Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 issuing this guidance document to provide you, blood collection establishments and transfusion services, with recommendations to control the risk of bacterial contamination of room temperature stored platelets intended for transfusion. The recommendations in this guidance apply to all platelet products, including platelets manufactured by automated methods (apheresis platelets), whole blood derived (WBD) platelets, pooled platelets (pre-storage and post-storage) and platelets stored in additive solutions.

Additionally, this guidance provides licensed blood establishments with recommendations on how to report implementation of manufacturing and labeling changes under 21 CFR 601.12. This draft guidance replaces the draft guidance of the same title dated March 2016.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Room temperature stored platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component. The risk of bacterial contamination of platelets is a leading risk of infection from blood transfusion. Bacterial residual risk per transfused unit on the day of transfusion is 1/2300 (Ref. 1), and fatal transfusion reactions from undetected

contaminated platelet collections continue to occur (Ref. 2). This risk has persisted despite numerous interventions, including the widely used method of primary culture to test platelets prior to transfusion (Refs. 3, 4, 5, 6).

The reported rates of septic transfusion reactions from platelets vary from 1/100,000 by passive surveillance to 1/10,000 by active surveillance when testing with primary culture alone (Refs. 1, 7). Surveillance data on platelets stored up to 5 days have shown that 95-100% of platelet transfusion-related septic reactions (Refs. 3, 4, 8) and 100% of associated fatalities have occurred with transfusion of day 4 and day 5 stored platelets (Ref. 8).

FDA has established regulations to address the control of bacterial contamination of platelets. Under 21 CFR 606.145(a), 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.

Currently, this risk can be controlled by bacterial testing or pathogen reduction methods. Bacterial testing includes the use of culture-based or rapid detection tests.[1] While primary testing is typically performed by culture and within 24 hours of collection, secondary testing is performed at later times of storage prior to transfusion. Pathogen reduction is performed shortly after platelet collection.

Under 21 CFR 610.53(b), the dating period for platelets with a storage temperature between 20 and 24 degrees Celsius is 5 days from the date of collection, unless a different dating period is specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA. Accordingly, implementation of the recommendations in this guidance on extension of platelet dating beyond day 5 is contingent on the use of cleared or approved and suitably labeled platelet storage containers, bacterial detection tests and pathogen reduction devices.[2] The current maximum dating period (expiration date) for platelets in the United States (U.S.) is up to 7 days in the cleared storage containers.

Most recently, FDA convened a Blood Products Advisory Committee (BPAC) meeting in July 2018 (Ref. 9) to discuss bacterial contamination of platelets and strategies to control the risk. At this meeting, BPAC considered the scientific evidence and operational considerations of all available strategies to control the risk of bacterial contamination of platelets with 5-day and 7-day dating, including bacterial testing strategies using culture-based devices, rapid bacterial

[1] Bacterial tests are labeled as a "safety measure" when clinical studies have shown benefit for detection of bacterial contamination not revealed by previous bacterial testing or have analytical sensitivity at least equivalent to a previously cleared "safety measure" device or qualify by other methods found acceptable to FDA.

[2] Currently, storage systems that ensure platelet efficacy past 5 days of storage, and up to 7 days of storage, of platelets treated by pathogen reduction technology (PRT) are not available. Extended dating past 5 days based on pathogen reduction of apheresis platelets may not be implemented until such technologies are approved for use in this blood component (21 CFR 606.65(e)).

detection devices, and the implementation of pathogen reduction technology. The data presented and BPAC's discussion at the July 2018 meeting provided the foundation for the recommendations in this guidance.

III. RECOMMENDATIONS FOR THE CONTROL OF BACTERIAL CONTAMINATION OF PLATELETS

Table 1 summarizes recommended strategies for 5-day platelet storage and 7-day platelet storage.

