American National Standard

ANSI/AAMI BF64:2002

Leukocyte reduction filters

AAMI Association for the Advancement of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

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Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

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Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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Leukocyte reduction filters

Developed by
Association for the Advancement of Medical Instrumentation

Approved 30 December 2002 by
American National Standards Institute, Inc.

Abstract: This standard contains labeling requirements, performance requirements, test methods, and terminology for disposable filters used for the reduction of leukocytes from blood or blood components.

Keywords: blood, filter, leukocyte, leukoreduction, reduction, safety

AAMI Standard

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Contents

Glossary of equivalent standards

International standards adopted in the United States may include normative references to other international standards. For each international standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the international standard. (Note: Documents are sorted by international designation.)

Other normatively referenced international standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:2002	ANSI/AAMI/ISO 10993-4:2002	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	ANSI/AAMI BE78:2002	Minor technical variations
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:2002	ANSI/AAMI/ISO 10993-12:2002	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995 and Amdt 1:2001	ANSI/AAMI/ISO 11137:1994 and A1:2002	Identical
ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations

International designation	U.S. designation	Equivalency
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO TS 11139:2001	ANSI/AAMI/ISO 11139:2002	Identical
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:2003	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000	ANSI/AAMI/ISO 14971:2000	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical
ISO 25539-1:2003	ANSI/AAMI/ISO 25539-1:2003	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Blood Filter Committee

This standard was developed by the AAMI Blood Filter Committee. Committee approval of the standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the **AAMI Blood Filter Committee** had the following members:

Cochairs:
Leonard S. Berman, PhD
George Silvay, MD, PhD

Members:
James P. AuBuchon, MD, Dartmouth-Hitchcock Medical Center, representing American Association of Blood Banks and College of American Pathologists
Leonard S. Berman, PhD, Pall Corporation
Steve B. Binion, PhD, Baxter Healthcare Corporation
Walt Lee Carpenter, Medtronic Profusion Systems
Lauren Clark, Terumo Medical Corporation
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Mark Holmes, Gambro BCT Inc.
Jaroslav G. Vostal, MD, PhD, U.S. Food and Drug Administration/Center for Biologics Evaluation and Research

NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Foreword

This standard was developed by the Blood Filter Committee of the Association for the Advancement of Medical Instrumentation. The objective of this standard is to describe those requirements that will ensure the safe, effective, and reproducible reduction of the leukocyte content of blood components. This standard contains referee test methods used to ensure that the performance requirements are met.

The concepts incorporated by this document should not be considered inflexible or static. This standard, like any other standard, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as advances are made in technology and new data come forward.

Establishing compliance with this standard may involve the use of hazardous materials, operations, and/or equipment. Therefore, users of this document should establish appropriate safety practices and proceed with caution.

This standard reflects the conscientious efforts of concerned health care professionals, in consultation with medical device manufacturers, to develop a standard for those performance levels that could be reasonably achieved at this time.

As used within the context of this standard, “shall” indicates requirements strictly to be followed in order to conform to the standard; “should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is discouraged but not prohibited; “may” is used as a statement of possibility and capability. “Must” is used only to describe “unavoidable” situations.

Suggestions for improving this standard are invited. Comments and/or suggested revisions should be sent to AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—This foreword is not a part of the American National Standard *Leukocyte reduction filters* (ANSI/AAMI BF64:2002).

Leukocyte reduction filters

1 Scope

1.1 General

This standard describes safety and performance requirements for disposable filters used for the reduction of leukocytes from blood or blood components before, during, or after storage.

1.2 Inclusions

Included within the scope of this standard are disposable filters for the reduction of leukocyte content of blood and blood components. These are sometimes also referred to as leukocyte reduction filters.

1.3 Exclusions

Excluded from the scope of this standard are filters used for extracorporeal service and other filters not intended for blood transfusion. Also excluded are components of standard infusion sets designed to remove readily visible particulates.

NOTE—For an explanation of the need for this standard, and the rationale for its provisions, see annex A.

2 Normative references

The following normative references contain provisions that, through reference in this text, constitute provisions of this standard. For dated references, subsequent amendments to or revisions of any of these publications do not apply. However, parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies.

NOTE—In addition to the following normative references, other requirements for leukoreduction filter use and performance may apply, such as those in the pertinent sections of 21 CFR, FDA/CBER guidance memoranda, and the current version of the *Circular of Information for the Use of Human Blood and Blood Components* (AABB, 2002).

