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Draft Guidance for Industry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
Center for Biologics Evaluation and Research
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Table of Contents

I. INTRODUCTION 1

II. BACKGROUND 2

A. General 2
B. Use of Pathogen Reduction Technology of Platelets 2
C. Bacterial Testing of Platelets 2
D. Platelet Dating Period 4

III. CONSIDERATIONS FOR THE EXTENSION OF APHERESIS PLATELETS DATING FOR UP TO 7 DAYS 4

A. Extension of Dating Based on Additional Rapid Testing 5
B. Extension of Dating Based On Additional Culture-Based Testing 5

IV. PRIMARY AND SECONDARY BACTERIAL TESTING OF PLATELETS 6

A. Primary Testing of Platelets 6
B. Secondary Testing of Platelets 6
C. Secondary Testing of Platelets to Support Extension of Dating 6

V. FDA RECOMMENDATIONS FOR MEETING THE REQUIREMENTS FOR THE CONTROL OF BACTERIAL CONTAMINATION OF PLATELETS [21 CFR 606.145] 6

VI. FDA RECOMMENDATIONS TO BLOOD COLLECTION ESTABLISHMENTS 7

A. Apheresis Platelets 7
B. Pre-Storage Pooled Platelets 8
C. Single Units of WBD Platelets 9

VII. FDA RECOMMENDATIONS TO TRANSFUSION SERVICES FOR PLATELETS STORED THROUGH DAY 5 10

A. Pathogen-Reduced Apheresis Platelets 10
B. Apheresis Platelets and Pre-Storage Pooled Platelets Previously Tested Using a Culture-Based Test 11
C. Post-Storage Pooled Platelets 11
D. Single Units of WBD Platelets Not Intended For Pooling and Not Previously Tested. 11

VIII. FDA RECOMMENDATIONS TO TRANSFUSION SERVICES AND BLOOD COLLECTION ESTABLISHMENTS FOR EXTENDING PLATELET DATING BEYOND DAY 5 AND UP TO DAY 7 12

A. Recommendations to Transfusion Services 13
B. Additional Recommendations for Transfusion Services and Blood Collection Establishments 14

IX. SUMMARY TABLE OF FDA RECOMMENDATIONS 14

X. LABELING OF BACTERIALLY TESTED PLATELETS 18

A. Labels on the Container 18
B. Circular of Information (21 CFR 606.122) 19

XI. REPORTING IMPLEMENTATION FOR BACTERIAL DETECTION TESTING OF PLATELET PRODUCTS FOR LICENSED BLOOD ESTABLISHMENTS—REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA) 19

A. Prior Approval Supplement (PAS) 20
B. Supplement - Changes To Be Effected In 30 Days (CBE30) 22
C. Changes To Be Described In An Annual Report 22

XII. TRANSFUSION SERVICES—REGISTRATION AND BLOOD PRODUCT LISTING 23

XIII. IMPLEMENTATION 24

APPENDIX: 25

I. CONTAMINATION OF PLATELETS WITH BACTERIA 25

II. PLATELET COMPONENT USAGE AND PLATELET DATING PERIOD IN THE UNITED STATES 26

III. METHODS TO DETECT BACTERIAL CONTAMINATION IN PLATELET COMPONENTS 26

A. Culture-Based Devices 27
B. Non-Culture-Based Rapid Bacterial Detection Devices 31

IV. METHODS FOR PATHOGEN REDUCTION OF PLATELET PRODUCTS 33

V. PUBLIC MEETINGS ON THE ISSUE OF BACTERIAL CONTAMINATION OF PLATELETS 34

VI. PUBLIC MEETING ON THE TOPIC OF PATHOGEN REDUCTION OF PLATELETS 35

XIV. REFERENCES 37

Contains Nonbinding Recommendations

Draft – Not for Implementation

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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I. INTRODUCTION

We, FDA, are issuing this guidance document to provide blood collection establishments and transfusion services with recommendations to control the risk of bacterial contamination of room temperature stored platelets through the performance of pathogen reduction technology (PRT), or bacterial testing of platelets intended for transfusion. PRT is performed shortly after platelet collection by blood collection establishments. Bacterial testing encompasses initial testing (primary testing) of platelets by blood collection establishments, and subsequent retesting (secondary testing) prior to transfusion principally by transfusion services, but also by blood collection establishments. With the introduction of PRT, the recommendations for pathogen reduction, and those for secondary testing of previously cultured but not pathogen-reduced platelets, as described in the guidance, would provide for adequate control of the risk of bacterial contamination in these products. We are also providing recommendations to allow the use of secondary testing of platelets as the basis to extend the dating period of platelets when appropriately labeled bacterial detection devices and storage containers are used.

Additionally, we are providing recommendations to licensed blood establishments for submitting Biologics License Application (BLA) supplements to include bacterial testing of platelet components[1]. This guidance addresses all platelet products, including platelets manufactured from Whole Blood (Whole Blood Derived (WBD) platelets), platelets collected by automated methods from a single donor (apheresis platelets), pooled platelets, and platelets stored in additive solutions. This draft guidance replaces the draft guidance entitled "Bacterial Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion," dated December 2014, and, when finalized, is intended

[1]FDA recommendations for the implementation of pathogen reduction will be addressed in a separate guidance document.

to supersede the recommendation in section VII.A.2, in regard to bacterial contamination testing in the document entitled "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods" dated December 2007.

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

A. General

Platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component, and the risk of bacterial contamination of platelets stands out as a leading risk of infection from blood transfusion. This risk has persisted despite numerous interventions including the introduction, in the last decade, of analytically sensitive culture-based bacterial detection methods that are widely used to test platelets prior to their release from blood collection establishments to transfusion services (Refs. 1, 2, 3). We are issuing this guidance based on the knowledge we have gained over the past 15 years regulating bacterial detection devices and their use in blood establishments. The Appendix to this document provides more details on the background, history, and science of bacterial contamination of platelets, and the current methods of pathogen reduction of platelet products.

B. Use of Pathogen Reduction Technology of Platelets

FDA has approved a psoralen/UV irradiation-based pathogen reduction method for use on apheresis platelets within 24 hours after collection.[2] The disposable kit, including the platelet storage containers of the FDA-approved pathogen reduction system, has been validated to maintain the quality and efficacy of the treated platelets through 5 days of storage.

C. Bacterial Testing of Platelets

1. Sampling volume and culture medium for culture-based devices

Studies of culture-based devices that include aerobic and anaerobic media bottles labeled for use with 4-10 mL sampling volume have shown that sampling of an 8-10 mL volume into a single aerobic culture bottle would provide reasonable

[2]http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM427512.pdf.

sensitivity for detection of the most clinically relevant organisms. This is based on a demonstration of comparable sensitivity, for clinically relevant organisms, of the 8 mL aerobic culture to a set of 4 mL aerobic and 4 mL anaerobic cultures (Refs. 4, 5, 6, 7). Superiority of a single 8 mL sample to a single 4 mL sample has been shown in multiple studies (Refs. 6, 7, 8, 9).

Larger sample volumes increase culture sensitivity, but are associated with higher rates of false positive cultures and, additionally, consume a larger proportion of the platelet product (Refs. 10, 11, 12, 13, 14). Delayed sampling would be expected to increase the bacterial yield. However, it was found in one study on apheresis platelets, that inoculating a total of 16 mL volume, at 36 to 48 hours after collection, into an aerobic and an anaerobic bottle, yielded a detection rate (1/5,000) similar to that obtained by inoculating an 8 mL sample at 24 hours into a specific aerobic bottle only (1/5,061) (Refs. 4, 15). Clinical studies, as well as spiking studies, have also shown equivalent sensitivity of an alternative aerobic-only culture that samples approximately a 3-4 mL volume, consistent with its instructions for use (Refs. 16, 17, 18).

Based on the information presented above, sampling the platelet product with the upper limit of the sampling volume range permitted in the testing device instructions for use, and inoculating the volume into at least an aerobic culture medium, is expected to achieve sensitivity comparable to that obtained by culturing 4 mL, each into an aerobic and an anaerobic culture. Though the incremental benefit of using an extra anaerobic bottle in detecting clinically relevant bacterial organisms is limited (Refs. 5, 10, 19, 20), we do not discourage the use of both an aerobic and an anaerobic bottle. We are not recommending a specific single sample volume because the sampling volume upper range limit may differ for different devices.

