Advancing Transfusion and Cellular Therapies Worldwide

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American Red Cross

16 May 2016

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2014–D–1814, "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services To Enhance the Safety and Availability of Platelets for Transfusion" draft guidance, 15 March 2016.

Dear Dockets Manager:

We appreciate the opportunity to provide joint comments to the Food and Drug Administration (FDA) on the second draft guidance titled "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services To Enhance the Safety and Availability of Platelets for Transfusion." These recommendations were drafted by the Bacterial Contamination Work Group (BCWG), a group which reports through AABB's Transfusion Transmitted Diseases (TTD) Committee. The American Red Cross and America's Blood Centers provide representatives to the BCWG and the TTD Committee.

We submitted comments to the previous draft guidance issued December 2014 and are pleased to see several of the major requests included in the new draft guidance. Firstly, establishments are provided the option of using either bacterial testing or pathogen reduction technology (without a requirement to use bacterial testing as a primary or secondary test) as their risk control strategy. We also note and appreciate that secondary testing of platelets on day 4 and 5 is now recommended rather than suggested as a consideration. For some transfusion services, an understanding of "recommended" may not be clear and we suggest that the agency use clear language in the "Background" and "Introduction" of the final document.

The pathway to 7-day platelets is clearly delineated, as requested in our previous submission to the docket. However, multiple pathways to 7-day platelets described by the FDA in the current draft guidance are quickly noted by the agency to be unavailable at the current time due to "lack of instruction for use…" in the package insert. AABB strongly encourages the FDA to engage with product manufacturers in available venues to help them understand what is expected in a

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submission to the FDA to achieve the "…instruction for use…" that is judged to be missing. For instance, we understand that a rapid test that can be used to test single whole blood-derived platelet units, while deconstructing a positive virtual pool does not have instructions for use with a single whole blood-derived platelet that is not intended to be pooled.

Comments to specific recommendations in the guidance document are arranged in the following format:

> **Section** – language from draft guidance reprinted.
> **Recommendation or Request for Clarification** – recommendation or clarification request.
> **Rationale/Supporting Information** – rationale in support of the recommendation /clarification request.

II. Background
C. Bacterial Testing of Platelets
1. Sampling volume and culture medium for culture-based devices
Two statements on page 3

- 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)

Clarification Requested / Provided

- The guidance dismisses the value of delayed sampling based on similar detection rates reported in the 2 references cited. Similar detection rates do not equal similar sensitivity of two screening methods, since the prevalence in the two populations screened could be different. Later in this document we make a valid recommendation for the use of delayed sampling that can also achieve an extension of platelet dating beyond 5 days.
- We do not believe the equivalency of the two culture-based test systems, one using 3-4 mL of platelets as the inoculum, with a single reading after 24 hours of incubation, vs. one using 8-10 mL or higher volumes read continuously during extended incubation, is adequately established based on the 3 references cited.

Section – III. CONSIDERATIONS FOR THE EXTENSION OF APHERESIS PLATELETS DATING FOR UP TO 7 DAYS
B. Extension of Dating Based on Additional Culture-Based Testing.
Page 5
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).

Clarification Requested / Provided
We agree that a 2-day relative safety period is supported by data; it may be appropriate to qualify this as 2 days when an 8 mL sample is taken at 24-36 hours in an aerobic bottle. The relative safety period for a larger sample volume at a later time (48-72 hours) inoculated into aerobic only or aerobic and anaerobic bottles is "unknown," but could be longer. This is suggested by data accumulating by the National Health Service Blood and Transplant.

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

Footnote 4, page 5
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.

B. Extension of Dating Based on Additional Culture-Based Testing.
NOTE, page 5
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.

Recommendation – We continue to recommend that the requirement for a "safety measure" claim be applied only to rapid/point of issue devices.

Rationale – The requirement for culture-based bacterial detection devices to have a "safety-measure" claim is not scientifically valid. We believe that the agency is attempting to address a known sensitivity issue with non-culture-based tests and should acknowledge that validated studies are not needed to prove the (superior) sensitivity of incubated culture-based tests used to detect bacterial contamination in platelet products. Applying the requirement for a "safety measure" claim only to rapid/point of issue devices will increase the options available for blood establishments.

Recommendation – We continue to propose an alternate mechanism to extend dating to day 7. Blood centers could choose to delay primary culturing of part of their inventory until 48 hours. Primary culture screening performed on each split apheresis product delayed until 48 hours should allow for 7-day storage for the same reasons stated below.