Table 1. Summary Table of FDA's Recommendations

Recommendations to control the risk of bacterial contamination in platelets		
Dating	Method	Applicable components
5-day storage	Primary culture + secondary culture (no earlier than Day 3)	• Apheresis • Pre-storage pools
	Primary culture + secondary rapid testing	• Apheresis • Pre-storage pools
	Pathogen Reduction Technology	• Apheresis[3]
7-day storage	Primary culture + secondary culture (no earlier than Day 4)	• Apheresis
	Primary culture + secondary rapid testing	• Apheresis
	Large volume delayed sampling[4]	• Apheresis

A. General Considerations

1. Use FDA-cleared or approved bacterial detection tests, pathogen reduction devices, and platelet storage containers.

2. Bacterial detection testing, pathogen reduction, and the use of platelet storage containers must be performed consistent with the instructions for use of the device (21 CFR 606.65(e)).

[3] This strategy could apply to other platelet products in the future if appropriately labeled devices become available.
[4] The instructions for use of the culture-based device currently labeled as a "safety measure" require a primary culture and secondary test to extend dating of platelets. Therefore, the large volume, delayed sampling strategy cannot be implemented until appropriately labeled devices are available.

3. Blood collection establishments and transfusion services should have in place measures to promptly alert the collection establishment or transfusion service if a distributed platelet product is subsequently identified as positive for bacterial contamination.

B. Primary Culture Testing

This section provides general information pertaining to recommendations for primary culture testing. Primary culture testing is used as one of several strategies discussed in this guidance.

Culture-based primary testing should be performed no sooner than 24 hours after collection. Testing should include methods to identify both aerobic and anaerobic organisms. To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for each of the aerobic and anaerobic cultures. If you opt to sample a volume larger than the upper limit of the volume range described in the device's instructions for use for one culture, we recommend that the amount of the sample that is in excess of the upper limit volume recommended for use be inoculated into additional culture.

If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.

C. 5-Day Platelet Storage

The following strategies apply to platelets with 5-day storage:

1. Primary culture followed by secondary culture performed no earlier than Day 3

This strategy applies to apheresis platelets and pre-storage pools and includes the following steps:

- Initial primary culture (see section III.B of this guidance).
- Secondary culture on Day 3 or Day 4.

Secondary culture:

To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for use, taken from the main collection, and inoculating the sample into an aerobic media. Use of an anaerobic culture, in addition to the aerobic culture, should be considered.

If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend that you establish a minimum incubation time period in your Standard Operating Procedures (SOPs).

2. Primary culture, followed by secondary rapid testing

This strategy applies to apheresis platelets and pre-storage pools, and includes the following steps:

- Initial primary culture (see section III.B. of this guidance).
- Secondary testing with a rapid test.

3. Pathogen reduction

This strategy applies to apheresis platelets.[5,6] Platelets that have been treated by pathogen reduction need no further measures because pathogen reduction technology adequately controls the risk of bacterial contamination of platelets

D. 7-Day Platelet Storage

Storage may be extended beyond 5 days if:

- The platelets are stored in a container cleared or approved by FDA for 7-day storage, and
- Individual platelet units are subsequently tested for bacterial detection using a bacterial detection device cleared by FDA and labeled for use as a "safety measure." [7]

The following strategies are recommended for storage of platelets of up to 7 days:

1. Primary culture, followed by a secondary culture with a device labeled as a "safety measure" performed no earlier than Day 4

This strategy applies to apheresis platelets, and includes the following steps:

[5] This strategy could apply to other platelet products in the future if appropriately labeled pathogen reduction devices and storage systems become available.
[6] See footnote 2.
[7] See footnote 1.

- Initial primary culture (see section III.B. of this guidance).
- Secondary culture no earlier than Day 4, using a device labeled as a "safety measure."

Secondary culture:

To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for use, inoculated into both an aerobic culture and an anaerobic culture.

If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.

2. Primary culture, followed by a secondary rapid test labeled as a "safety measure"

This strategy applies to apheresis platelets, and includes the following steps:

- Initial primary culture (see section III.B of this guidance).
- Secondary testing with a rapid test labeled as a "safety measure."