2.1 U.S. PHARMACOPEIAL CONVENTION. *United States Pharmacopeia* (24). Taunton (MA): Rand McNally, 2000.

2.2 AMERICAN SOCIETY FOR TESTING AND MATERIALS (ASTM). *Standard Test Methods for Microscopical Sizing and Counting Particles from Aerospace Fluids on Membrane Filters* (ANSI/ASTM F312-97). Philadelphia: ASTM, 1969.

2.3 SOCIETY OF AUTOMOTIVE ENGINEERS. *Evaluation of Particulate Contamination in Hydraulic Fluid—Membrane Procedure* (ARP-4285). Warrendale (PA): Society of Automotive Engineers, 1960 (1969).

2.4 AMERICAN ASSOCIATION OF BLOOD BANKS (AABB). *Technical Manual.* 14th ed. Bethesda (MD): American Association of Blood Banks, 2002.

2.5 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION (AAMI). *Biological evaluation of medical devices—Part 1: Evaluation and testing* (ANSI/AAMI/ISO 10993-1:1997). Arlington (VA): AAMI, 1997.

2.6 AMERICAN ASSOCIATION OF BLOOD BANKS (AABB). *Standards for Blood Banks and Transfusion Services.* 21st ed. Bethesda (MD): American Association of Blood Banks, 2002.

2.7 U.S. FOOD AND DRUG ADMINISTRATION/CENTER FOR DEVICES AND RADIOLOGICAL HEALTH. *Policy for Expiration Dating* (Memorandum RB92-G). Washington (DC): FDA/CDRH, 30 October 1992.

2.8 HENRY JB. *Clinical Diagnosis and Management by Laboratory Methods.* 19th ed. Philadelphia: Saunders, 1996.

2.9 PRATI D, BRANDWEIN H, CAPELLI C, et al. Multicenter evaluation of the 3 % paraformaldehyde method for white cell counting in leukocyte-reduced red blood cells. *Vox Sang*, 1996, vol. 70, pp. 241–245.

3 Definitions

For purposes of this American National Standard, the following definitions apply:

3.1 fiber: Particle longer than 100 µm with a length-to-width ratio of greater than 10:1, regardless of composition.

3.2 indated blood: Unit of a blood component that has been stored under proper conditions for a period not exceeding the established limit that ensures viability and efficacy of the primary elements for which the transfusion is occurring and the safety of the recipient. For example, red blood cells may currently be stored for 35 days at 1 °C to 6 °C in CPDA-1, or for 42 days in an additive solution (e.g., AS-1, AS-3, AS-5). Platelets (derived either from units of whole blood or through plateletpheresis using a closed system) may be stored for five days at 20 °C to 24 °C with constant gentle agitation. For further information and definition of other blood components, refer to the current edition of the *Standards for Blood Banks and Transfusion Services* (American Association of Blood Banks).

3.3 inspection: Examination (e.g., visual, auditory) and/or investigation, without the use of special laboratory appliances or procedures.

3.4 leukoreduction device: Enclosed filter and attached tubing used to reduce the leukocyte content of a transfusible blood component.

3.5 outdated whole blood: Blood that has been stored at 1 °C to 6 °C but not used within the stated shelf-life as written on the label.

3.6 particle size: Maximum dimension of the particle which, for a sphere, is the diameter.

3.7 platelets: Prepared from individual units of whole blood by centrifugation and later pooled for transfusion or prepared by apheresis. Platelets from whole blood should contain at least 5.5×10^{10} platelets in sufficient plasma (usually 50 mL to 70 mL) to maintain a pH ≥ 6.2 throughout the storage period. Platelets from apheresis should contain at least 3.0×10^{11} platelets in sufficient plasma as defined by the device to maintain a pH ≥ 6.2 throughout the storage period.

3.8 poststorage filtration: Filtration occurring at any time after the periods defined for “prestorage” filtration.

3.9 prestorage filtration: Filtration performed before or early in the storage period of a blood component.

NOTE—For prestorage filtration of red blood cells, typical practice is to filter within three days after collection, although FDA-cleared labeling for some products provides for filtration up to five days after collection. For platelets, typical practice for pre-storage filtration is to filter within one to two days of collection. Regardless, the time limits for testing units per this standard should reflect the full window of use intended by a given filter’s labeling. The time limits in this standard do not necessarily reflect the actual requirements or guidelines applied in clinical applications.