Rationale - The United Kingdom has experience with delayed primary culturing that favors the recommendation we have made. [McDonald C, Ball J, Allen J, et al. The first year of bacterial screening of platelet components—the English experience. (abstract). Vox Sang 2012;103(Suppl 1):341.] We understand that McDonald et al. have now screened in excess of 1,311,970 units with still only 4 breakthrough cases (in three cases the contaminated platelet was recognized on visual inspection prior to distribution to the ward and therefore was not transfused; the transfused platelet did not cause a severe adverse reaction in the patient).Their paper is in the process of

submission for publication. While a negative primary culture at 24 hours postcollection allows for a 2-day relative safety period, delaying the primary culture until 48 hours is a different scenario. It is expected to provide a longer safety interval for the following reasons:

- With delayed sampling, bacterial growth kinetics are different in that many organisms that were in a lag phase earlier have now entered an exponential growth phase. Thus bacterial titer will be higher and there is a higher probability of organisms being present in the culture inoculum sample if they are present in the apheresis product.
- Delayed sampling culture, as proposed, will be performed on units that have already been split. Thus sample volume inoculated into the culture system represents a greater proportion of the volume of the split apheresis unit as compared to a similar volume cultured from the mother bag on day 1.

(N.B. Health Canada has approved a similar approach whereby primary culture is delayed until 48 hours, and a 20 mL of sample of each component is inoculated into two bottles that are incubated for 12 hours before release. Platelets with negative cultures to date can be stored and transfused through 7 days).

VI. FDA RECOMMENDATIONS TO BLOOD COLLECTION ESTABLISHMENTS
A. Apheresis Platelets 2. Culture-based testing (primary testing)
B. Pre-Storage Pooled Platelets
C. Single Units of WBD Platelets

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

- 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 the distributed platelet product is subsequently identified as positive for bacterial contamination.

VII. FDA RECOMMENDATIONS TO TRANSFUSION SERVICES FOR PLATELETS STORED THROUGH DAY 5
B. Apheresis Platelets and Pre-Storage Pooled Platelets Previously Tested Using a Culture-Based Test

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

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

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; [*no instructions for incubation period prior to release*]

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

A. Recommendations to Transfusion Services

The modalities for performing secondary testing are as follows:

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.

Recommendation – The FDA should recommend 12 hours as the minimal incubation period at every instance when the instructions for use of the bacterial detection device do not specify a minimal incubation period.

Rationale – There are data to support 12 hours. 24 hours is not warranted, especially when used in delayed sampling or secondary sampling/testing.

Section – 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.

Recommendation – We recommend that you delete the recommendation contained in Step 2 – Labeling for secondary testing.

Rationale – Step 1 (The container label) contains a recommendation to remain compliant with 21 CFR 606.121(c)(4)(i); that is, the expiration date and time of the product must be correct. The additional information recommended in Step 2 serves no useful purpose for ordering physicians.

Section – X. LABELING OF BACTERIALLY TESTED PLATELETS
B. Circular of Information (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."

Recommendation – Delete "We recommend that the circular of information inform the transfusion services that the platelet products have undergone primary bacterial detection testing." Reword the remaining part of the paragraph to read: "We recommend that the circular of information include a statement such as: All platelet products have undergone bacterial detection testing or treatment using pathogen reduction technology that was approved/cleared by the FDA."

Rationale – The statement recommended for deletion 1) does not include the option to use pathogen reduction technology, and 2) is redundant to the second statement that we recommended to be reworded to be inclusive of all platelet products and the use of pathogen reduction technology. This is consistent with the May 2015 Final Rule. Recommending a statement "such as" will allow the AABB Circular of Information Task Force time to work out final language with its FDA liaisons and reviewers of the Circular.

AABB is an international, not-for-profit association representing individuals and institutions involved in the field of transfusion medicine and cellular therapies. The association is committed to improving health by developing and delivering standards, accreditation and educational programs that focus on optimizing patient and donor care and safety. AABB membership consists of nearly 2,000 institutions and 8,000 individuals, including physicians, nurses, scientists, researchers, administrators, medical technologists and other health care providers. AABB members are located in more than 80 countries.

Founded in 1962, America's Blood Centers is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the U.S., and a quarter of the Canadian blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The American Red Cross shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Thank you for the opportunity to offer these comments. We look forward to continuing to work with the FDA on patient and donor safety initiatives. Questions concerning these comments may be directed to acarrgreer@aabb.org.

Sincerely,

M. Allene Carr-Greer
Director, Regulatory Affairs