Manufacture of Blood Components Using a Pathogen Reduction Device in Blood Establishments: Questions and Answers

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Guidance for Industry

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Contains Nonbinding Recommendations

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Guidance for Industry

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I. INTRODUCTION

We, FDA, are providing you, blood establishments that collect or process blood and blood components, with recommendations for implementing a pathogen reduction device for the manufacture of pathogen-reduced blood components. We have received specific questions from blood establishments who have chosen to use the INTERCEPT® Blood System for Platelets and Plasma and who have questions on implementation of this pathogen reduction device. As a result, we are providing guidance in a question and answer format, addressing the most frequently asked questions. This guidance also provides recommendations to licensed manufacturers on reporting the manufacturing changes associated with implementation of a pathogen reduction device under Title 21 of the Code of Federal Regulations 601.12 (21 CFR 601.12).

The recommendations in this guidance apply to blood establishments that intend to manufacture pathogen-reduced platelet and plasma products using an FDA approved pathogen reduction device. Currently, the INTERCEPT® Blood System has been approved for the manufacture of certain pathogen-reduced platelet and plasma products, and the preparation of cryoprecipitated fibrinogen complex. If the product platforms for this FDA approved device change or FDA approves another pathogen reduction device with a similar intended use in the future, the Agency will consider providing additional recommendations to blood establishments.

This guidance finalizes the draft guidance entitled "Implementation of Pathogen Reduction Technology in the Manufacture of Blood Components in Blood Establishments: Questions and Answers, Draft Guidance for Industry" dated December 2017.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations,

unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

II. QUESTIONS AND ANSWERS

A. General Information

1. After blood establishments implement a pathogen reduction device for the manufacture of pathogen-reduced blood components, are they required to perform the infectious disease testing required in 21 CFR 610.40?

Yes. Under 21 CFR 610.40(a) testing is required of each donation for evidence of infection due to relevant transfusion-transmitted infections (RTTI) unless an exception applies, or, in accordance with 21 CFR 610.40(a)(2)(iii) and 21 CFR 610.40(a)(3)(ii), adequate and appropriate alternative procedures have been found acceptable for this purpose by FDA. If identified, we will announce such alternative procedures in a guidance document.

2. After blood establishments implement a pathogen reduction device for the manufacture of pathogen-reduced blood components, can they modify the donor history questionnaire to remove questions related to risk of disease transmission?

No. You must continue to assess the donor's medical history for factors associated with an increased risk for, or evidence of, an RTTI, in accordance with 21 CFR 630.10(e)(1). We may consider revised recommendations for complying with the requirements for assessing a donor's medical history in 21 CFR 630.10, and would announce such recommendations in a guidance document.

3. Which blood components can undergo pathogen reduction using the INTERCEPT® Blood System?

Please refer to the manufacturer's instructions (operator's manual and processing sets package inserts) for information about which specific blood components can be pathogen-reduced with this device.

4. Can pathogen reduction using the INTERCEPT® Blood System substitute for irradiation of platelets to prevent the risk of transfusion-associated graft versus host disease (TA-GVHD)?

Yes. As described in the FDA-approved labeling, the INTERCEPT® Blood System for Platelets can be used as an alternative to gamma irradiation for prevention of transfusion-associated graft versus host disease (TA-GVHD).

5. Can pathogen reduction of platelets substitute for bacterial detection testing to reduce bacterial contamination in platelets?

Yes. When used in accordance with the manufacturer's instructions, we consider use of the INTERCEPT® Blood System acceptable to control the risk of bacterial contamination in platelets as required in 21 CFR 606.145.

In the future, we may approve or clear other pathogen reduction devices that would be acceptable to control the risk of bacterial contamination of platelets.

6. Can pathogen-reduced plasma undergo fractionation for further manufacturing into plasma derivatives?

The impact on product quality of using pathogen-reduced plasma in the manufacture of plasma derivatives is not known at this time. Consignees should contact FDA before using pathogen-reduced plasma for further manufacture.