3.10 red blood cells: Residual red cell volume following removal of most of the plasma. Usually in the U.S., a saline additive system is added to the red cells to produce a hematocrit of 50 % to 60 %. Otherwise, the usual hematocrit is 70 % to 80 %.

4 Requirements

4.1 Labeling requirements

4.1.1 General

The term labeling denotes any and all printed matter that appears on the medical device, all accessory components, all portions of the container, and all documentation that accompanies the device. In addition to federal regulations applicable to the labeling of all medical devices, the requirements contained in this clause shall apply to medical devices within the scope of this standard.

4.1.2 Primary package labeling

The following information shall appear on that part of the package panel or label that is visible to the customer under typical conditions:

a) product name prominently displayed;

b) product identification or re-order code/number;

c) product’s intended use;

d) name and address of the manufacturer and/or distributor;

e) a statement of sterility and nonpyrogenicity, or nonsterility, of contents;

f) the following or similar caution: “Federal (USA) law restricts this device to sale by or on the order of a physician”;

g) net contents in number of units;

h) the manufacturer’s or distributor’s lot number or other control number, which will allow traceability of the components and materials used in the manufacture of the device; and

i) expiration date.

4.1.3 Instructions for use

The following shall appear on the package, package label, or a package insert:

a) directions for use;

b) statement regarding the number of units that may be filtered through the filter;

c) any requirement for storage or handling;

d) contraindications (if applicable);

e) precautions;

f) appropriate use of trademarks, service marks, or pertinent symbols of the manufacturer;

g) notice that the filtrations performed at ambient temperatures shall be completed within eight hours, unless data has been submitted to support transferring the product to 1 °C to 6 °C for continued filtration;

h) blood component hold time prior to filtration as required; and

i) statement that: “The filter has been designed and validated to meet the criteria of a leukoreduction filter for <specify the component and/or component preparation condition>. The filter’s performance must be validated using your facility’s standard operating procedure (SOP) on component preparation and handling. Any filtration that fails to meet the filtration specifications established by the facility's validation should be evaluated for residual leukocytes and red blood cell (RBC) recovery after filtration. Note that unusual attributes such as sickle cell trait, excessive blood clotting and gel formation, and poor mixing during collection and processing of components can contribute to the failure of a filtration to meet filtration specifications.”

4.1.4 Supporting information

4.1.4.1 Leukocyte reduction characteristics

Information on the leukocyte reduction characteristics and other blood constituents shall be generated by the manufacturer.

Product labeling or other information available from the manufacturer should provide performance information (e.g., filtration times, information regarding the potential for ineffective filtration in leukoreduction for donors with sickle cell trait) that would serve as a guide for the end user.

4.1.4.2 Cellular recovery

The recovery of the cellular component of the unit shall be ≥ 85 %.

4.2 Performance requirements

4.2.1 Packaging

The package that contains a leukoreduction device shall meet the following requirements (see also 2.7 and 2.8):

a) Package design, construction, and material shall be adequate to protect the device during customary conditions of storage, handling, and shipping.

b) Packaging shall permit aseptic removal or provide for maintenance of the sterile fluid pathway(s).

c) The device should not be damaged in any way during routine opening of the package and removal, and these actions shall not contribute to deposition of filter material or other foreign matter in the fluid pathways.

4.2.2 Structural integrity

The following requirements shall be met:

The filter housing shall be capable of withstanding a static internal gas pressure of at least 450 mmHg (8.7 psi, gauge) applied at a minimum rate of 45 mmHg/s (0.87 psi/s), without visible evidence of leakage.

NOTE—Based on housing design or application conditions, situations may exist in which a greater or lower pressure may be required than that specified here. If so, alternate test conditions may be required and used, as long as the justification is documented.

4.2.3 Filter performance

4.2.3.1 Filter cleanliness

The filter shall provide no more than the following effluent particle levels when subjected to the water or other solvent flush tests of 5.2.3.1:

a) = 1 particle per milliliter of solvent flush larger than 25 micrometers;

b) = 10 particles per milliliter of solvent flush larger than 10 micrometers;

c) = 100 particles per milliliter of solvent flush larger than 5 micrometers.