2. Rapid testing of platelets on day 4 and day 5

A study has shown that a rapid bacterial detection test, performed on the day of transfusion, was able to detect contaminated units that were missed by a culture conducted early in the storage of the units (Ref. 21). Considering the increased rates of transfusion-related septic reactions and fatalities associated with transfusion of day 4 and day 5 stored platelets, and after considering the outcome of performing a rapid bacterial detection test on the day of transfusion, the FDA Blood Products Advisory Committee (BPAC or Committee) recommended in September 2012 testing of day 4 and day 5 stored platelets with a rapid test prior to transfusion even when a primary culture-based test performed on day 1 was negative (Refs. 13, 21). When performed in accordance with the instructions for use of the FDA-cleared rapid bacterial detection devices, rapid testing of apheresis platelets is conducted within 24 hours prior to transfusion.

D. Platelet Dating Period

Currently, instructions for use for blood-collecting, processing, and storage systems approved for such use by the Director, CBER, allow for dating up to 7 days. Surveillance data on platelets stored for up to 5 days have shown that 95 percent of platelet transfusion-related septic reactions and 100 percent of associated fatalities have occurred with transfusion of day 4 and day 5 stored platelets, with almost even distribution between these two days (Ref. 22). However the number of platelet products transfused was not available, thus the septic reaction and fatality rates could not be established for these days. A shortening of platelet dating to 3 or 4 days might reduce the rates of these adverse events. However, assuring adequate platelet supplies in the relatively short time interval during which platelets may be transfused under a 3 to 4 day dating period policy would be challenging for most transfusion services, and could result in overall reduced platelet availability.

III. CONSIDERATIONS FOR THE EXTENSION OF APHERESIS PLATELETS DATING FOR UP TO 7 DAYS

NOTE: Implementation of the recommendations in this guidance on extension of platelet dating beyond day 5 is contingent on the use of approved and suitably labeled PRT systems, bacterial detection tests, and platelet storage containers. (See detailed note in section VIII.)

Under 21 CFR 610.53(c), the dating period for platelets is *either* 72 hours from the time of collection of source blood, provided the labeling recommends storage at 20°C to 24°C or between 1°C and 6°C, *or* as specified in the instructions for use for the blood-collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluation and Research (CBER). Supplies and reagents, including bacterial detection devices and platelet storage containers, must be used in a manner consistent with the instructions provided by the manufacturer (21 CFR 606.65(e)). The current maximal dating period for platelets in the U.S. is up to 7 days in the cleared storage containers.

In section VIII. of this document, FDA is providing additional recommendations to blood establishments who wish to extend the dating period beyond 5 days and up to 7 days for apheresis platelets that have undergone primary bacterial testing, or have been treated with PRT[3] after collection. Dating may be extended if: 1) the platelets are collected in FDA-cleared or approved 7-day platelet storage containers with labeling that requires testing every product with

[3] Currently, storage systems that ensure platelet efficacy through 7 days of storage of platelets treated by PRT are not available. The recommendation to extend dating based on secondary testing of pathogen-reduced apheresis platelets may not be implemented until such technologies are approved for use in this blood component (21 CFR 606.65(e)).

a bacterial detection device cleared by FDA and labeled for use as a "safety measure;"[4] and 2) the platelets are subsequently individually tested for bacterial detection using such a device, consistent with its instructions for use, and according to one of the following two strategies:

A. Extension of Dating Based on Additional Rapid Testing

The use of an FDA-cleared rapid bacterial detection device labeled as a "safety measure," one-time, could support a dating extension of up to 24 hours following the time of the test, and not exceeding the 7-day expiration date of leukocyte reduced apheresis platelets that had tested negative by early culture, or had been treated by PRT[3], and were stored in FDA-cleared or approved 7-day platelet storage containers, thereby extending the dating period through day 6 or day 7.

B. Extension of Dating Based on Additional Culture-Based Testing

Considering that transfusion-associated septic reactions and related fatalities rise on days 4 and 5 of storage, a repeat culture of the platelet product on day 4 or day 5 using a device cleared by FDA and labeled as a "safety measure," could be expected to identify contaminated units that were missed by the early culture and likely associated with organisms that have transitioned from the lag to the logarithmic growth phase (Ref. 19) late in storage. Such a repeat culture testing strategy could potentially allow for the safe extension of platelet dating. Late in storage, the probability of missing organisms in a sample drawn from a bacterially contaminated unit is expected to be smaller than on day 1 because, by then, most bacterial organisms would have proliferated to detectable levels. However bacteria with an extended lag phase may elude detection on days 4 or 5, and proceed to proliferate on days 6 and 7, potentially causing a septic reaction in the recipient. For that reason a repeat culture, late in storage, could safely extend dating for only two additional days, up to 6 or 7 days, depending on when the repeat culture is conducted (day 4 or 5, respectively). This is analogous to the relative assurance of a day 1 culture which provides a 2-day relative safety period prior to the rise in the rate of septic reactions and related fatalities (Ref. 22).

NOTE: Currently, culture-based bacterial detection devices labeled as a "safety measure" for the extension of dating beyond day 5 are not available. The recommendations to extend platelet dating beyond day 5 (section VIII. of this document) using a culture-based device may not be implemented until the availability of such devices.

[4] FDA's current review practice is to permit labeling of tests for bacterial detection in platelets for transfusion as a "safety measure" when clinical studies have shown benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined.

IV. PRIMARY AND SECONDARY BACTERIAL TESTING OF PLATELETS

A. Primary Testing of Platelets

Primary testing of platelets is the initial/first time testing of a platelet component to detect the presence of bacterial contamination. Early in storage, testing is conducted using a culture-based device or other adequate or appropriate method found acceptable by FDA.

B. Secondary Testing of Platelets

Secondary testing of platelets is any additional test of a platelet component to detect the presence of bacterial contamination in a unit that previously showed no bacterial contamination upon primary testing.

1. Secondary testing of platelets is usually conducted late in the storage period of platelet components, and is intended to detect bacterial contamination not revealed by primary testing.

2. Secondary testing of platelets may be conducted with either a culture-based bacterial detection device, or a rapid bacterial detection device, based on the needs of the blood establishment.

C. Secondary Testing of Platelets to Support Extension of Dating

Secondary testing of platelets for the purpose of extending the dating period of platelet components past 5 days must be conducted only with a test labeled as a "safety measure," according to its instructions for use. Additionally, platelets must be stored in FDA-cleared or approved 7-day platelet storage containers (see 21 CFR 610.53(c) and 606.65(e)). Please see "important note on platelet dating beyond day 5" in section VIII.

V. FDA RECOMMENDATIONS FOR MEETING THE REQUIREMENTS FOR THE CONTROL OF BACTERIAL CONTAMINATION OF PLATELETS (21 CFR 606.145)

Under 21 CFR 606.145(a)[5], blood collection 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.

Accordingly, this requirement can be met by either 1) testing for bacterial contamination the platelet collection, or the transfusable product during its storage, with an FDA-cleared device

[5] See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacture Use; Final Rule (80 FR 29842, May 22, 2015). The rule is effective May 23, 2016.

intended for use in detecting bacteria in platelets for transfusion, consistent with the recommendations in this guidance, or 2) pathogen-reducing the platelet collection using an FDA-approved pathogen reduction device.

- Apheresis platelets are addressed in section VI.A
- Pre-storage pooled platelets are addressed in section VI.B
- Post-storage pooled platelets are addressed in section VII.C
- Single units of WBD Platelets are addressed in sections VI.C and VII.D

Additional requirements of the Final Rule[6] related to the control of bacterial contamination of platelets, donation suitability, donor eligibility and donor notification are found in 21 CFR 606.145(b), (c), and (d), and in 21 CFR 630.30(b)(3) and (4) and 630.40(a).

NOTE: Following the implementation on May 23, 2016 of the Final Rule[6], and *pending the implementation date of the recommendations of this Guidance when finalized*, the requirements of the Final Rule can be met by either 1) testing for bacterial contamination *at least once* on the platelet collection or the transfusable platelet product with an FDA-cleared device intended for use in detecting bacteria in platelets for transfusion according to its instructions for use; or 2) pathogen-reducing the platelet collection using an FDA-approved pathogen reduction device according to its instructions for use.

NOTE: We recommend that blood collection establishments have in place measures to promptly alert transfusion services in the event that a distributed platelet product is subsequently identified as positive for bacterial contamination.

NOTE: Date of manufacture and expiration of platelets are governed by the regulations (21 CFR 610.50 and 21 CFR 610.53), the manufacturing processes, the labeling of the platelet storage container, and additional testing as described in this guidance.

VI. FDA RECOMMENDATIONS TO BLOOD COLLECTION ESTABLISHMENTS

A. Apheresis Platelets

Blood collection establishments should control the risk of bacterial contamination in apheresis platelets either by the application of pathogen reduction technology, or the performance of a culture-based test, according to the following recommendations:

[6] Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacture Use; Final Rule (80 FR 29842, May 22, 2015).