B. Manufacture of Pathogen-Reduced Blood Components by Blood Establishments

1. Where can blood establishments find information on additional specifications for manufacturing pathogen-reduced blood components using the INTERCEPT® Blood System?

You should refer to the INTERCEPT® Blood System manufacturer's instructions for additional specifications regarding the manufacture of pathogen-reduced platelet and plasma products and cryoprecipitated fibrinogen complex.

2. According to the manufacturer's instructions for the INTERCEPT® Blood System for platelets, platelets must be pathogen-reduced within 24 hours of collection. Should the platelets be agitated prior to the pathogen reduction process?

Yes. Under 21 CFR 640.25(a), platelets stored at 20°C to 24°C must be gently agitated continuously during the storage period. This includes during the storage of the platelet products both before and after pathogen reduction.

3. Can blood establishments prepare Cryoprecipitated AHF from apheresis plasma or Whole Blood-derived pooled plasma that was pathogen-reduced using the INTERCEPT® Blood System?

Yes, provided the pathogen-reduced apheresis plasma or Whole Blood-derived pooled plasma is placed in the freezer within 8 hours after collection (for Whole Blood-derived pools – within 8 hours after collection of the oldest unit in the pool) or within the timeframe specified in the directions for use for the blood

collecting, processing, and storage system, in accordance with the requirements in 21 CFR 640.54(a)(2).

Cryoprecipitated AHF prepared from pathogen-reduced apheresis plasma or Whole Blood-derived pooled plasma must contain acceptable levels of antihemophilic factor and fibrinogen in the final product in accordance with the requirements in 21 CFR 640.54(b) and 21 CFR 606.122(n)(2).

4. How long can Whole Blood-derived plasma be kept at room temperature before it is pathogen-reduced using the INTERCEPT® Blood System?

The time at room temperature must be determined by the regulations applicable to the products you intend to manufacture. For example, if you intend to manufacture pathogen-reduced Fresh Frozen Plasma, you must place the plasma in a freezer within 8 hours after collection (21 CFR 640.34(b)). According to the manufacturer's instructions for the INTERCEPT® Blood System for Plasma, all manufacturing steps, including separating plasma from red blood cells, performing the pathogen reduction process, and placing the pathogen-reduced plasma in the freezer, must be completed within 24 hours after collection. The manufacturer's instructions for the INTERCEPT® Blood System for Plasma do not specify how long Whole Blood-derived plasma can be stored at room temperature before it is pathogen-reduced.

5. The manufacturer's instructions for the INTERCEPT® Blood System state that the red blood cell content of the platelets and plasma before pathogen reduction should be < 4.0 x 10^6 RBC/mL. Do blood establishments need to determine the red blood cell content of each platelet and plasma product before they undergo the pathogen reduction process?

Yes. Unless otherwise stated in the manufacturer's instructions, you may use tools, such as the color comparator provided by the manufacturer, to estimate the red blood cell content of the platelets and plasma before pathogen reduction. Products that do not meet the standards stated in the manufacturer's instructions (e.g., contain more than the acceptable red blood cell content) must not undergo the pathogen reduction process (21 CFR 606.65(e)).

6. What other testing should be performed to qualify platelet and plasma products before these products are pathogen-reduced using the INTERCEPT® Blood System?

Blood establishments should refer to the manufacturer's instructions of the FDA approved pathogen reduction device for input specifications for the manufacture of pathogen-reduced platelet and plasma products. The manufacturer's instructions will guide what further testing needs to be performed (21 CFR 606.65(e)).

7. Should blood establishments determine platelet retention (i.e., platelet yield after pathogen reduction compared to platelet yield before pathogen reduction) as part of their validation and quality control testing? If so, what would be an acceptable retention value?

