

Implementation of Pathogen Reduction Technology in the Manufacture of Blood Components in Blood Establishments: Questions and Answers

Draft Guidance for Industry

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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. FDA has received specific questions from blood establishments concerning implementation of the INTERCEPT® Blood System for Platelets and Plasma. As a result, FDA is 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 pathogen reduction under 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. If the product platform for this FDA approved device changes 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.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidelines means that something is suggested or recommended, but not required.

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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. 21 CFR 610.40(a) requires testing of each donation for evidence of infection due to relevant transfusion-transmitted infections (RTTI) unless an exception applies or adequate and appropriate alternative testing procedures have been found acceptable for this purpose by FDA.

In the future, we may find alternative testing procedures for RTTIs acceptable in accordance with 21 CFR 610.40(a)(2)(iii) and 21 CFR 610.40(a)(3)(ii).¹ We would announce such alternative procedures in a guidance document.

Please note: FDA provided recommendations on the use of FDA-approved pathogen reduction devices to reduce the risk of Zika virus transmission by platelets and plasma in the guidance entitled, “Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components; Guidance for Industry” dated August 2016 (Ref. 1). The guidance states if blood establishments implement pathogen reduction technology using an FDA-approved pathogen reduction device as specified in the Instructions for Use of the device, the platelets and plasma donations do not need to be tested for Zika virus.

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?

At this time, we recommend that you continue to use your current donor history questionnaire. In the future, we may consider revised recommendations for complying with the requirements in 21 CFR 630.10 in assessing a donor’s medical history, and would announce such recommendations in a guidance document.

¹See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015), effective May 23, 2016.

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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)?

The manufacturer's instructions (operator's manual and processing sets package inserts) indicate that treatment of platelets with the INTERCEPT® Blood System potentially lowers the risk of TA-GVHD. The transfusion medicine physician and/or treating physician should determine whether to replace irradiation with pathogen reduction to prevent TA-GVHD.

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

Yes. Under 21 CFR 606.145, blood establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA. We consider use of the INTERCEPT® Blood System acceptable to control the risk of bacterial contamination in platelets.

In the future, we may find other FDA approved or cleared pathogen reduction technologies to be acceptable to control the risk of bacterial contamination in platelets, as specified in the Instructions for Use of the device. We would announce such findings in a guidance document.

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 must contact FDA before using pathogen-reduced plasma for further manufacture (see 21 CFR 601.12(b)).

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B. Manufacture of Pathogen-Reduced Platelets and Plasma in Blood Establishments

- 1. 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 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.

- 2. Where can blood establishments find information on additional specifications for manufacturing pathogen-reduced platelets and plasma using the INTERCEPT® Blood System?**

Blood establishments may refer to the INTERCEPT® Blood System manufacturer's instructions (operator's manual and processing sets package inserts) for additional specifications regarding the manufacture of pathogen-reduced platelet and plasma products.

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

Yes, provided the pathogen-reduced apheresis plasma is placed in the freezer within 8 hours after collection 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).

Applications for licensure of Cryoprecipitated AHF prepared from pathogen-reduced apheresis plasma should include at a minimum, data demonstrating acceptable levels of Factor VIII and fibrinogen in the final product (21 CFR 640.54(b) and 21 CFR 606.122(n)(2)).

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

Yes, provided the pathogen-reduced pooled plasma is placed in a freezer within 8 hours after collection of the oldest unit in the pool (see 21 CFR 640.54(a)(2)).

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Applications for licensure of Cryoprecipitated AHF prepared from pathogen-reduced pooled plasma should include at a minimum, data demonstrating acceptable levels of Factor VIII and fibrinogen in the final product (21 CFR 640.54(b) and 21 CFR 606.122(n)(2)).

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

The manufacturer's instructions (operator's manuals and processing sets package inserts) 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. We recommend that the time at room temperature be determined by the applicable regulations regarding the manufacture of the product you intend to manufacture. For example, if you will manufacture pathogen-reduced Fresh Frozen Plasma, applicable regulations require that you must place the plasma in a freezer within 8 hours after collection (21 CFR 640.34(b)). According to the INTERCEPT® Blood System for Plasma manufacturer's instructions, your process should ensure all manufacturing steps, including separating plasma from red blood cells, the pathogen reduction process and placing the pathogen-reduced plasma in the freezer, are completed within 24 hours after collection.

6. The manufacturer's Instructions for Use for the INTERCEPT® Blood System states that the red blood cell content of the platelets and plasma before pathogen reduction should be $< 4.0 \times 10^6$ 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. The presence of excess red blood cells may impact the effectiveness of the pathogen reduction process on platelets and plasma. Unless otherwise stated in the manufacturer's instructions (operator's manuals and processing sets package inserts), 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) should not undergo the pathogen reduction process.

7. What other testing should be performed to qualify platelet and plasma products before these products undergo the pathogen reduction process?

The testing performed before the pathogen reduction process will determine if the starting product meets the specifications in the manufacturer's instructions (operator's manuals and processing sets package inserts) for the processing set in order to be pathogen-reduced.

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Blood establishments should refer to the manufacturer's instructions (operator's manual and processing sets package inserts) of the FDA approved pathogen reduction device for specifications regarding the manufacture of pathogen-reduced platelet and plasma products.

8. 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?