1. Pathogen reduction[7]

   Apheresis platelets should be pathogen-reduced using an FDA-approved pathogen reduction device according to its instructions for use.

2. Culture-based testing (primary testing)

   a. Apheresis platelets should be tested using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection. 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, and inoculation of the sample into at least an aerobic culture medium. If the blood collection establishment opts to sample a volume larger than the upper limit of the volume range described in the package insert, the amount of the sample that is in excess of the upper limit volume recommended for use in the culture bottle should be inoculated into additional bottles or pouches.

   b. We recommend that tested products be released for transfusion under the following conditions:

      i. If the instructions for use of the bacterial detection device specify a minimal incubation period, release products consistent with the incubation period specified in the instructions for use of the bacterial detection device.

      ii. If the instructions for use of the bacterial detection device do not specify a minimal incubation period, we recommend that blood collection establishments have in place measures to promptly alert the receiving establishments in the event that the distributed platelet product is subsequently identified as positive for bacterial contamination.

B. Pre-Storage Pooled Platelets

1. We recommend you test pre-storage pooled platelets using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection of the freshest unit in the pool, as per the pooling system instructions for use (Ref. 23). 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, and inoculation of the

[7] Pathogen reduction may not be applied to platelet products other than as specified in the instructions for use of the relevant device. At this time, PRT has not been approved by FDA for the treatment of platelet products other than apheresis platelets.

sample into at least an aerobic culture medium. If the blood collection establishment opts to sample a volume larger than the upper limit of the volume range described in the package insert, the amount of the sample that is in excess of the upper limit volume recommended for use in the culture bottle should be inoculated into additional bottles or pouches.

2. We recommend that tested products be released for transfusion under the following conditions:

    a. If the instructions for use of the bacterial detection device specify a minimal incubation period, release products consistent with the incubation period specified in the instructions for use of the bacterial detection device.

    b. If the instructions for use of the bacterial detection device do not specify a minimal incubation period we recommend that blood collection establishments have in place measures to promptly alert the receiving establishments in the event that the distributed platelet product is subsequently identified as positive for bacterial contamination.

3. FDA-approved pathogen reduction technologies may be used on pre-storage pooled platelets in lieu of bacterial testing, as available.

    NOTE: Pathogen reduction may only be applied to platelet products as specified in the instructions for use of the relevant device. At this time, PRT has only been approved by FDA for the treatment of apheresis platelets.

C. Single Units of WBD Platelets

1. For blood collection establishments that perform cultures on single units of WBD platelets, and considering the small volume of a single unit of WBD platelets, we recommend sampling, no sooner than 24 hours after collection, the largest *practical* volume within the range permitted by the FDA-cleared device's instructions for use and inoculation of the sample into at least an aerobic culture medium.

2. We recommend that culture-tested products be released for transfusion under the following conditions:

    a. If the instructions for use of the bacterial detection device specify a minimal incubation period, release products consistent with the incubation period specified in the instructions for use of the bacterial detection device.

b. If the instructions for use of the bacterial detection device do not specify a minimal incubation period we recommend that blood collection establishments have in place measures to promptly alert the receiving establishments in the event that a distributed platelet product is subsequently identified as positive for bacterial contamination.

3. Blood collection establishments may use an FDA-cleared rapid bacterial detection device to detect the presence of bacteria in single units of WBD platelets, as available.

   NOTE: Rapid bacterial detection tests may only be used as specified in the instructions for use of the relevant device. At this time, rapid tests have not been cleared for use on single units of WBD platelets

4. FDA approved pathogen reduction technologies may be used on single units of WBD platelets in lieu of bacterial testing, as available.

   NOTE: Pathogen reduction may only be applied to platelet products as specified in the instructions for use of the relevant device. At this time, PRT has only been approved by FDA for the treatment of apheresis platelets.

VII. FDA RECOMMENDATIONS TO TRANSFUSION SERVICES FOR PLATELETS STORED THROUGH DAY 5

NOTE: Following the implementation on May 23, 2016 of the Final Rule (80 FR 29842) on the Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacture Use, and *pending the implementation date of the recommendations of this guidance when finalized*, the requirements of the Final Rule can be met by either 1) testing for bacterial contamination *at least once* on either the platelet collection or the transfusable platelet product with an FDA-cleared device intended for use in detecting bacteria in platelets for transfusion according to its instructions for use; or 2) treating the platelet collection by an FDA-approved pathogen reduction system according to its instructions for use.

Upon their implementation, the recommendations in this guidance will provide for adequate control of the risk of bacterial contamination for the following platelet products:

A. Pathogen-Reduced Apheresis Platelets

Apheresis platelets that have been treated by pathogen reduction at the blood collection center require no further measures.

B. Apheresis Platelets and Pre-Storage Pooled Platelets Previously Tested Using a Culture-Based Test

We recommend implementing secondary testing of previously cultured apheresis platelets and pre-storage pooled platelets to enhance platelet safety through day 5 of storage as described below:

1. On the day of transfusion, perform rapid testing on day 4 or day 5 platelets using a device cleared by FDA. Consistent with the instructions for use of the FDA-cleared rapid bacterial detection device, rapid testing of apheresis platelets is conducted within 24 hours prior to transfusion;

   or,

2. Culture on day 4, using a device cleared by FDA, and release as follows:

   a. If the instructions for use of the bacterial detection device specify a minimal incubation period, release the platelet product consistent with the incubation period specified in the instructions for use of the bacterial detection device.

   b. If the instructions for use of the bacterial detection device do not specify a minimal incubation period, release the platelet product at least 12 hours after sampling if the establishment has in place measures to promptly alert the receiving establishments receiving in the event that a distributed platelet product is subsequently identified as positive for bacterial contamination.

   c. If you wish to release the platelet product during the incubation period of the culture, we recommend performing a test using an FDA-cleared rapid bacterial detection device prior to release, and within 24 hours prior to transfusion.

C. Post-Storage Pooled Platelets

Transfusion services should perform an FDA-cleared rapid bacterial detection test within 4 hours prior to transfusion on pools of WBD platelets if the constituent single units were not previously tested.

D. Single Units of WBD Platelets Not Intended For Pooling and Not Previously Tested

For single units of WBD platelets that are not intended for pooling (such as for the neonatal patient population) and that have not been previously tested, transfusion services should test according to either or both of the following strategies:

1. Considering the small volume of the single unit of WBD platelets we recommend sampling, no sooner than 24 hours after collection, the largest *practical* volume within the range permitted by the FDA-cleared device's instructions for use and inoculation into at least an aerobic culture medium; and/or

2. Transfusion services may use an FDA-cleared rapid bacterial detection device to detect the presence of bacteria in single units of WBD platelets, as available.

   NOTE: Rapid bacterial detection tests may only be used as specified in the Instructions for Use of the relevant device. At this time, rapid tests have not been cleared for use on single units of WBD platelets.

VIII. FDA RECOMMENDATIONS TO TRANSFUSION SERVICES AND BLOOD COLLECTION ESTABLISHMENTS FOR EXTENDING PLATELET DATING BEYOND DAY 5 AND UP TO DAY 7

IMPORTANT NOTE ON PLATELET DATING BEYOND DAY 5

1. PRT systems may not be used to store platelets beyond day 5 unless and until they have been approved by FDA for such indication based on the ability of the PRT system to ensure 1) platelet efficacy through 7 days of storage; and 2) safety from bacterial contamination through 7 days of storage.

2. Currently, culture-based bacterial detection devices labeled as a "safety measure"[8] for the extension of dating beyond day 5 are not available. The recommendations to extend platelet dating beyond day 5 (section VIII of this document) using a culture-based device may not be implemented until such devices are cleared for this purpose.

3. Currently no platelet storage containers have been cleared or approved by FDA to store pre-storage pooled platelets for up to 7 days. The recommendations to extend platelet dating beyond day 5 (section VIII of this document) may not be implemented for pre-storage pooled platelets until such technologies are cleared for use in this blood component.

4. Rapid bacterial detection tests may only be used as specified in the Instructions for Use of the relevant device. At this time, rapid tests have not been cleared for use on single units of WBD platelets. The recommendations to extend single unit WBD platelet dating beyond day 5 (section VIII of this guidance) using a rapid test may not be implemented until such technologies are cleared for use in this blood component.

[8] FDA's current review practice is to permit labeling of tests for bacterial detection in platelets for transfusion as a "safety measure" when clinical studies have shown benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined.

