Guidance for Industry

Use of Sterile Connecting Devices in Blood Bank Practices

Comments and suggestions regarding this document may be submitted at anytime to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the title of this guidance document.

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

For questions on the content of the document contact Martin Northern at 301-827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
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Table of Contents

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GUIDANCE FOR INDUSTRY

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This guidance document represents the agency's current thinking on the use of sterile connecting devices in blood banking. It does not create or confer any rights, privileges, or benefits on or for any person and does not operate to bind FDA or the public. An alternate approach may be used if such approach satisfies the requirements of the applicable statutes and regulations, or both.

I. INTRODUCTION

Sterile connecting devices produce sterile welds between two pieces of compatible tubing. This procedure permits sterile connection of a variety of containers and tube diameters. This guidance describes recommended practices and procedures for use of these devices. This guidance does not address the data or information that a manufacturer of a sterile connecting device must submit to FDA in order to obtain approval or clearance for marketing. It is also important to note that the use of an approved or cleared sterile connecting device for purposes not authorized in the labeling may cause the device to be considered adulterated and misbranded under the Federal Food, Drug and Cosmetic Act.

This document supercedes the August 5, 1994, and August 12, 1994, Food and Drug Administration (FDA) memoranda to Blood Establishments regarding "Use of an FDA Cleared or Approved Sterile Connecting Device (STCD) in Blood Bank Practice". This guidance is essentially unchanged from the previous memorandum, dated August 5, 1994. The only substantive change made in the revised document is the removal of a statement from the previous blood guidance that there is only one manufacturer which has FDA clearance for a sterile connecting device. There are now are several manufacturers with FDA clearance to market this type of device.

II. RECOMMENDATIONS

Manufacturers of blood products who propose to routinely use an FDA-cleared STCD should incorporate information regarding such use in standard operating procedure (SOP) manuals for each blood product. These entries should include record keeping, product tracking, tube weld quality control, lot numbers of software and disposables (including source(s) of elements to be added). Quality control procedures should include a test of the integrity of each weld.

Applications of the STCD

The user should be aware that use of the device may create a new product or significantly modify the configuration of a regulated product for which safety and efficacy have not been demonstrated. For those "new products" subject to licensure, applications, or application supplements must be submitted to FDA in addition to submission of a SOP. In general, pooling or mixing that involves cellular components represents a change in the product that requires

submission and approval of a license application or application supplement. Such applications and application supplements should contain data and descriptions of manufacturing procedures that demonstrate that the "new product" is safe and effective for its intended use throughout the proposed dating period.

The following comments are provided as guidance on the more common uses of an FDA cleared or approved STCD:

A. Adding a new or smaller needle to a blood collection set

1. Using the STCD to add a needle prior to the initiation of a procedure (whole blood collection, plateletpheresis or source plasma collection) is not considered to open a functionally closed system. If a needle is added during a procedure, only an STCD approved to weld liquid-filled tubing should be used. If the test of weld integrity is satisfactory, the use of an STCD is not considered to open a functionally closed system.

   Platelets, Pheresis prepared in an open system should be labeled with a 24 hour outdate and Platelets, Pheresis products prepared in a functionally closed system should be labeled with a five day outdate (See Revised Guideline for Collection of Platelets, Pheresis, October 7, 1988).

2. The source and specifications of added tubing and needles should be addressed in the blood center's SOP and records. Using the STCD to add needles does not represent a major change in manufacturing for which licensed establishments need preapproval.

B. Using the STCD to prepare components

When the STCD is used to attach additional component preparation bags, records should be properly maintained identifying the source of the transfer packs and the appropriate verification of blood unit number and ABO/Rh. All blood and blood components must be appropriately labeled (21 CFR 606.121).

Examples:

- Adding a fourth bag to a whole blood collection triple-pack for the production of Cryoprecipitated AHF from Fresh Frozen Plasma.

- Connection of an additive solution to a red blood cell unit.