Section 606.140(a) requires that laboratory procedures include the establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective. Accordingly, to ensure manufacturing consistency, we recommend that platelets that have been pathogen-reduced using the INTERCEPT® Blood System should have at least 80% platelet retention. We recommend that you use a statistically sound sample size and testing procedures that will ensure, with 95% confidence, that greater than 95% of the pathogen-reduced platelets will meet this specification consistent with previously recommended statistical parameters. See the Appendix of this guidance.

8. What other quality control procedures are recommended for pathogen-reduced platelets?

For purposes of the quality control testing required under 21 CFR 640.25, we recommend that you consider pathogen-reduced platelets as a distinct product from platelets that are not pathogen-reduced. Quality control testing for pathogen-reduced platelet products should be performed separately from quality control testing of platelet products that are not pathogen-reduced.

In addition, we recommend that quality control testing be performed separately for pathogen-reduced platelets in platelet additive solution and pathogen-reduced platelets in 100% plasma.

The quality control testing of the pathogen-reduced platelets should include platelet yield and pH using a scientifically valid statistical sampling plan such as the binomial distribution (Ref. 1) or hypergeometric distribution (Ref. 2). The samples used for quality control testing can be composed of platelet products collected at any blood establishment operating under the same license. Since the Instructions for Use for the INTERCEPT Blood system provide that the starting platelet product is leukocyte-reduced platelets, we are not recommending that the residual white cell count be performed after the pathogen reduction process (21 CFR 606.65(e)).

The Appendix of this guidance contains recommendations for platelet quality control monitoring after pathogen reduction using the INTERCEPT® Blood System.

9. Where can blood establishments find information about product codes for labeling pathogen-reduced blood components?

We recognize the consensus standards prepared by the International Council for Commonality in Blood Banking Automation (ICCBBA) as an acceptable format to comply with the labeling requirements for blood and blood components in 21 CFR 606.121. You may consult ICCBBA for the product names and codes that have been assigned to pathogen-reduced blood components.

C. Reporting Implementation of a Pathogen Reduction Device in Licensed Blood Establishments

1. How should licensed blood establishments submit requests to manufacture pathogen-reduced blood components?

An establishment that distributes blood components in interstate commerce must have an approved Biologics License Application (BLA), in accordance with section 351 of the Public Health Service Act (42 U.S.C. 262). Licensed blood establishments must report major changes to their approved BLAs by submitting a Prior Approval Supplement (PAS) in accordance with 21 CFR 601.12(b): Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes). You must not distribute in interstate commerce blood components made using a new or changed manufacturing process requiring a PAS until you have received FDA approval of your PAS (21 CFR 601.12(b)(3)).

We believe a PAS submission is appropriate in the following situations:

a. You are already licensed to manufacture the blood components you intend to pathogen reduce using an FDA approved device.

b. You are not already licensed to manufacture the blood components you intend to pathogen reduce using an FDA approved device. In accordance with 21 CFR 601.12(b)(3)(iv), your submission must include, among other things, information about how the blood components are manufactured prior to pathogen reduction, e.g., standard operating procedures (SOPs) and quality control data.

c. You may consider submitting a Comparability Protocol as a PAS under 21 CFR 601.12(e) if you will be implementing the pathogen reduction process using the same procedures in multiple locations. A Comparability Protocol is not required, but an approved Comparability Protocol may permit a reduced reporting category for implementing the pathogen reduction process in multiple locations.

Questions may be submitted via email to CBEROBRRBPBInquiries@fda.hhs.gov.