A. Recommendations to Transfusion Services

For transfusion services that intend to extend platelet dating beyond 5 days, we recommend you perform secondary testing on apheresis platelets previously cultured or PRT-treated[9] or on single units of WBD platelets[10] previously cultured, using a device cleared by FDA as a "safety measure." You may extend the dating period beyond day 5 and through day 6 or day 7, after registering with FDA as a blood establishment as described in section XII of this document.

The modalities for performing secondary testing are as follows:

1. Perform rapid testing, within 24 hours prior to transfusion, using a test cleared by FDA and labeled as a "safety measure." A negative rapid test result extends the dating period of the product for a period of up to 24 hours following the time of the test, and not exceeding the 7-day expiration date of the product, *or*

2. Culture on day 4 using a test cleared by FDA and labeled as a "safety measure" and extend up to 48 hours (through day 6) following a negative result 24 hours after the time of day 4 sampling, *or*

3. Culture on day 5 using a test cleared by FDA and labeled as a "safety measure" and extend up to 48 hours (through day 7) following a negative result 24 hours after the time of day 5 sampling.

   NOTE: See section XII of this document for registration requirements associated with extension of dating beyond day 5.

   NOTE: Currently, culture-based bacterial detection devices labeled as a "safety measure" for the extension of dating beyond day 5 are not available. The recommendations to extend platelet dating beyond day 5 (section VIII of this document) using a culture-based device may not be implemented until the availability of such devices.

   NOTE: If a culture is performed on platelets to extend dating, the platelets may still be transfused within 24 hours after sampling, provided they are transfused through day 5, and the recommendations in section VII.B.1 are followed.

[9]Currently, PRT storage systems that ensure platelet efficacy through 7 days of storage are not available. The recommendation to extend dating based on secondary testing of pathogen-reduced apheresis platelets may not be implemented until the availability of such systems.

[10] Rapid bacterial detection tests may only be used as specified in the instructions for use of the relevant device. At this time, rapid tests have not been cleared for use on single units of WBD platelets.

B. Additional Recommendations for Transfusion Services and Blood Collection Establishments

Platelet products that remain in the transfusion service inventory on day 4 and day 5 of storage and intended for extension through day 7 may be shipped to cooperating blood collection establishments for secondary rapid or culture testing, using a device cleared by FDA as a "safety measure." Testing and release of products may be conducted under the conditions set forth in section VIII of this document.

IX. SUMMARY TABLE OF FDA RECOMMENDATIONS

IMPORTANT NOTE ON PLATELET DATING BEYOND DAY 5

1. PRT systems may not be used to store platelets beyond day 5 unless and until they have been approved by FDA for such indication based on the ability of the PRT system to ensure 1) platelet efficacy through 7 days of storage; and 2) safety from bacterial contamination through 7 days of storage.

2. Currently, culture-based bacterial detection devices labeled as a "safety measure[11]" for the extension of dating beyond day 5 are not available. The recommendations to extend platelet dating beyond day 5 (section VIII of this document) using a culture-based device may not be implemented until such devices are cleared for this purpose.

3. Currently no platelet storage containers have been cleared or approved by FDA to store pre-storage pooled platelets for up to 7 days. The recommendations to extend platelet dating beyond day 5 (section VIII of this document) may not be implemented for pre-storage pooled platelets until such devices are cleared for use in this blood component.

4. Rapid bacterial detection tests may only be used as specified in the Instructions for Use of the relevant device. At this time, rapid tests have not been cleared for use on single units of WBD platelets. The recommendations to extend single unit WBD platelet dating beyond day 5 (section VIII of this guidance) using a rapid test may not be implemented until such technologies are cleared for use in this blood component.

[11] Note: FDA's current review practice is to permit labeling of tests for bacterial detection in platelets for transfusion as a "safety measure" when clinical studies have shown benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined.

Recommendations to Blood Collection Establishments	A. Apheresis Platelets 1. Pathogen reduction: Apheresis platelets should be pathogen-reduced using an FDA approved pathogen reduction device.[12] 2. Culture-based primary testing: a. Test using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection, and inoculate the sample into at least an aerobic culture medium. Maximize the sensitivity of the primary culture by sampling the upper limit of the sampling volume permitted by the device's instructions for use. If sampling volume larger than upper limit, inoculate two bottles or pouches. b. If the instructions for use of the bacterial detection device specify a minimal incubation period, release products consistent with the incubation period specified in the instructions for use of the bacterial detection device. If the instructions for use of the bacterial detection device do not specify a minimal incubation period we recommend that blood collection establishments have in place measures to promptly alert the receiving establishments in the event that a distributed platelet product is subsequently identified as positive for bacterial contamination. B. Pre-Storage Pooled Platelets 1. Test using an FDA-cleared culture-based bacterial detection device no sooner than 24 hours after collection of the freshest unit of the pool, and inoculate the sample into at least an aerobic culture medium. Maximize sensitivity as per paragraph A.2.a in this table. 2. Recommendations for product minimal incubation period and release: see paragraph A.2.b in this table. 3. Pathogen reduction technologies may be used in lieu of bacterial testing when such technologies are approved for use in this blood component.

[12] Pathogen reduction may not be applied to platelet products other than as specified in the instructions for use of the relevant device. At this time, PRT has not been approved by FDA for the treatment of platelet products other than apheresis platelets.

Recommendations to Blood Collection Establishments (continued)	C. Single Units of WBD Platelets 1. If a blood collection establishment elects to test single units of WBD platelets, sample no sooner than 24 hours after collection the largest *practical* volume within the range permitted by FDA-cleared culture-based bacterial detection device into at least an aerobic culture medium. 2. Recommendations for product minimal incubation period and release: see paragraph A.2.b in this table. 3. FDA-cleared rapid bacterial detection devices may be used when such technologies are cleared for use in this blood component. 4. Pathogen reduction technologies may be used in lieu of bacterial testing when such technologies are approved for use in this blood component.
Additional Recommendations to Blood Collection Establishments	Platelet products that remain in the inventory of transfusion services on day 4 and day 5 and are intended for extended dating may be shipped to cooperating blood collection establishments for secondary rapid or culture-based testing, using a device cleared by FDA as a "safety measure" and re-issued to transfusion services, provided extension of dating is available and apheresis platelets are collected in FDA-cleared or approved 7-day platelet storage containers.
Recommendations to Transfusion Services for Platelets Stored through Day 5	A. Pathogen- Reduced Apheresis Platelets Require No Further Measures B. Apheresis Platelets and Pre-Storage Pooled Platelets Previously Cultured: 1. Perform rapid testing on day 4 or 5 with an FDA-cleared rapid bacterial detection device within 24 hours prior to transfusion, or 2. Perform a culture-based test on day 4 and release either after the incubation period specified in the testing device instructions for use, or after 12 hours if the testing device has no specified incubation period *and* the establishment has in place measures to promptly alert the receiving establishments in the event that the distributed platelet product is subsequently identified as positive for bacterial contamination. If releasing the product during the incubation period, FDA recommends conducting a rapid test with an FDA-cleared rapid bacterial detection device.

Recommendations to Transfusion Services for Platelets stored through Day 5 (continued)	C. Post-Storage Pools of WBD Platelets if Constituent Single Units Were Not Previously Tested: test the platelet pool using an FDA-cleared rapid bacterial detection device within 4 hours prior to transfusion. D. Single Units of WBD Platelets Not Intended For Pooling and Not Previously Tested: 1. Sample and test the unit no sooner than 24 hours after collection using the largest *practical* volume within the range permitted by FDA-cleared culture-based device into at least an aerobic culture medium; and/or 2. FDA-cleared rapid bacterial detection devices may be used, when such technologies are cleared for use in this blood component.
Recommendations for Transfusion Services and Blood Collection Establishments for Extending Dating Beyond Day 5 and up to Day 7 Recommendations for Transfusion Services and Blood	A. Recommendations to Transfusion Services Perform secondary testing of apheresis platelets previously cultured or PRT-treated,[13] or of single units of WBD platelets[14] previously cultured, to extend the dating period, provided extension of dating is available, through day 6 or day 7 using: 1. 7-day platelet storage containers with labeling that requires testing every product with a bacterial detection device cleared by FDA and labeled as a "safety measure," and 2. Bacterial detection devices cleared by FDA and labeled as a "safety measure." The secondary testing modalities are as follows: a. Perform testing using an FDA-cleared rapid bacterial detection device labeled as a "safety measure" within 24 hours prior to transfusion for day 6 or day 7 platelets; or b. Perform testing using a culture-based bacterial detection device labeled as a "safety measure"[15] on day 4 with a 48-hour extension through day 6 if negative result at least 24 hours after sampling; or

[13] Currently, PRT storage systems that ensure platelet efficacy through 7 days of storage are not available. The recommendation to extend dating based on secondary testing of pathogen-reduced apheresis platelets may not be implemented until the availability of such systems.