- Addition of an in-line filter that has been FDA cleared for use in manufacturing components.

- Addition of a third storage container to a plateletpheresis harness.

For the above stated uses, SOPs should be developed and records maintained, but licensees need not have FDA approval in order to institute the procedures.

C. Using the STCD to pool blood products

Appropriate use of an STCD to pool Platelets prepared from Whole Blood collection may obviate potential contamination from the spike and port entries commonly used. Pooling performed immediately before transfusion is an example of such appropriate use. Pooled Platelets should be administered not more than 4 hours after pooling (See 21 CFR 606.122(l)(2)).

However, pooling and subsequent storage may increase the risk compared to administration of random donor units; if one contaminated unit is pooled with others and stored before administration, the total bacterial inoculum administered may be increased as a result of replication in the additional volume. Accordingly, the proposed use of an STCD to pool and store platelets for more than 4 hours should be supported by data which satisfactorily addresses whether such pooling is associated with increased risk. Such platelet pooling constitutes manufacture of a new product.

Pooling or mixing that involves platelets is considered the manufacture of a new product that requires submission and approval of a license application or application supplement if the storage period is to exceed four hours.

D. Using the STCD to prepare an aliquot for pediatric use and divided units

Pediatric units and divided units for Whole Blood, Red Blood Cells, and Fresh Frozen Plasma prepared using an STCD will not be considered a new product for which a biologics license application (BLA) supplement is required providing the following conditions are met:

1. The manufacturer should have an approved biologics license or license supplement, for the original (i.e., undivided) product, including approval for each anticoagulant used.

2. Labels should be submitted for review and approval before distribution. A notation should be made under the comments section of FDA Form 2567, Transmittal of Labels and Circulars.

3. Final product containers approved for storage of the component being prepared should be used.

Platelets manufactured under licensure must contain at least 5.5 X $(10)^{10}$ platelets (21 CFR 640.24 (c)). Platelets, Pheresis manufactured under licensure should contain at least 3.0 X $(10)^{11}$ platelets (See Revised Guideline for the Collection of Platelets, Pheresis, October 7, 1988).

SOPs to be followed regarding the use of an STCD to prepare divided products from Whole Blood collections and from plasma and platelets prepared by automated hemapheresis procedures should include descriptions of:

- How the apheresis harness or collection container will be modified with an FDA-cleared STCD;
- the minimum volume of the split plasma or whole blood products;
- the volume and platelet concentration of the split plateletpheresis products;
- storage time of the product. The product should be in an approved container and should be consistent with the storage time on the label of such container;
- method(s) to be used to label and track divided products in the blood center's records.

NOTE: Procedures for labeling the aliquots should be clearly stated in the SOP. Record keeping should be adequate to permit tracking and recall of all components, if necessary.

E. Using an STCD to connect additional saline or anticoagulant lines during an automated plasmapheresis procedure

SOPs for such procedures should be developed and records maintained consistent with the instrument manufacturer's directions for use, but licensees need not have FDA approval in order to institute the procedures.

F. Using the STCD to attach processing solutions

When using an STCD to attach containers with processing solutions to washed or frozen red blood cell products, the dating period for the resulting products is 24 hours, unless data are provided in the form of license applications or application supplements to CBER to support a longer dating period (21 CFR 610.53(c)). Exemptions or modifications must be approved in writing from the Director, CBER (21 CFR 610.53(d)).

G. Using an STCD to add an FDA-cleared leukocyte reduction filter

Some leuko-reduction filters are not integrally attached to the Whole Blood collection systems. SOPs for use of an STCD for pre-storage filtration should be consistent with filter manufacturers' directions for use.

Leukocyte reduction prior to issue constitutes a major manufacturing change. Therefore, for new leukocyte-reduced products prepared using an STCD, manufacturers must submit biologics license applications (21 CFR 601.2) or prior approval application supplements to FDA (21 CFR 601.12).