See 2.1.

NOTE—See also *Japanese Pharmacopoeia*, 13th ed. (1996) and *European Pharmacopoeia*, 3rd ed. (1997).

4.2.3.2 Reduction characteristics

A filter used in a leukoreduction process is expected to achieve 95 % confidence that at least 95 % of the units intended for transfusion have no more than 1×10^6 residual leukocytes per unit of red blood cells, per unit of apheresis platelets, or per unit of pooled whole blood platelets in controlled testing conditions. The manufacturer should have data documenting the confidence interval for leukocyte residuals over the range of filtration conditions indicated for use. The manufacturer should provide filter users with training and support on specific filter applications to ensure that white blood cell (WBC) residuals are within the manufacturer's expected range for the type and age of the unit being filtered.

NOTE—Manufacturers demonstrate filtration capabilities in controlled testing conditions. State-of-the-art leukoreduction filters are designed with capabilities to exceed a minimum requirement with 95 % confidence that 95 % of the blood component units filtered will achieve 5×10^6 WBC per unit in routine operational situations.

4.2.3.3 Duration of filtration

The duration of filtration is dependent on the filter design and preparation of the blood component. Manufacturers' quality systems, under which filters are designed and manufactured, specify, control, and document parameters that influence filtration time. A given filter will show variability in filtration time due to variations in the apparent viscosity of the blood component preparation or clogging of the filter. These variations can be influenced by blood donation and component preparation conditions such as mixing, plasma expression, temperature, the addition of additives, and formation of clots and gels. Manufacturers are expected to provide users with expected filtration times over a variety of conditions through product literature and studies. Users should establish filtration time estimates for process control at their sites during filter validation using the intended SOPs for blood component preparation and handling.

4.2.3.3.1 Bedside filters

Leukoreduction filters used at the bedside shall have mean filtration times of less than one hour for filtration of red blood cells and less than 30 minutes for filtration of platelets (for a standard unit of the type and storage age defined by the manufacturer as intended for the filter, under gravity flow).

4.2.3.3.2 Prestorage filters

Measurement of the filtration times should be made during development of any filter for a prestorage leukoreduction application. However, no specific requirements apply within this standard as long as WBC reduction and component recovery requirements are met.

4.3 Interface characteristics

4.3.1 Filters with attached administration sets

4.3.1.1 The male luer (needle) adapter shall accept conventional hubs for needles and catheters.

4.3.1.2 The spike, outlet port, and male luer (needle) adapter shall provide secure seals at conventional junctions and avoid leakage under a static internal gas pressure of 450 mmHg (8.7 psi, gauge) applied at a minimum rate of 45 mmHg/s (0.87 psi/s).

4.3.2 Dockable filters

Filters intended for use with a sterile connection device must have tubing dimensions appropriate to the sterile connection device manufacturer's recommendations.

4.4 Material safety

4.4.1 Toxicity potential evaluation

Materials in the fluid pathway shall pass toxicology test procedures. See 2.5.

4.4.2 Sterility

Each filter shall be sterile, unless clearly labeled to the contrary.

4.4.3 Pyrogenicity

Each sterile filter shall be nonpyrogenic.

5 Tests

This clause contains test methods to provide means of verifying the performance of leukocyte reduction filters. These test methods and procedures are for use in determining compliance with the requirements of clause 4. All instrumentation and measurement equipment shall be appropriate for measuring the test parameter in question and shall be calibrated and adjusted periodically or prior to use, against devices traceable to international or national standards; where no such standards exist, the basis used for calibration shall be recorded. The referee test methods and procedures of this clause are not intended for design qualification purposes or quality control testing; therefore, no confidence limits are specified. A change in design or construction material may, however, be accompanied by the reapplication of the appropriate test methods and procedures to establish continued compliance with the requirements of clause 4.

NOTE—The paragraph numbering of this clause corresponds to that of clause 4, except for the first digit. For example, the requirements of 4.2.2 are tested in accordance with the methods of 5.2.2.

5.1 Labeling

5.1.1 General

Compliance with the requirements of 4.1.1 can be determined by visual inspection.

5.1.2 Primary package labeling

Compliance with the requirements of 4.1.2 can be determined by visual inspection.

5.1.3 Instructions for use

Compliance with the requirements of 4.1.3 can be determined by visual inspection.