[14] Currently, rapid tests are not cleared for use on single units of WBD platelets. The recommendations to extend single unit WBD platelet dating beyond day 5 using a rapid test may not be implemented until such devices are available.

[15] Currently, culture-based bacterial detection devices labeled as a "safety measure" for the extension of dating beyond day 5 are not available. The recommendations to extend platelet dating beyond day 5 (section VIII of this document) using a culture-based device may not be implemented until the availability of such devices.

Collection Establishments for Extending Dating Beyond Day 5 and up to Day 7 (continued)	c. Perform testing using a culture-based bacterial detection device labeled as a "safety measure"[12] on day 5 with a 48-hour extension through day 7 if negative result at least 24 hours after sampling. B. Recommendations for Transfusion Services and Blood Collection Establishments Platelet products that remain in inventory on day 4 and day 5, and intended for extension through day 7, may be shipped to cooperating blood collection establishments for secondary rapid or culture-based testing using a device cleared by FDA as a "safety measure" and re-issued to transfusion services provided extension of dating is available and apheresis platelets are collected in FDA-cleared or approved 7-day platelet storage containers.

X. LABELING OF BACTERIALLY TESTED PLATELETS

A. Labels on the Container

1. The container label

   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 collected in FDA-cleared or approved 7-day platelet storage containers 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. Labeling for secondary testing

Following secondary testing, we recommend that you maintain a labeling process that relays the following information and is integral to the container (e.g., on the container label or an attached tie-tag) and label accordingly.

a. Type of bacterial detection test that was performed (rapid or culture test).

b. Date and time the bacterial detection test was performed.

B. Circular of Information (21 CFR 606.122)

1. A circular of information must be available for distribution if the product is intended for transfusion (21 CFR 606.122).

2. We recommend that the circular of information inform the transfusion services that the platelet products have undergone primary bacterial detection testing. We recommend that the circular of information include the following statement:

> "All apheresis and pre-storage pooled platelet products have been tested no earlier than 24 hours after collection using an FDA-cleared culture-based bacterial detection device."

3. Interim statements added to the circular of information may be on a label or stamp that is applied to available blank space on the paper circular.

XI. REPORTING IMPLEMENTATION FOR BACTERIAL DETECTION TESTING OF PLATELET PRODUCTS FOR LICENSED BLOOD ESTABLISHMENTS—REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)[16]

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 BLAs 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 and single units of WBD platelets with a 6 or 7-day dating period (or "expiration date"). You should prominently label each submission with the reporting category under which you are reporting your change, for example, "Prior Approval Supplement," "Changes Being Effected in 30 Days," or "Annual Report."

[16] FDA recommendations for the implementation of pathogen reduction will be addressed in a separate guidance document.

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).

Under this regulation, the following examples of manufacturing changes would fall within this category, warranting submission of your request to implement the following changes to your approved BLA as a PAS:

a. You do not currently hold an approved BLA to manufacture apheresis, single WBD platelets, and pre-storage pooled WBD platelets (but you hold an approved BLA for other blood components) and you would like to manufacture and distribute these platelet products in interstate commerce.

b. You currently hold an approved BLA to manufacture single WBD platelets and apheresis platelets with a 5-day expiration date and you choose to increase the storage time of single WBD platelets and apheresis platelet products to a 6-day or 7-day expiration date following secondary testing using FDA-cleared or approved 7-day platelet storage containers and distribute these products in interstate commerce.

c. 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 manufactured apheresis platelets and single WBD platelets with a 6-day or 7-day expiration date following secondary testing using collection and storage systems that are approved to store platelets more than 5 days in multiple locations.

2. To comply with the requirements in 21 CFR 601.12(b)(3) and 601.12(f), the following should be included in your PAS.

a. Identification of the components involved and manufacturing facility (facilities) and a detailed description of the manufacturing change (including name of device used for bacterial detection). We recommend that this information be documented in a cover letter and on Form FDA 356h.

b. Standard Operating Procedures (SOPs) – to allow us to assess the manufacturing change, we recommend that you include copies of the following procedures:

   i. Component manufacturing (if the SOPs were previously approved by FDA, include the reference number under which they were reviewed).
   ii. Bacterial detection testing, including when the platelet product is sampled and when the product will be released.[17]
   iii. Labeling the platelet product based on the results of the bacterial detection testing, including the timeframe after which the negative results are no longer valid.
   iv. Measures to promptly alert the transfusion service that product has tested positive for bacterial contamination.
   v. Quarantine and disposition of unsuitable products.
   vi. Investigation of units with positive test results.
   vii. Communicating to your consignees the type of storage container the platelets are stored in, for example, a storage container approved for 5-day storage or storage container approved for 7-day storage and when the bacterial detection testing was performed.

c. Labeling – include the following labeling in your supplement:

   i. Container Labels: A container label for each platelet product, unless previously approved by FDA, which includes the expiration date and time, if applicable, of the product based on bacterial detection testing.
   ii. Labels for Secondary Testing: An example of the labeling that will relay information about the secondary bacterial detection testing.
   iii. Circular of Information: A copy of the revised circular of information that informs the transfusion services that the platelet products have undergone primary bacterial detection testing.

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

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

[17] You must perform the bacterial detection testing in a manner consistent with the manufacturer's instructions for use (21 CFR 606.65(e)).

f. Two consecutive months of quality control data for each product type you will be making (WBD platelets and apheresis platelets). Include a description of your sampling plan and the results for the following parameters:

   i. Residual white blood cell count;
   ii. Platelet yield; and
   iii. pH at expiration or issue.

g. For Comparability Protocol submissions 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. Supplement - Changes To Be Effected In 30 Days (CBE30)

Under 21 CFR 601.12(c), if you make any change to your product, production process, quality controls, equipment, facilities or responsible personnel that has a moderate potential to have an adverse effect on the safety or effectiveness of the product, you must submit a supplement to FDA at least 30 days prior to distribution of the product made using the change.

You may report subsequent supplements for changes approved in your Comparability Protocol as a CBE30. Include the following information in your CBE30 supplement:

1. Identification of the components involved and manufacturing facility (facilities). We recommend that this information be documented in a cover letter and on the Form FDA 356h.

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

3. Summary of the validation data.

C. Changes To Be Described In An 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 application.

Under this regulation, the following examples of manufacturing changes would fall within this category, warranting submission of the following changes to your approved BLA in your annual report noting the date the process was implemented:

1. You are a licensed blood collection establishment and you implement the 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 are a licensed blood collection establishment and either you or your contractor change from one type of FDA cleared bacterial detection device to another type of FDA-cleared bacterial detection device of the same methodology (culture-based or rapid method).

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

XII. 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 are required to 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(a). The implementation of a bacterial detection device that is used to re-label the platelet product with a 6 or 7-day expiration date 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 five-day expiration date are not required to register and list because they are not extending the dating period of platelets, which is a manufacturing step requiring registration and listing.

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 acceptability of platelet products to be released on day 6 or day 7 after collection, you must register your blood establishment with FDA and list the blood products you manufacture. We recommend that you note you are performing bacterial detection testing on platelet products in the "Other" field in the Products section.

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

XIII. IMPLEMENTATION

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

APPENDIX:

I. CONTAMINATION OF PLATELETS WITH BACTERIA

All blood components are susceptible to bacterial contamination. Platelet components, however, are uniquely vulnerable to bacterial outgrowth because they are stored at room temperature (20°C-24°C). They can serve as a favorable medium for bacterial proliferation to high titers that may lead to sepsis and related fatality in patients transfused with contaminated platelet products.

Skin flora are the most common source of bacterial contamination. Contamination could also originate from asymptomatic occult donor bacteremia, or be introduced during processing of the platelet unit.