H. Using an STCD to remove samples from blood product containers for testing (e.g., using an STCD to obtain a sample of platelets from a container of Platelets or Platelets, Pheresis for cross matching).

If the volume and/or cell count of the product after sample withdrawal differ from what is stated on the original label or in the circular of information, the label on the product should be modified to reflect the new volume and/or cell count. For example, samples may not be removed that reduce the platelet count of a unit of Platelets to less than 5.5 x $(10)^{10}$ platelets (21 CFR 640.24 (c)).

III. ADDITIONAL COMMENTS

SOPs should include special instructions for product disposition if subsequent inspection of the weld reveals signs of leakage or air bubbles.

The preparation of non-standard blood components using an STCD is limited to research settings only, and should be conducted only under an investigational new drug exemption.

IV. ADDITIONAL INFORMATION

An appendix has been included in this guidance with the currently approved dating periods for blood components and source plasma (21 CFR 610.53) and currently recommended dating periods for automated plateletpheresis products (See Revised Guideline for Collection of Platelets, Pheresis, issued October 7, 1988).

This guidance presents general guidance as well as specific information and examples concerning specifications for submission of applications and application supplements to FDA addressing use of an STCD. If further questions arise concerning appropriate use of an STCD, concerns should be directed to the Office of Blood Research and Review, Center for Biologics Evaluation and Research.

Technical questions should be addressed to:

Division of Hematology, HFM-330
Office of Blood Research and Review
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852
Phone: (301) 827-3524
FAX: (301) 827-3534

Application forms and labeling transmittal forms may be obtained from:

Division of Blood Applications, HFM-370
Office of Blood Research and Review
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852
Phone: (301) 827-3524
FAX: (301) 827-3534

V. APPENDIX

USE OF AN APPROVED STERILE CONNECTING DEVICE (STCD) IN BLOOD BANK PRACTICE

Currently Approved Dating Periods for Blood Components and Source Plasma

PRODUCT	DATING PERIOD
Cryoprecipitated AHF	12 months from the date of collection of source blood, provided labeling recommends storage at -18°C or colder
Fresh Frozen Plasma	1 year from date of collection of source blood (-18°C or colder)
Liquid Plasma	a) 26 days from date of collection of source blood (between 1 and 6 °C) b) 40 days from the date of collection of source blood only when CPDA-1 solution is used as the anticoagulant (between 1 and 6 °C).
Plasma	5 years from the date of collection of source blood (-18 °C or colder).
Platelet Rich Plasma	72 hours from time of collection of source blood, provided labeling recommends storage between (20-24 °C or between 1 and 6 °C). 5 days if certain approved containers are used (20-24 °C).
Platelets, Pheresis	24 hours if collected in an open system.
Platelets, Pheresis	5 days if collected in a functionally closed system.
Source Plasma	10 years (at the recommended storage temperature stated on the label).
ACD Red Blood Cells	a) 21 days from the collection of source blood, providing labeling recommends storage between 1 and 6 °C and the hermetic. seal is not broken during processing. b) 24 hours after plasma removal, providing labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
CPD Red Blood Cells	a) 21 days from the collection of source blood, providing labeling recommends storage between 1 and 6 °C and the

	hermetic seal is not broken during processing. b) 24 hours after plasma removal, providing labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
CPDA-1 Red Blood Cells	a) 35 days from the collection of source blood, providing labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. b) 24 hours after plasma removal, providing labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
Red Blood Cells glycerolized	24 hours after removal from storage at -65 °C or colder, provided labeling recommends storage between 1 and 6 °C.
ACD Whole Blood	21 days from date of collection, providing labeling recommends storage between 1 and 6 °C.
CPD Whole Blood	21 days from date of collection providing labeling recommends storage between 1 and 6 °C.
CPDA-1 Whole blood	35 days from date of collection providing labeling recommends storage between 1 and 6 °C.