5.1.4 Supporting information

Hematocrit, erythrocyte count (cells/unit), leukocyte count (cells/unit), and platelet count (cells/unit) shall be determined according to one of the standard methods given in 2.8. In all cases, measurements shall be made at the extremes of all temperature ranges for which the manufacturer specifies that the filter is to function. The test shall be repeated with at least 10 representative filter units under each specified usage condition. Measurements must be made on units of the type indicated for the filter's application and that have been stored for the length(s) of time in which the filter is designated to be applied. Prestorage filters shall be tested with blood components prepared within the required time frames and holding/storage temperatures before the 24th hour (platelets) and 72nd hour (for red cells only) after collection (see 3.9, prestorage filtration, for the purposes of this standard). Filters designated for poststorage application should be tested with units three to seven days of age and on or after the last day of their storage period which conforms to product label.

Measurements of blood constituents, e.g., biochemical markers of cellular injury, shall be made according to standard methods (such as in 2.4, or equivalent) and at the identified times to avoid subsequent disintegration of platelets and leukocytes. Filters shall be primed and operated in accordance with the manufacturer's instructions. Postfiltration measurements shall be made after passage of a single unit and again after the maximum number of

units capable of being filtered in accordance with referee test method 5.2.3.3 have been filtered consecutively through a single filter unit. If the filter is intended for application on more than one unit, a pool of units equal to the largest size of intended application shall be made of ABO-identical units, and filtration of this pool shall be regarded as one filtration study.

Measurement of cellular recovery shall utilize the smallest unit size indicated for use. Filters shall be primed and operated in accordance with the manufacturer's instructions. Postfiltration measurements shall be made after passage of a single unit or after the minimum number of units have been filtered consecutively through a single filter unit. If the filter is intended for application on more than one unit, a pool of units equal to the smallest size of intended application shall be made of ABO-identical units, and filtration of this pool shall be regarded as one filtration study.

The tests for blood constituents and cellular recovery shall be repeated with representative filter units, and all data shall be utilized. All pre- and postfiltration data shall be collected, recovery calculated, and statistically evaluated to determine the mean with a power of 0.80 to determine a statistically significant difference of the mean from the target or required value with a $p < 0.05$.

NOTE—Pooling of compatible RBC units is not recommended for determination of WBC removal capability. Overestimation of WBC removal capabilities can result.

5.1.4.1 For filters intended for use with RBC units or units from which RBCs will later be derived, the recovery of red cells (as determined by red cell concentration or hemoglobin determination and total volume or mass of unit) shall be ≥ 85 % of the starting red cell content.

5.1.4.2 For filters intended for use with platelets (single units or pools, derived from whole blood), the recovery of platelets (as determined by platelet concentration and total volume or mass of unit) shall be ≥ 85 % of the starting platelet content.

5.1.4.3 For filters that are integrated into an apheresis application, the specific recovery specifications may not be applicable. However, product specifications for the specific blood component shall be met.

5.2 Performance requirements

5.2.1 Packaging

Compliance with the requirements of 4.2.1 can be determined by visual inspection.

5.2.2 Structural integrity

a) Pressure shall be applied at a minimum rate of 45 mm of mercury (0.87 psi, gauge) with nitrogen gas or oil-free compressed air to one port of the test unit with the other port(s) occluded so that a static pressure of 450 mmHg is reached, the unit being immersed neither less than 3 cm nor more than 25 cm under water. Failure shall be indicated by a steady stream of bubbles (defined as 5 or more per second) rising from the bonded sites or the housing itself. The leakage measurement period shall be at least five seconds in duration, following a premeasurement immersion period of 10 seconds with the pressure maintained at 450 mmHg for the full 15 second test period.

   NOTE—Sensitive pressure decay measurements or mass flow measurements can meet or exceed detection capabilities of the "look for bubbles" method outlined above.

b) If the filter is provided with an attached administration set, then occlusion shall be at a point distal to the site of mating and the test performed as in 5.2.2(a) above, with the additional stipulation that leakage at mating sites also shall constitute failure.