When bacteria are present, the bacterial load in the collection at sampling time is estimated to vary approximately between 1 and 65 colony forming units (CFU) per platelet storage container, which corresponds to a concentration ranging from less than 0.002 to 0.26 CFU/mL, depending on a collection volume range of 250 to 750 mL (Refs. 10, 11, 12, 27, 28, 29). For platelet components that become contaminated, a number of mechanisms may contribute to a low bacterial concentration at the time of sampling, which generally occurs no earlier than 18-24 hours post collection: 1) inactivation by antibacterial factors in plasma; 2) a prolonged lag phase of growth; 3) bacterial species that grow poorly in the aerobic conditions of platelet storage; 4) long generation time; 5) the existence of the bacteria as biofilms coating the container making them unavailable for sampling; and 6) phagocytosis of bacteria by white blood cells (Ref. 27). Thereafter, the initial bacterial load, if present, may follow one of several growth models: 1) it may become non-viable and die; 2) after a short lag phase, viable bacteria enter a logarithmic growth phase; 3) viable bacteria persist at low concentration in an extended lag phase before undergoing logarithmic growth; or 4) viable bacteria may simply persist at low concentrations throughout the platelet storage period (Ref. 27). Bacterial organisms have different generation (doubling) times; the generation time of most bacteria in platelets at 22°C varies between 1 and 4 hours with an average of approximately 2 hours for the most frequently encountered organisms (Ref. 28). Contaminating organisms may be fast or slow growers, Gram positive or Gram negative, aerobic or anaerobic, and may be more or less virulent (Refs. 4, 29, 30). The patient's susceptibility to bacteremia also varies, for example, with immune suppression and/or administration of antimicrobial therapy.

A number of strategies have been implemented in the U.S. to control the risk of bacterial contamination of platelet products, including donor health screening to ensure that the donor is in good health at donation, skin disinfection, use of collection containers that divert the first 15-40 mL of the collection (an initial aliquot that is likely to contain the skin flora) away from the product, visual inspection of the platelet storage container for signs of gross contamination and the use of bacterial detection devices. Additionally, a psoralen/UV irradiation-based pathogen reduction technology was approved in the U.S. in 2014, which is applicable to certain platelet products.

II. PLATELET COMPONENT USAGE AND PLATELET DATING PERIOD IN THE UNITED STATES

Approximately 2.2 million platelet transfusions are administered yearly in the U.S. (Ref. 31). Of those, about 91 percent are apheresis platelets and 9 percent are pools of WBD platelets, with each pool composed, on average, of 5 single units of WBD platelets. WBD platelets are pooled either within the 4 hours prior to transfusion (post-storage pooling), or pooled shortly after collection in a system cleared by FDA for extended storage of pooled platelets (pre-storage pooling).

Under 21 CFR 610.53(c), the dating period of platelets is *either* 72 hours from the time of collection, provided labeling recommends storage at 20°C to 24°C or between 1°C and 6°C, *or* as specified in the instructions for use for the blood collecting, processing, and storage system approved for such use by the Director, CBER. The current maximal dating period for platelets in the U.S. is 7 days based on the instructions For use on current blood collection systems.

In 2003, FDA approved a New Drug Application (NDA) Supplement for a storage system from a single manufacturer for the storage of single units of WBD platelets for up to 7 days with the requirement that the product must be tested for bacterial contamination using a bacterial detection system cleared by FDA for release of platelets for transfusion.

Thereafter, three additional platelet storage containers were cleared by FDA through the 510(k) regulatory pathway, for the storage of apheresis platelets for up to 7 days when the platelets are coupled with 100 percent screening for bacterial contamination using a device cleared by FDA for that purpose with its recommended methods prior to transfusion. Of these three containers, two were relabeled in 2015 to indicate that, for extension of dating beyond day 5, every platelet product must be tested with a bacterial detection device cleared by FDA and labeled as a "safety measure."

The 7-day dating period is available with 1) the use of FDA-cleared or approved 7-day platelet storage containers labeled with a requirement to test individual products with a bacterial detection device cleared by FDA and labeled as "safety measure;" and 2) the subsequent testing of each individual platelet product for bacterial detection using a device labeled as a "safety measure," consistent with its instructions for use. Please see section VIII of the main text of the guidance document for more details.

III. METHODS TO DETECT BACTERIAL CONTAMINATION IN PLATELET COMPONENTS

Two main methodologies are used in the U.S. to detect bacteria in platelets: culture-based methods, which rely on the growth of bacterial organisms to levels detectable by the testing device; and rapid testing, which directly recognizes components of the bacterial organisms.

A. Culture-Based Devices

1. Current practices with culture-based devices

Culture-based devices have high analytical sensitivity (a low limit of detection) and an extensive record of clinical use in the U.S. since the devices were first cleared in 2002. They are traditionally used early in the storage of platelets. Currently available culture-based devices require the use of a significant sampling volume relative to the product, and they necessitate the concurrent use of equipment for incubation and detection.

Following the implementation in 2004 of an AABB Standard on testing platelets for bacterial contamination, culture-based devices have been used by most blood collection centers to routinely test virtually all apheresis platelet collections (Ref. 32). However, the exact sampling and culture practices by blood collection centers vary even in the use of a particular device (Ref. 33). Product sampling commonly occurs at least 18-24 hours after collection to allow for any organisms that are present to proliferate to levels that may be detectable by the device based on its sensitivity. Sampling is followed by a variable hold period prior to product release in order to permit time for adequate incubation of the culture.

Products tested by culture-based devices with continuous monitoring are distributed as "negative-to-date" based on the status of the culture at the time the unit is released to the transfusion service. The culture may turn positive after distribution of the unit, triggering notification of the transfusion service and product retrieval. Platelets tested using culture-based devices without continuous monitoring are released based on a single point-in-time measurement.

2. Rate of bacterial contamination following the use of a culture-based device

a. Apheresis products

The rate of bacterial contamination in apheresis platelets, as determined by sampling of platelets ≥ 24 hours after collection (commonly referred to as day 1 or early culture), varies between 1/2,836 and 1/8,431 based on confirmed culture results (Refs. 4, 5, 6, 10, 11, 16, 19, 34). However, studies have shown that a risk of bacterial contamination persists on the day of transfusion, or at outdate, in apheresis platelets that had tested negative by early culture, and that risk has been shown to vary between 1/1,500 – 1/2,747 (Refs. 5, 19, 35). The sensitivity of the early culture has been calculated to range between 11 percent and 47 percent; i.e., between 53 percent and 89 percent of bacterial contaminations of platelet products are missed by the early culture (Refs. 5, 17). The residual risk of bacterial

contamination has been shown to be mostly associated with slow-growing Gram positive organisms, providing evidence of the relative effectiveness of the early culture in interdicting the fast-growing Gram negative bacteria. The decrease over time in reported sepsis and related fatalities from platelet transfusion, and in the proportion of such fatalities attributed to Gram negative bacteria, is supported by the transfusion-related fatality reports submitted to FDA (Refs. 36, 37).

The false negative results with early culture are believed to be due to the presence of a very small bacterial load at the time of sampling, resulting in a sampling error such that no bacterial organisms are present in the sample, while organisms remaining in the apheresis unit continue their proliferation to levels capable of causing bacteremia and potential clinical sepsis. As mentioned earlier, the bacterial load, at sampling time in contaminated units, is estimated to range from less than 0.002 to 0.26 CFU/mL with an average ranging, in different studies, from 0.1 CFU/mL to 0.25 CFU/mL (Refs. 10, 11). Thus, the recovery of bacteria in a sample is considered a rare event and its occurrence has been modeled by a Poisson probability distribution. The number of bacteria present in a sample is a function of the sampling volume, and of the bacterial concentration in the bag. Detection by culture also depends on the incubation parameters such as the duration of incubation, and the aerobic or anaerobic conditions.

A published Poisson distribution model predicts that an early culture sampling volume of 4 mL, 8 mL, and 16 mL would respectively detect 46 percent, 71 percent, and 91 percent of bacterially contaminated platelet products at a contamination level of 0.154 CFU/mL (Refs. 25, 27). The caveat is that the Poisson distribution model is a mathematical construct being applied to a biologic process and rests on a number of assumptions that may not consistently and uniformly apply to all apheresis platelet products (Refs. 12, 25, 27). While the detection rates predicted by the Poisson model have been validated in a separate *experimental* seeding study in which low levels of a single bacterial organism were spiked into a platelet product that was subsequently repeatedly sampled and tested for bacterial detection, they are at significant variance with the day 1 early culture *clinical* sensitivity described above (Ref. 38). The discordance has been ascribed by the authors of the Poisson model to differences in platelet collection, sampling method, sample volume, and culture conditions between the different studies, and by the wide error margins inherent in studying rare events (Ref. 25).

The Poisson probability distribution has also been used to model the residual rate of bacterial contamination based on the *unconfirmed* day 1 positive culture results (a repeat sample having shown a negative result).