3. Large volume delayed sampling [8]

This strategy applies to apheresis platelets, and includes the following steps:

- A single culture performed using a culture-based bacterial detection device no sooner than 48 hours after collection with a sampling volume of at least 16 mL, inoculated evenly into an aerobic culture and an anaerobic culture.

- Each apheresis unit should be sampled for culture. If the apheresis product is split, each split product should be sampled.

- If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.

[8] The instructions for use of the culture-based device currently labeled as a "safety measure" require a primary culture and secondary test to extend dating. Therefore, the large volume, delayed sampling strategy cannot be implemented until appropriately labeled devices are available.

E. Post-Storage Pooled Platelets

Transfusion services should perform a rapid bacterial detection test prior to transfusion on pools of WBD platelets if the constituent single units were not previously tested. Post-storage pooled platelets expire 4 hours from the time of preparation (21 CFR 606.122(l)(2)).

F. Single Units of WBD Platelets

Single units of WBD platelets may be stored for 5 days. For single units of WBD platelets that have not been previously tested and are not intended for pooling, testing should be performed according to either or both of the following strategies:

1. Sample no sooner than 24 hours after collection, the largest practical volume within the range permitted by the device's instructions for use and inoculate into a culture. Use of an aerobic and an anaerobic culture may be considered; and/or

2. Perform testing with a rapid test.

G. Labeling

1. Labels on the Container

   a. The container labels must comply with 21 CFR 606.121 and 21 CFR 610.60. Blood collection establishments and transfusion services, as appropriate, must also follow the general requirements for labeling operations described in 21 CFR 606.120.

   b. The container labels must include the expiration date and time, if applicable, of the product based on bacterial detection testing (21 CFR 606.121(c)(4)(i)).

   c. If secondary testing of platelets is performed consistent with this guidance, and the expiration date is extended to 6 or 7 days based on the bacterial testing performed, the blood establishment or transfusion service that performed the secondary testing must update the container label to reflect the new expiration date (21 CFR 606.121(c)(4)(i)).

2. Circular of Information

You must update your Circular of Information to include appropriate statements regarding bacterial detection testing or pathogen reduction (21 CFR 606.122).

IV. REPORTING IMPLEMENTATION OF MANUFACTURING AND LABELING CHANGES

An establishment that distributes platelet products in interstate commerce must have an approved BLA, in accordance with section 351 of the Public Health Service Act.

Licensed establishments must report changes to their approved biologics license applications (BLA) in accordance with 21 CFR 601.12. The information below is intended to assist you in determining which reporting mechanism is appropriate for a change to your approved BLA, as it applies to the bacterial testing of platelet products and the manufacture of apheresis platelets with a 6 or 7-day dating period. [9] You should prominently label each submission with the reporting category under which you are reporting your change, for example, "Prior Approval Supplement," or "Annual Report."

A. Prior Approval Supplement (PAS)

1. Changes requiring supplement submission and approval prior to distribution of the product made using the change (21 CFR 601.12(b)).

Under 21 CFR 601.12(b), changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Prior Approval Supplement (PAS). 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 currently licensed to manufacture apheresis platelets with a 5-day expiration date and you choose to extend the storage time to a 6-day or 7-day expiration date and distribute these products in interstate commerce.

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

[9] FDA's recommendations for the implementation of pathogen reduction are addressed in the guidance document titled, "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 draft guidance, when finalized, will represent FDA's current thinking on this topic.