5.2.3 Filter performance

5.2.3.1 Filter cleanliness

All operations shall be performed in an operating, certified laminar flow hood equipped with high-efficiency particulate air (HEPA) filters. Install a dummy filter (i.e., a filter housing not containing any filter medium) in a fixture containing a test sample holder, fluid circulation apparatus, and an analysis membrane holder downstream of the test sample holder. The fluid shall be *U.S. Pharmacopeia* water-for-injection filtered through a 0.8 µm filter. Wash the test fixture and both sides of a black-gridded 0.8 µm pore-size blank analysis membrane using this fluid. Install the analysis membrane using smooth-tip forceps, and allow fluid flow through the dummy filter at a rate of 500 cc/min, or at a maximum pressure drop of 450 mmHg (8.7 psi, gauge) for five minutes. Remove the analysis membrane, place it in a petri dish container with the cover slightly ajar, dry in a laminar flow hood, and count microscopically the particles collected on the membrane surface (as per 2.2 and/or 2.3). Repeat the procedure from the beginning using a test filter sample in place of the dummy. The blank count may not exceed 10 % of the maximum acceptable counts

given in 4.2.3.1. Calculate the difference between the test and blank counts for all particles larger than 10 µm in diameter, larger than 25 µm in diameter, and all fibers. Alternatively, filter cleanliness may be evaluated by the test methods of *U.S. Pharmacopeia*, *Japanese Pharmacopoeia*, or *European Pharmacopoeia* as indicated in 4.2.3.1. All counts shall be less than or equal to those given in 4.2.3.1.

5.2.3.2 Reduction characteristics

Utilize units of human blood components of the type specified for application of the leukoreduction device. If the various possible types of anticoagulants or other elements of the units intended to be used with the device are substantially different, representative portions of each subset of components filtered shall be included in the study. Perform the filtration according to the instructions supplied to the user, applying in different filtrations the extremes of all of the criteria identified as critical for leukoreduction efficiency, such as those listed in 4.2.3.2. Leukocyte concentration and content may be determined by an electronic particle counter or manually in a sample from the component prior to filtration by a method that has a sensitivity at least equal to the claims of residual leukocyte concentration. For claims of residual leukocyte content of $\leq 1.0 \times 10^6$/unit, the postfiltration leukocyte concentration and content shall be determined by the paraformaldehyde concentration method of Prati, et al. (see 2.9) or a method documented to have the sensitivity and reproducibility to statistically make the residual leukocyte claim. Determine leukocyte content as soon as practical after filtration to avoid further loss of leukocytes during storage.

5.2.3.3 Duration of filtration

a) For bedside filters, select a unit that is at the maximum storage time for that component. At the beginning of the test, the component unit shall be at its usual storage temperature; however, if the filtration is conducted at an ambient temperature different from that of the usual storage temperature of the component, the unit may be allowed to equilibrate with the ambient temperature during the filtration. Connect the filter device and a unit of the intended type, and attach it to a standard blood infusion set containing at least 100 cm length of 0.118 inch nominal inside diameter tubing with a 1 inch to 1.5 inch 16-gauge needle at the end of the administration set. Use the filter device according to instructions. Position the unit so that its midpoint is 100 cm above the point of the needle. Fill the tubing with the component and then open the flow limiter on the tubing and begin timing. Allow the component to drain into an open or vented vessel. Stop timing when the last of the component reaches the upstream side of the filter. Test at least 10 filters; in at least eight trials, the unit must require no more than 60 minutes to filter red cells and 30 minutes for platelets in order to meet the requirements of 4.2.3.3.1.

b) If the filter is intended to be applied to multiple units, apply a filter consecutively to one less than the maximum number using the method detailed in 5.2.3.3(a), but stopping the flow and removing the spike to the next unit as soon as the component has drained from the bag. Take care not to lose the prime of the filter when switching units. Then connect the last unit and repeat 5.2.3.3(a), timing the flow of the unit. Test at least 10 filters; in at least eight tests, the last unit must require no more than 60 minutes to filter red cells and 30 minutes for platelets in order to meet the requirements of 4.2.3.3.1.

5.3 Interface characteristics

5.3.1 Filters with attached administration sets

5.3.1.1 Attach a representative number of samples of conventionally hubbed needles and catheters into the administration set needle adapters of an equal number of filters. Observe the ease of attachment or lack thereof.

5.3.1.2 Using the units assembled in referee test method 5.3.1.1, occlude the needle or catheter. Follow referee test method 5.2.2(a), and, in addition, look for leaks in the needle/administration set junction.