This approach suggests that unconfirmed positive results serve as an indirect measure of low level dormant bacteria that cannot be repeatedly detected by the early culture (Ref. 39). Based on this model, the authors have estimated that for every confirmed positive apheresis platelet donation detected by the early culture there may be as many as 19 donations contaminated with viable bacteria that remain dormant at the time of sampling but which may proliferate during prolonged platelet storage to clinically significant levels.

b. Pre-storage pooled WBD platelets

Single units of WBD platelets may be pooled and tested ≥ 24 hours after collection, and stored in an FDA-cleared container for extended pool storage for up to 5 days consistent with the container package insert (Refs. 23 and 40). The rate of bacterial contamination in such pre-storage pooled platelets varies from ~ 1/1,000 to ~ 1/2,500 (Refs. 17, 41). For pre-storage pooled platelets that had tested negative by early culture, the residual risk of bacterial contamination at the time of transfusion ranges between ~ 1/1,000 and ~ 1/6,000 and the calculated sensitivity of early culture of pre-storage pooled platelets varies between 54 percent and 70 percent (Ref. 17).

Thus the residual risk at the time of transfusion of pre-storage pooled platelets appears comparable to that of apheresis platelets when a culture has been conducted early in storage.

c. Post-storage pooled WBD platelets

Single units of WBD platelets may also be stored as single units and pooled within 4 hours prior to transfusion. Such practice is referred to as post-storage pooling. Pools constituted just prior to transfusion from bacterially untested single units prepared by the PRP (platelet-rich plasma) method have been cultured with a bacterial contamination rate estimated at ~ 1/418 (Ref. 42) in one study by sampling 1-2 mL from the *final constituted pool* (the single units having been leukoreduced at collection) onto a traditional plate culture just prior to transfusion. Another study that has sampled a 7.5-10 mL volume obtained *by pooling samples* drawn from individual leukoreduced single units into an automated culture method bottle at least 24 hours after collection, showed a contamination rate of 1/5,683 (Ref. 34). The disparity in detection rate between the two studies was most likely related to the difference in product sampling time. In the latter study, sampling occurred early in storage, whereas in the former study sampling was late in storage when bacterial load and bacterial detection are expected to be the highest.

d. Single units of WBD platelets

Individual single units of WBD platelets prepared by the platelet-rich plasma method are typically not cultured; however, using an automated culture system on a 4.5 mL sample taken *at least 24 hours after collection*, a study on 13,579 leukoreduced single units detected one true positive (Ref. 43). A different study on 12,062 leukoreduced single units of WBD platelets tested *between one day and 5 days after collection*, using a different automated culture system that sampled 2-3 mL, resulted in 4 confirmed positive results (~1/3,000) (Ref. 44). As discussed in the preceding paragraph, the disparity in detection rate between the two cited studies was most likely associated with a difference in product sampling time.

3. Risks of sepsis and sepsis-related fatality

Passive hemovigilance reports (initiated by the transfused patient's clinical team after a transfusion reaction is diagnosed) for distributed apheresis platelets that had tested negative by early culture reveals rates approximating 1/100,000 for transfusion-related sepsis (38 septic reactions/4 million apheresis units), and 1/210,000 (1 fatality/210,000 apheresis units) to 1/million (4 fatalities/4 million apheresis units) for sepsis-related fatalities (Refs. 4, 34, 39). Additionally, 42 percent and 53 percent of reported septic reactions occurred with day 4 and day 5 transfusions, respectively, and all related fatalities were evenly split between days 4 and 5 transfusions (Ref. 22).

For pools of WBD platelets prepared by the platelet-rich plasma method and constituted just prior to transfusion, the rate for sepsis by passive hemovigilance reporting is approximately 1/25,000 (Refs. 34 and 41), and that for sepsis-related fatalities is approximately 1/253,504 (Ref. 41). This is in harmony with reported rates of bacterial contamination and of septic transfusion reactions of about 5 times higher in post-storage pooled platelets than in apheresis platelets (Refs. 45, 46). This finding is consistent with the average number of five single units of WBD platelets combined together to make a pooled product, and the absence of pooling in apheresis platelets.

However, active reporting (based on prospective follow-up on transfused recipients) at a single institution (Ref. 45) has shown a rate of transfusion-associated septic reactions of about 10 times that identified by passive reporting (1/6,400 vs. 1/66,000) indicating that the latter mode of reporting, which is predominant in the U.S., grossly underreports septic transfusion reactions.

B. Non-Culture-Based Rapid Bacterial Detection Devices

1. Rapid testing characteristics

FDA-cleared rapid bacterial detection devices have a rapid turn-around time (typically with a read-out of less than one hour), require a small sampling volume (< 1 mL), and can be used just prior to transfusion. The lower analytical sensitivity (higher limit of detection) of currently available rapid tests compared to culture-based devices dictates their use late in storage when the bacterial load present in the platelet product is expected to be higher than in early storage due to bacterial proliferation.

Consistent with the instructions for use of the FDA-cleared devices, rapid testing of apheresis platelets is conducted within 24 hours prior to transfusion. Testing of post-storage WBD platelet pools is performed within the 4 hours prior to transfusion based on the limitation on the storage period of the pooling storage container.

2. Clinical performance of rapid devices

a. Apheresis products

In a clinical field study on apheresis platelets that were screened as negative by early culture, the products were retested with a rapid device on the day of transfusion (Ref. 21). A detection rate of 1/3,069 (0.033 percent) was found for the rapid device, with a concurrent culture test rate of 1/2,302. Thus the rapid device was able to detect contaminated platelet units that were missed by the day 1 culture method. The false positive rate of the rapid device based on a recommended repeat test strategy was 0.51 percent, and it was 0.91 percent based on an initial reactive result only. An analysis of a subset of the study showed a false negative rate of 0.02 percent and approximate sensitivity and specificity of 60 percent and 99.3 percent, respectively.

In a similar but smaller clinical study, a rapid test on day 4 detected no bacterial contamination in 3,505 apheresis platelets previously screened as negative by the early culture (Ref. 47). The false positive rate was 0.14 percent and 0.71 percent based on repeat and single testing strategy, respectively.

A rapid test with a high false positive rate could lead to the discard of a number of otherwise suitable platelet products, and potentially limit the availability of HLA, or ABO-matched platelets, or of fresh platelets. Platelet inventories in facilities where platelet inventory is low, and

transfusions are administered infrequently, would be particularly impacted by a high false positive rate.

Variability in the analytical performance of a rapid test has been described, and it has been linked, in some studies, to a deficiency in its detection technology leading to test sensitivity below the performance stated in the package insert (Refs. 21, 30, 48, 49, 50). Such a decrease in sensitivity resulted in a false negative rapid test result on a clinical product that was ultimately transfused, causing a septic reaction in the recipient (Ref. 21).

Theoretically, a proliferating organism may reach the limit of detection of the device minutes or hours after the test is performed. The relative safety period following a negative rapid test depends on many factors, including the sensitivity of the test, the species and particular strain of the proliferating organism, the bacterial load at sampling time, the clinically significant increase in bacterial proliferation during product storage following a negative test result, and the status of the patient. Testing at a time most proximate to transfusion would be expected to increase product safety.

Nevertheless, bacterial growth kinetics and outcomes of current culture-based testing strategies favor a rationale for a 24-hour relative safety period following a negative rapid test result. As stated previously, day 1 cultures have been relatively effective in interdicting the fast-growing more pathogenic bacterial organisms. The residual risk later in storage has been mostly associated with slow growing organisms, or organisms with an extended lag phase that may be less likely to be clinically relevant. Fast-growing organisms that were missed by the early culture due to sampling error would have proliferated, by day 4 or day 5, to titers that are unlikely to fall below the limit of detection of a rapid test performed on those days (Refs. 25, 27). Slow-growing organisms, while potentially undetectable by day 4 or day 5 rapid testing, are unlikely to proliferate to levels that would be detectable shortly after the performance of the test precisely because of their growth kinetics and prolonged doubling time.

Transfusion of platelets within 24 hours of a negative test permits testing of the product no more than once a day, thereby limiting the number of entries through sterile docking and the opportunities for contamination from product entry, as well as minimizing product loss.

b. Post-storage pooled WBD platelets

In a U.S. study, 70,561 non-leukoreduced post-storage WBD platelet pools were tested with a rapid test (Ref. 51). The overall contamination

rate was 1:10,080 (0.01 percent), and the false-positive rate was 1:292 (0.34 percent) for a false positive/true positive ratio of 34. The contamination rate in this study was approximately 3 times lower than that encountered in a study described above using the same rapid test but on culture-negative apheresis platelets (Ref. 21). It was also 25 times lower than that detected in a similar, but leukoreduced WBD pooled platelet product (Ref. 51). This discrepancy in detection rate has been ascribed to the ability of leukocytes, in non-leukoreduced platelet products, to phagocytize bacteria (Ref. 52).

