component do not contribute to product efficacy and may be regarded as contaminants that potentially reduce transfusion safety. Although adverse transfusion reactions have been associated with the use of leukocyte reduction filters, advances in blood cell separation technology enable the safe and substantial reduction of residual leukocytes thereby increasing product purity and safety. Aside from specific device (filter) failures, there are no clinically significant adverse effects associated with leukocyte reduction.

FDA's Current Thinking on Leukocyte Reduction

FDA current thinking differs from the agency's earlier recommendations contained in the May 1996 memorandum. Specifically, the agency is considering: (1) the inclusion of a leukocyte reduction step in blood manufacturing, to the extent feasible; (2) the use of a more stringent product specification of 1.0×10^6 rather than 5.0×10^6 residual leukocytes per blood unit; (3) the use of a statistical approach in monitoring the quality of the leukocyte reduction process, to assure with 95% confidence that at least 95% of the blood units meet intended product specifications; and (4) the presentation of multiple regulatory options, each at a different level of reporting burden, towards streamlining blood licensure. The agency's current thinking has been shaped in part by the outcome of a recent FDA-sponsored public workshop entitled "Implementation of Universal Leukocyte Reduction" held in December 1999.

Draft Model of Methods for Leukocyte Reduction of Blood Components

FDA is considering a model which recommends that Whole Blood and blood components intended for transfusion may be leukocyte reduced pre-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 attached to a blood container using an FDA-cleared STCD,
- (3) leukocyte reduction simultaneous with platelet or plasma collection using direct automated cytapheresis, and
- (4) in the case of plasma, routine laboratory centrifugation without the use of a special leukocyte reduction step.

Model leukocyte reduction methods as applied to specific leukocyte reduced blood components are listed in Table 1, along with corresponding product specifications (leukocyte content and product recovery).

Table 1: Leukocyte reduced blood components and leukocyte reduction methods
(LR = Leukocytes Reduced; STCD = sterile tubing connection device; LC = laboratory centrifugation)

Blood Component	Leukocyte Content	Product Recovery	Applicable Methods
Whole Blood, LR	$\leq 1.0 \times 10^6$	85 %	STCD-filtration; In-line filtration
Red Blood Cells, LR			STCD-filtration; In-line filtration; Preparation from Whole Blood, LR
Platelets, Pheresis, LR			STCD-filtration; In-line filtration; Automated plateletpheresis
Plasma, LR			STCD-filtration; LC; Preparation from Whole Blood, LR; Automated plasmapheresis
Platelets, LR	$\leq 1.7 \times 10^5$		STCD-filtration

Draft Model for Standard Operating Procedures

Standard operating procedures (SOP) for leukocyte reduction must be maintained [21 CFR 606.100(b)]. FDA is considering SOPs which identify: (1) leukocyte reduced blood to be manufactured, (2) blood product specifications, (3) leukocyte reduction methods, and (4) leukocyte reduction device and its manufacturer, which device is either cleared or approved by the Center for Biologics Evaluation and Research.

The SOP should describe in sufficient detail process validation and quality monitoring as well as investigation of any process failures. In addition, the SOP should address leukocyte reduction of blood collected from donors with Sick Cell Trait because leukocyte reduction by filtration often fails for Whole Blood or Red Blood Cells collected from donors with sickle cell trait and routine sickle trait donor screening may be impractical.

Draft Model Product Labeling: Content and Format

The FDA-approved product insert for blood intended for transfusion use, *Circular of Information for the Use of Human Blood and Blood Components (Circular)* describes in detail the indications, contraindications, side effects, hazards, dosage, and administration of leukocyte-reduced products.

The container label must follow a format accepted by FDA [21 CFR 606.121 (a)]. 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. 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: Names to be used on container labels and product inserts

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

Draft Model for Process Validation and Quality Monitoring

Process validation requirements for finished pharmaceuticals [21 CFR 210, 211] apply to the manufacture of leukocyte reduced blood and leukocyte reduction devices, respectively. Accordingly, the entire leukocyte reduction process should be tested initially in sufficient detail to establish process stability and acceptable process performance. Following successful validation, the leukocyte reduction process should be tested periodically to detect a potential unstable manufacturing process that may compromise blood product quality. Process validation includes the leukocyte reduction process, equipment, personnel performance, and monitoring operations.

Each facility should implement a quality monitoring program which assures, at 95% confidence level, that more than 95% of the units intended to be labeled as leukocyte reduced meet product specifications, without direct testing. The concept of quality monitoring programs includes sample collection and testing for residual leukocytes and product recovery. Therefore, FDA intends to discuss and is considering numerous methods to enumerate low numbers of residual leukocytes and in calculation product recovery.

Draft Model for 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 must be also licensed for leukocyte reduction, in accordance with Section 351 of the Public Health Service Act.

At this time, FDA is considering options for licensure. In the event FDA publishes a guidance document recommending specific procedures for leukocyte reduction, FDA may permit a licensed facility that changes its blood manufacturing procedures to include leukocyte reduction in accordance with all recommendations contained in the guidance, to supplement its biologics license to include leukocyte reduction by submitting the following as changes being effected (CBE) [21 CFR 601.12 (c)(5)]: (1) form FDA 356h, (2) quality control data from the initial process validation of the leukocyte reduction process, and (3) evidence of supervisory review of manufacturing records. Licensing of leukocyte reduction would be facility-specific; an applicant would need to submit a separate request for each facility. A CBE license application permits interstate product distribution upon FDA's receipt of the CBE filing, prior to approval.

Prior to issuance of any guidance document, and as an alternative to following any recommended procedures specified in future guidance, a licensed facility that wishes to manufacture leukocyte reduced blood and blood components should submit an application as a prior approval supplement (PAS) [21 CFR 601.12 (b)] which describes each method in detail. An applicant wishing to obtain 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. If the CP is approved by FDA, the applicant may then submit facility-specific data as CBE in accordance with the approved CP. Each of these licensing options is further described below. Table 3 summarizes the submission contents for: (1) a PAS which describes methods, (2) a CP which describes methods at multiple facilities, and (3) a CBE supplement when leukocyte reduction is performed in accordance with recommendations contained in a guidance document.

Table 3: License Application Contents

(PAS = prior approval supplement; CBE = changes being effected)

Submission Elements	PAS Alternative to Guidance	Comparability Protocol Alternative to Guidance		CBE Follows Guidance
		Protocol (PAS)	Data (CBE)	
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		
Product container labels Product insert (<i>Circular</i>)	X	X	X	X
Description of process validation Quality monitoring plan	X	X		
Quality control data from first two pre-defined manufacturing periods	X		X	X
Evidence of supervisory review, manufacturing records	X		X	X
Protocol and rationale (for multiple facilities)		X		