5.4 Material safety

5.4.1 Toxicity potential evaluation

Material safety concerns should be addressed by conducting testing described in 2.5. This may be applied to the finished filter or separately to the materials of which it is composed.

5.4.2 Sterility

The test shall be conducted as for parenteral devices as stated in 2.1.

5.4.3 Pyrogenicity

The test shall be conducted as for pyrogen testing using either the method described in 2.1 or an equivalent limulus amebocyte lysate test.

Annex A
(informative)

Rationale for the development and provisions of this standard

A.1 Introduction

This annex provides the rationale for the initiation of a standards-development effort on blood leukocyte reduction transfusion filters, and the rationale for each of the specific requirements of the standard. It also reflects, as nearly as possible, committee deliberations that resulted in the requirements of clause 4 and the test methodologies of clause 5.

A.2 Need for this standard

Leukoreduction filtration is used in many situations to achieve a variety of clinical effects related to transfusion therapy. Clear definition of the performance expectations of these filters is necessary to ensure that users apply a filter that is intended to meet their needs. Furthermore, the probability of certain requirements being met should be specified by the manufacturer so that the certainty of the clinical outcome can be gauged using a particular filter.

A.3 Definitions

Rationale for this clause is contained within the text.

A.4 Rationale for the specific provisions of this standard

A.4.1 Labeling requirements

A.4.1.1 General

There are two factors that control the label content of a medical device. First, there are the requirements defined in Part 820, Chapter 1, Title 21 of the *Code of Federal Regulations—Good Manufacturing Practice for Medical Devices*—specifically sections 820.120, 820.121, and 820.130. These regulations establish requirements for proper handling, legibility, expiration dates, and many other aspects of labeling pertaining to good manufacturing practices. Second, Part 801, Chapter 1, Title 21 of the *Code of Federal Regulations* and Section 502 of the Federal Food, Drug, and Cosmetic Act (as amended in October 1976) specifically state what constitutes proper labeling and misbranding for a drug or device. These two sets of requirements comprise the federal regulations referred to in 4.1.1 of this standard. All labeling pertaining to leukocyte reduction transfusion filters is controlled by these regulations and must comply with them. They are included in this voluntary standard for informational purposes and completeness. In addition, see the May 29, 1996 memorandum from the FDA/Center for Biologics Evaluation and Research regarding leukoreduction requirements, “Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products.”

However, this standard requires other important labeling information concerning the use, safety, and expected performance of the device. Therefore, specialized labeling requirements particular to blood transfusion leukocyte reduction filters were developed and are included in 4.1.2, 4.1.3, and 4.1.4 of this standard.

A.4.1.2 Primary package labeling

These requirements are intended to furnish the user with reliable information concerning those parameters that ordinarily must be taken into account during a procedure.

A.4.1.3 Instructions for use

These requirements ensure that adequate information about the expected performance of the device is provided when the device is supplied to the user. The committee also considered specifying that the maximum period of time during which any single filter may be employed be the same as the period of ambient use recommended for blood and blood components, but the committee concluded that this stipulation is beyond the scope of this standard.

A.4.1.4 Supporting information

For safety, the user and others in the patient care system should be aware of any effects of filtration on normal blood constituents. While filtration of fresh blood has not been indicated in medical practice, the great fragility of constituents of fresh blood represents the most stressful clinical situation that may be encountered and any detrimental effects should be noted. Filtration of stored blood under high pressure infusion represents the most likely

clinical situation, and therefore should be investigated also. Standard test methods are cited as references, for guidance only, since several equivalent protocols are available and users may prefer to exercise their own judgment (Band et al., 1971; Biggs, 1976; Henry, 1996).

For safety, the user and others in the patient care system should be aware of any effects of filtration on blood components used in transfusion therapy. However, supporting information on certain blood components such as platelet concentrates was considered beyond the scope of this standard because of currently limited clinical use.

A.4.2 Performance requirements

A.4.2.1 Packaging

These requirements consider both the outer and inner packaging and address the risk of loss of sterility and contamination. The outer package protects the filter from mechanical abuse and the inner package (including protective end caps, if any) prevents loss of integrity that could lead to a loss of sterility. Consideration also was given to static resistivity and decay of packaging materials, but requirements have not been included in the standard because these factors were not considered hazards. In addition, functional requirements rather than packaging material specifications were addressed.