IV. METHODS FOR PATHOGEN REDUCTION OF PLATELET PRODUCTS

Three main pathogen reduction technologies have been described for treatment of platelet products. A psoralen-based system and a riboflavin-based system use a combination of ultraviolet (UV) light and chemicals with affinity for nucleic acids to reduce bacterial, viral, and parasitic load in the treated products, and are in clinical use outside the United States (U.S.). A third technology that relies on UVC light alone is in current development. Only the psoralen/UV irradiation system (INTERCEPT Blood System for Platelets, CERUS Corporation), is presently FDA approved for pathogen reduction of platelets and is currently in use in the U.S.

The INTERCEPT Blood System for Platelets (INTERCEPT) has demonstrated effectiveness against a range of Gram-positive, Gram-negative, anaerobic and spirochete bacteria when treatment occurs within 24 hours from apheresis platelet collection, and has received FDA marketing approval. The bacterial load log reduction varied from 3.7 to $\geq$ 6.8. Bacterial spores are typically resistant to chemical agents including photochemical treatment, and spore-forming *Bacillus cereus* was the least sensitive organism to PRT treatment in the tested panel (Ref. 53). The INTERCEPT system, including the platelet storage containers, has been validated for maintaining the quality and efficacy of the treated platelets through 5 days of storage.

A critical element in the PRT process is the timing of treatment relative to the collection of the product. An effective PRT should be able to inactivate fast growing bacteria at high concentrations, as well as slow growing bacteria at low concentrations (Ref. 54). Treatment should be performed before the fastest growing pathogens have exceeded the capacity of the technology to inactivate them. Therefore, it would be necessary to validate the timeframe within which the treatment should be conducted. Such a validation study was conducted (Ref. 55) in which platelets inoculated with 2-53 CFU per container of two fast and two slow-growing bacteria were treated 24 hours after inoculation, then stored for 7 days. By treatment time, the fast-growing organisms had grown by 5 to 6 logs, and the slow-growing organisms by up to 2 logs. After inactivation, all units were culture negative on days 2, 5, and 7, thus supporting the 24-hour window period within which to perform treatment with the psoralen-based technology for the tested organisms.

A separate independent study assessed the efficacy of the psoralen-based inactivation technology when performed at 12 hours after inoculating 100 CFU or 1000 CFU of 8 clinically relevant

bacteria (4 replicates each) into both apheresis units and buffy coat platelet pools (Ref. 56). Post treatment, all apheresis units were culture negative on days 5 and 7. Pooled units spiked with 100 CFU/pool were culture negative post treatment for all bacterial replicates except for one *Klebsiella pneumoniae* replicate out of 4 tested, which was positive on both days 5 and 7. Pooled units spiked with 1000 CFU/pool were all culture negative except for two out of 4 *Klebsiella pneumoniae* replicates, and two out of 4 *Bacillus cereus* replicates which were positive on both days 5 and 7. For the fast growing *Klebsiella pneumoniae* organisms, the breakthroughs occurred at levels exceeding 10^6 CFU/mL. The incomplete inactivation of the *Bacillus cereus* organisms was believed to be the result of spore formation.

One study spiked double collections, each with one of 7 different bacterial species, and the paired split product bacterial titers were 1-10 CFU, 10-100 CFU, or 100-1000 CFU per container. Of each pair, one split was treated with pathogen reduction after overnight hold, and the other was not (Ref. 57). Post-inoculation cultures used both aerobic and anaerobic bottles. On days 1, 2 and 5 post inoculation, all units that had been treated by PRT were negative by culture. In the control arm, 10 of 21 units (1 low-level, 3 mid-level, 6 high-level titers), 12 of 20 (2 low-level, 4 mid-level, 6 high-level titers), and 14 of 20 units (4 low-level, 5 mid-level, 5 high-level titers) were culture positive on days 1, 2, and 5, respectively.

The psoralen-based pathogen reduction method has been implemented in the Alsace region of France since 2006. In the period from 2006 to 2014, 179,577 INTERCEPT platelets were transfused with no associated septic reaction or fatality reported (Ref. 58). During the same period, the transfusion of 2,298,932 conventional platelets led to 47 septic reactions and 8 related deaths. In France, conventional platelets are not bacterially tested and platelet dating for both INTERCEPT and conventional platelets is 5 days.

In Switzerland, INTERCEPT platelets were phased into routine use in 2011 with 7-day dating (Refs. 59, 60). Since then, and through 2014, 130,785 INTERCEPT platelets have been transfused with no septic reaction or fatality reported. By comparison, from 2005 to 2011, 191,700 untested conventional platelets were transfused and led to 16 septic transfusion reactions including 3 deaths. Thus, the combined French and Swiss data show that 310,362 INTERCEPT platelets were associated with no septic reaction or death while about 2.5 million conventional platelets led to 62 septic transfusion reactions and 11 deaths.

V. PUBLIC MEETINGS ON THE ISSUE OF BACTERIAL CONTAMINATION OF PLATELETS

In 2012, two public meetings were held to discuss the issue of bacterial contamination of platelets. AABB sponsored a workshop on secondary testing of platelets in July 2012, and the FDA BPAC discussed the issue in September 2012 (Refs.4, 13).

During these public meetings, a number of transfusion services expressed reservations as to the implementation of rapid testing of platelet components prior to their transfusion. Logistical challenges and cost issues were cited as hurdles to the implementation of a strategy intended to

prevent rare adverse events. It was noted that rapid devices have a relatively high false positive rate that may lead to the discard of otherwise suitable products, thereby compromising platelet availability. Concerns were expressed that the false positive rates could disproportionally impact hospitals with limited platelet inventory that annually transfuse a small number of platelets. In these small hospitals a false positive result on a product dedicated to a specific patient (such as an HLA-matched or ABO compatible product) could result in a significant delay of a needed platelet transfusion. Additionally, the challenges of implementation of rapid testing in a fixed resource environment were believed to lead to an increase of risks by creating constraints elsewhere in the hospital laboratory and blood bank. Other transfusion services reported on the feasibility and successful implementation of rapid testing on pools of WBD platelets, noting that only a small proportion of units had to be released before completion of the testing because of clinical urgency (Ref. 51). Compared to testing with a pH indicator (a surrogate marker for the presence of bacteria widely used prior to the advent of rapid testing), the adoption of rapid testing has led to a reduction in the number of platelet units that were discarded due to false positive results (Ref. 51).

BPAC recommended that additional measures be taken to decrease the risk of transfusing contaminated platelets, recommended against a reduction in dating to four days, and voted for instituting rapid testing on day 4 and day 5 platelets following the performance of an early culture. The Committee did not formally discuss or vote on FDA's proposal to extend dating to 7 days based on additional bacterial testing. However, some Committee members expressed concern about the quality of 7-day platelets and remarked that platelet efficacy decreases with length of storage. FDA indicated that 7-day apheresis platelet containers have been previously cleared by the Agency based on the same criteria applied to 5-day platelets; hence, there was no compromise in the minimum efficacy standards applied to the extension of platelets to 7 days (Ref. 13).

VI. PUBLIC MEETING ON THE TOPIC OF PATHOGEN REDUCTION OF PLATELETS

In April 2015, AABB convened a symposium to address the growing interest in implementing PRT following FDA's approval of technologies to treat platelet and plasma products. The consensus of the conference was that the most beneficial application of PRT would be in mitigating the current risk of bacterial contamination of platelets, even though the technology could also provide, through a proactive approach, an additional layer of safety, especially regarding infectious disease window periods and emerging infections. Experimental bacterial spiking data were presented showing that PRT reduces the titers of a range of bacterial organisms commonly implicated in contamination of platelets. European hemovigilance data, particularly from France and Switzerland, reported no septic reactions or related fatalities from transfusion of pathogen reduced platelets (see discussion in section IV of the Appendix.)

While international experience in some settings supported the feasibility of the implementation of the technology outside the U.S., a number of obstacles were cited as hindering its broad adoption. Although the cost of PRT implementation could potentially be partially offset by the

elimination of some current testing and other blood safety interventions, the cost-effectiveness issue remains a powerful disincentive in an unfavorable heath economics environment and inadequate reimbursement schema. The lack of PRT technologies that would be applicable across all blood components was perceived as a significant barrier as well. There was discussion on the need to promote a risk-based decision making process framework for balancing risks, benefits, and cost effectiveness of blood safety interventions to help ensure the sustainability of the U.S. blood system.

Perspectives from hospitals on the potential implementation of PRT included observations that blood safety and blood costs are intimately linked, and that hospital administrators weigh the adoption of any new safety intervention against other hospital priorities. There was reference to a published editorial (Ref. 61) advocating an FDA mandate to use pathogen reduction in the U.S. based on safety and economics concern, and supported by a reimbursement mechanism.

There was support for the development of a robust hemovigilance system to track efficacy, safety, and any potential long-term effects of pathogen reduced products.

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