We recommend that platelets that have been pathogen-reduced using the INTERCEPT® Blood System should have at least 80% platelet retention. We further recommend that you use a statistically sound sample size and testing procedures that will ensure, with 95% confidence, that at least 95% of the pathogen-reduced platelets will meet this specification consistent with previously recommended statistical parameters (Ref. 2). See Appendix of this document.

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

For the purposes of quality control, 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 you consider pathogen-reduced platelets in platelet additive solution to be a distinct product from pathogen-reduced platelets in 100% plasma. Quality control testing should be performed separately for each type of pathogen-reduced platelet product.

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 (Refs. 2, 3) or hypergeometric distribution (Ref. 3). Since the starting platelet product must be leukocyte-reduced to undergo pathogen reduction, we are not recommending that the residual white cell count be performed after the pathogen reduction process.

See Appendix of this document for recommendations for monitoring platelet performance after the pathogen reduction process using the INTERCEPT® Blood System.

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

The FDA recognizes 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 Pathogen Reduction in Licensed Blood Establishments

1. How should blood establishments submit requests to implement pathogen reduction technology in the manufacture of 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. Licensed blood establishments must report 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 our approval of your PAS (21 CFR 601.12(b)(3)).

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

- a. You are licensed to manufacture the blood components described in the manufacturer's instructions for the FDA approved pathogen reduction device and you intend to implement the pathogen reduction process for these licensed blood components.
- b. You intend to implement the pathogen reduction process for your licensed blood components (as described in the manufacturer's instructions for the FDA approved pathogen reduction device) in multiple locations without using an approved Comparability Protocol.
- c. You may also consider submitting a Comparability Protocol as a PAS under 21 CFR 601.12(e) if you will be implementing collection and/or 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.

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- d. If you are a licensed blood establishment but are not licensed to manufacture the blood components that you would like to manufacture using a pathogen-reduction device, you should include a request to license such blood components in a PAS submission. Your submission must include the information needed to license the blood components you would like to manufacture, e.g., standard operating procedures (SOPs), quality control data and labeling.

Please contact your Consumer Safety Officer (CSO) in the Blood and Plasma Branch, DBCD, OBRR, CBER with questions.

2. What should be submitted to FDA to implement pathogen reduction technology using an FDA-approved pathogen reduction device in the manufacture of pathogen-reduced licensed blood components?

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. List of the blood components that will undergo the pathogen reduction process.
- c. Address and registration number of the manufacturing facility/facilities where the blood components will undergo the pathogen reduction process.
- d. A description of the manufacturing process for pathogen-reduced blood components. We recommend the submission of written SOPs that include:
 - i. The handling of blood components that were not successfully pathogen-reduced, including how process and non-process failures will be investigated (Ref. 3).
 - ii. Quality oversight of the manufacturing process.
 - iii. 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.

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- g. The validation protocol used and a summary of the results, including the results of any process and non-process failure investigations.
- h. Two months of quality control data for each type of platelet product that has undergone pathogen reduction (Ref. 3). For each pathogen reduction facility:
 - i. The platelet yield for pathogen-reduced platelets made at that facility. The platelet yield should be determined both before and after pathogen reduction.
 - ii. The percent platelet retention for pathogen-reduced platelets made at that facility.
 - iii. Platelets suspended in platelet additive solutions or in plasma should have separate quality control sampling testing and data.
- i. For all pathogen reduction facilities operating under the same license:
 - i. The pH for pathogen-reduced platelets.
 - ii. Platelets suspended in platelet additive solutions or in plasma should have separate quality control sampling testing and data.
- j. Comparability Protocol 21 CFR 601.12(e) submissions must also include the following:

The plan for implementing the pathogen reduction process at multiple manufacturing facilities. The plan should include a description of how you will validate the new process 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:

- i. Form FDA 356h, “Application to Market a New or Abbreviated New Drug or Biologic for Human Use.
- ii. The submission tracking number (STN) for the approved Comparability Protocol.
- iii. Description of the blood components that will undergo the pathogen reduction process.

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- iv. Address and registration number of the manufacturing facility (facilities) where the blood components will undergo the pathogen reduction process.
- v. A summary of the validation results, including any process and non-process failure investigations.
- vi. Two months of quality control data for each type of platelet product that undergoes pathogen reduction (as described in Section II.C. question 2.h. of this document).

If you have questions regarding your submission, contact your CSO in the Blood and Plasma Branch.

3. Once my supplement is approved, will the approval apply to all of my licensed blood establishment's manufacturing facilities?

No. These supplements are considered “site-specific” approvals. This means that each facility performing the pathogen reduction process must be individually approved to perform this process. If you want to implement the pathogen reduction process in multiple facilities, you may want to consider submitting a Comparability Protocol as discussed in Section II.C. question 1.c. of this document).

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III. REFERENCES

1. Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components; Guidance for Industry (August 2016), available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf>.
2. Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods (December 2007), available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM062946.pdf>
3. Guidance for Industry: Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion (September 2012), available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM320641.pdf>.

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

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

1. A binomial statistical sampling plan may be used for both process validation and quality control (Refs. 2, 3). A hypergeometric statistical sampling plan can only be used for quality control (Ref. 3).
2. Pathogen-reduced platelets with yields less than 3.0×10^{11} should be appropriately labeled with the actual yield (Ref. 3).
3. At issue or outdate after storage at 20 - 24° C (21 CFR 640.24(d)).