A.4.2.2 Structural integrity

Some bedside leukocyte reduction filters are intended for use in situations that could require rapid transfusion of large volumes of blood; housing or coupling failures requiring filter replacement prior to functional exhaustion consume valuable time and compromise function and sterility. A pressure of 450 mmHg was considered adequate for a leak test (as opposed to a burst test) because this is 1.5 times the typical use pressure. In addition, 45 mmHg/s is approximately 1.5 times the maximum pressure that can be applied by manually inflating a conventional blood bag pressure cuff. It also was noted that an air test is more stringent than a liquid test and that 450 mmHg is seldom exceeded in practice.

A.4.2.3 Filter performance

A.4.2.3.1 Filter cleanliness

Testing is necessary to ensure that the filter media itself neither migrates nor contains significant debris that could be infused as a nonbiodegradable aggregate into the patient. Microscopic counting allows quantification of the number and identification of the nature of particles and fibers. They are considered stringent but attainable by manufacturers. Stringent sizing standards are indicated because physiologic particles are distensible, while the manufacturing debris from filters is assumed to be essentially nondistensible. Therefore, equating equal passage for rigid filter material and distensible physiological particles is not valid. Water is suggested as the flush fluid because it is a physiological fluid that can be readily standardized, and is commonly used in microscopic counting.

A.4.2.3.2 Reduction characteristics

This requirement acts to ensure efficacy of the product.

Most current leukoreduction filters use a combination of separation by size and retention through adherence to filter material to achieve the clinically necessary degree of leukoreduction. Therefore, the function of the filter must be tested using the intended type of blood component.

A.4.2.3.3 Duration of filtration

The user and others in the health care system should be aware of the expected time frame to complete filtration. 21CFR 801.109 specifies that the duration be stated in the labeling.

A.4.2.3.3.1 Bedside filters

Transfusion duration is impacted by the filtration time. Multiple determinations are necessary since debris in stored blood, and even pooled blood or simulated blood suspensions, varies widely in magnitude and composition from one sample to another. (For example, blood pooling changes viscosity characteristics and does not necessarily yield the mean of the individual parameters.) In this way, filter capacity is determined in the same manner in which blood is actually administered. The maximum delivery times stated are based on the limits of practical utility.

A.4.2.3.3.2 Prestorage filters

As prestorage filtration occurs in a laboratory setting, not at bedside, the duration of a transfusion is not impacted by the filtration time as with bedside filters.

A.4.3 Interface characteristics

A.4.3.1 Filters with attached administration sets

For patient safety, it is important to ensure that the male luer (needle) adapter can be readily interfaced with conventional needles and catheters from different manufacturers without risk of separation or leakage under conditions of pressure infusion. It is hoped that needles and catheters will be standardized in the future.

A.4.4 Material safety

The materials comprising the “fluid pathway” should be evaluated to ensure minimum toxicity. Plastic components are pre-rinsed prior to testing to rule out handling as a source of toxic response.

Annex B
(informative)

Regional variations

Table B.1—Regional variations

NOTE—See 5.2.3.1.

***U.S. Pharmacopeia* 24 <788> Particulate Matter in Injections (Large volume injections > 100 mL)**	***Japanese Pharmacopoeia* (Chapter 34, Plastic Containers for Aqueous Solutions, (11) Fine Particles, Light-shielded Method**	***European Pharmacopoeia***
Light Obscuration Test Interpretation: Average # of particles present in the units tested ≤ 25 of ≥ 10 μm size per mL ≤ 3 of ≥ 25 μm size per mL	≤ 100 of 5 μm size per mL ≤ 10 of 10 μm size per mL ≤ 1 of 25 μm size per mL	3.2.6 Sets for the Transfusion of Blood & Blood Components, Extraneous Particles: No visible particles or filaments (assumed particles and filaments with a diameter ≥ 50 μm are visible to the naked eye)
Microscopic Particle Count Test Interpretation: Injection meets requirements of test if average # of particles present in the units tested ≤ 12 of ≥ 10 μm size per mL ≤ 2 of ≥ 25 μm size per mL		2.9.19 Particulate Contamination, Sub-visible Particles: Requirement—Per individual monograph
		2.9.20 Particulate Contamination, Visible Particles: Record presence of any particles
		2.9.21 Particulate Contamination, Microscopic Method Determination: Count and classify particles according to sizes previously chosen, ≥ 10 μm

Annex C
(informative)

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