2. What should be submitted to FDA under 21 CFR 601.12?

To comply with the requirements in 21 CFR 601.12(b)(3) and 21 CFR 601.12(f)(1), you must include the following minimum information in your PAS submission:

a. Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use."

b. A list of the blood components that will be pathogen-reduced.

c. The address and registration number of the facility/facilities where the pathogen-reduced blood components will be manufactured.

d. A description of the manufacturing process for the pathogen-reduced blood components, including the submission of written SOPs that include:

   i. Processes to ensure that blood components selected to undergo the pathogen reduction process meet the product specifications ("guardbands") described in the manufacturer's instructions.

   ii. The handling of blood components that were not successfully pathogen-reduced, including how process and non-process failures will be investigated.

   iii. Quality oversight of the manufacturing process.

   iv. Quality control procedures and the sampling plan.

e. Container labels for the pathogen-reduced blood components.

f. The Circular of Information for the pathogen-reduced blood components. If you are not using the current version of the circular recognized by FDA, include your circular in the PAS submission.

g. The pathogen reduction process validation protocol used and a summary of the results, including the results of any process and non-process failure investigations.

h. At least two months of quality control data for each type of platelet or cryoprecipitate product that is pathogen-reduced.

For each facility manufacturing pathogen-reduced blood components:

i. The platelet yield for pathogen-reduced platelets made at that facility.

ii. The percent platelet retention for pathogen-reduced platelets made at that facility.

iii. The antihemophilic factor and fibrinogen content of pathogen-reduced cryoprecipitate products.

For all facilities performing pathogen reduction operating under the same license:

- The pH for pathogen-reduced platelets.

Comparability Protocol submissions under 21 CFR 601.12(e) must also include the plan for implementing the process for manufacturing pathogen-reduced blood components in multiple manufacturing facilities. The plan should include a description of how you will validate the new processes and how staff will be trained.

You should include the following minimum information in your Changes Being Effected in 30 Days supplement (21 CFR 601.12(c)) for your approved Comparability Protocol:

a. Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use."

b. The submission tracking number (STN) for the approved Comparability Protocol.

c. A description of the blood components that will be pathogen-reduced.

d. The address and registration number of the facility/facilities where the pathogen-reduced blood components will be manufactured.

e. A summary of the validation results, including any process and non-process failure investigations.

f. Two months of quality control data for each type of pathogen-reduced platelet and cryoprecipitate product (as described in section II.B. questions 3 and 8, and section II.C. question 2.h. of this guidance).

Questions regarding your submission may be submitted via email to CBEROBRRBPBInquiries@fda.hhs.gov.

3. Once a supplement is approved, will the approval apply to all manufacturing facilities operating under the blood establishment's license?

No. These supplements are considered "site-specific" approvals. This means that each facility manufacturing pathogen-reduced blood components must be individually approved to perform this process. If you want to manufacture pathogen-reduced blood components in multiple facilities, you may consider submitting a Comparability Protocol as discussed in section II.C. question 1.c. of this guidance.

III. REFERENCES

1. Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods, December 2007, https://www.fda.gov/media/70720/download.

2. Guidance for Industry: Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion, September 2012, https://www.fda.gov/media/84460/download.

APPENDIX: FDA RECOMMENDATIONS FOR PLATELET QUALITY CONTROL MONITORING AFTER PATHOGEN REDUCTION USING THE INTERCEPT® BLOOD SYSTEM

Recommended Specifications	Recommended Criteria for Validation and Quality Control (For Storage in Platelet Additive Solution or in 100% Plasma)	Recommended Confidence Level/Degree of Conformity[1]
Platelet Yield[2]	$\geq 3 \times 10^{11}$	95%/75%[4]
Percent Platelet Retention	$\geq 80\%$	95%/95%[5]
pH[3]	≥ 6.2	95%/95%[5]

1. A binomial statistical sampling plan may be used for both process validation and quality control (Ref. 1). A hypergeometric statistical sampling plan can only be used for quality control (Ref. 2).
2. Pathogen-reduced platelets with yields less than 3.0×10^{11} should be appropriately labeled with the actual platelet count (Ref. 1).
3. At issue or outdate after storage at 20 - 24° C (21 CFR 640.24(d)).
4. We recommend 95% confidence that greater than 75% of the components meet the standard.
5. We recommend 95% confidence that greater than 95% of the components meet the standard.