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

b. List of the platelet products involved.

c. Address and registration number of the manufacturing facility/facilities.

d. A detailed description of the manufacturing process. We recommend the submission of written standard operating procedures (SOPs) that include:

   i. Component manufacturing (if these SOPs were previously approved by FDA, include the reference number under which they were reviewed).
   ii. Bacterial detection testing, including the name of the devices(s) used for bacterial detection, when the platelet product is sampled and when the product will be released.
   iii. How to label the platelet product based on the results of the bacterial detection testing and the timeframe after which the negative results are no longer valid.
   iv. Measures to alert the consignee that a distributed platelet product has tested positive for bacterial contamination.
   v. Quarantine and disposition of unsuitable products.
   vi. Investigation of units with positive test results.
   vii. A communication plan to notify your consignees the type of storage container the platelets are stored in, for example, a storage container approved for 5-day storage or for 7-day storage and when the bacterial detection testing was performed.

e. The name, address and registration number, if available, of any contractors who are performing bacterial detection testing of platelet products for you.

f. Validation plan for the bacterial detection testing method and a summary of the validation data.

g. Two consecutive months of quality control data for the pH at expiration or on the date the product is issued for each platelet product type that will have the expiration date extended based on bacterial detection testing.

h. Labeling – include the following in your supplement:

i. Container Labels: A container label for each platelet product, unless previously approved by FDA, that includes the expiration date and time, if applicable, of the platelet product based on bacterial detection testing.

ii. Circular of Information.

3. You may also consider submitting a Comparability Protocol as a PAS under 21 CFR 601.12(e). A Comparability Protocol is not required, but an approved Comparability Protocol may justify a reduced reporting category for manufacturing apheresis platelets with a 6-day or 7-day expiration date in multiple locations. In addition to the content listed in section IV.A. of the guidance, Comparability Protocol (21 CFR 601.12(e)) submissions must also include the plan for implementing the bacterial detection testing at multiple manufacturing sites. The plan should include a description of how you will validate the new procedures.

B. Annual Report

Under 21 CFR 601.12(d), changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the BLA.

We believe the following changes may be submitted in an Annual Report[10] noting the date the process was implemented:

1. Implementation of bacterial detection testing as described in this guidance without modification and the expiration date of apheresis, single units of WBD platelets, and pre-storage pooled WBD platelets remains at 5 days.

2. You or your contractor change from one type of FDA cleared bacterial detection device to another type of FDA-cleared bacterial detection device.

NOTE: For assistance in reporting your changes, see FDA's "Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture; Guidance for Industry" dated December 2014.

[10] See 21 CFR 601.12(a)(3).

The December 2014 guidance represents FDA's current thinking on this topic and can be found on FDA's website at: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htmn/Guidances/Blood/ucm354559.htm.

V. TRANSFUSION SERVICES—REGISTRATION AND BLOOD PRODUCT LISTING

Except as provided in 21 CFR 607.65, all owners and operators of blood establishments that engage in the manufacture of blood products must register with FDA and list the blood products they manufacture, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act and the implementing regulations under 21 CFR 607.7. The implementation of a bacterial detection device that is used to re-label a platelet product with a 6 or 7-day expiration date, thereby extending the dating of the platelet product, is a manufacturing procedure requiring registration and blood product listing, as described in 21 CFR 607.3(d). Transfusion services that implement secondary testing on platelets with a 5-day expiration date are not required to register and list because they are not extending the dating period of platelets.

If you are a transfusion service that is currently exempt from registration and blood product listing under the provisions of 21 CFR 607.65(f), and you implement a bacterial detection test to determine the suitability of platelet products to be released on day 6 or day 7 after collection, you are no longer considered exempt because you are engaging in blood product manufacturing under 21 CFR 607.3(d). You must therefore register your blood establishment with FDA and list the blood products you manufacture, pursuant to 21 CFR 607.7. Indicate that you are performing bacterial detection testing on platelet products by selecting "Bacterial Testing" as a process for the platelet products.

Instructions on how to register electronically with FDA can be found on FDA's website at: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/BloodEstablishmentRegistration/default.htm.

VI. IMPLEMENTATION

We recommend that you implement the recommendations contained in this guidance within 12 months after the final guidance is issued.

VII. REFERENCES

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8. Benjamin RJ. Blood Products Advisory Committee, September 21, 2012, transcript accessible at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm552872.htm

9. Blood Product Advisory Committee, July 18, 2018, transcript accessible at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm597841.htm