



Advancing Transfusion and
Cellular Therapies Worldwide

09 March, 2015

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

Submitted via <http://www.regulations.gov>

Re: Docket No. FDA-2014-D-1814 “Bacterial Detection Testing by Blood and Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion.”

Dear Dockets Manager:

We appreciate the opportunity to provide comments on the draft guidance titled “Bacterial Detection Testing by Blood and Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion.” AABB accessed the expertise of the Transfusion Transmitted Diseases Committee and its Bacterial Contamination Work Group to review the recommendations contained in the draft guidance and in compiling this response to the draft guidance. The AABB Board has reviewed the response. Over the past decade AABB has lead in several areas to reduce the risk of bacterially contaminated platelets (e.g., Association Bulletins, membership surveys, public workshop). These efforts combined with the requirements published in 2003 in the Standards for Blood Banks and Transfusion Services that “The blood bank or transfusion service shall have methods to limit and to detect or inactivate bacteria in all platelet components” have been instrumental in the decrease in fatalities reported to FDA since implementation in 2004.

Overarching recommendations to the Agency are:

- Since transmission of bacteria by platelet transfusion is an ongoing problem with the current measures that are in place, and additional measures to reduce this risk are available, AABB believes the Food and Drug Administration should mandate these measures. Specifically the guidance should mandate that one of two enhanced safety strategies be implemented:
 - Bacterial testing to include
 - Primary (e.g. culture) and secondary testing (e.g. culture or point of issue later in storage), or
 - Primary culture enhanced by delayed sampling with larger volumes (e.g. use of additional sample volume or sampling each transfusable unit, or “split”)
 - Pathogen reduction with FDA approved/cleared technologies (with no primary or secondary bacterial testing requirement)

In addition, our comments to specific sections of the draft guidance concerning extension of platelet dating beyond five days propose a delayed primary testing scheme that does not include secondary testing

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- The testing process (timeframes of valid test results, etc.) needs to be simplified to enable and encourage successful implementation by blood centers and/or transfusion services. In addition, recommendations (requirements) for secondary testing should be confined to a single, one-time use of such testing that is also sufficient to extend the expiration date of the platelet product through day 7. Recommendations to specific sections of the document relevant to this issue are included below.
- The pathway to licensing 7-day platelets should be clearly delineated and should be through:
 - Increased bacterial testing (either culture or a rapid test performed at Day 4 or later)
 - Pathogen reduction with FDA approved/cleared technologies

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.

Section – I.

Footnote found on page 1

¹This draft guidance does not address the use of platelets processed with pathogen reduction devices. We recognize the potential for the future use of pathogen reduction technology in the United States (U.S.), and we may address the use of such devices in future versions of this guidance document.

Recommendation – the footnote should be deleted from the final guidance.

Rationale – FDA should recognize that use of FDA approved/cleared pathogen reduction devices with platelets is equivalent to all uses of bacterial detection testing described in the guidance. See additional comments above.

Section – III.

CONSIDERATIONS FOR BACTERIAL TESTING OF PLATELETS BASED ON EVALUATION OF THE AVAILABLE SCIENTIFIC DATA

A. Sampling Volume and Culture Medium for Culture-Based Devices

Clinical studies also have shown equivalent sensitivity of an alternative aerobic-only culture that samples a 3-4 mL volume per its instructions for use (Refs. 12 and 13).

Recommendation – A minimum volume should be specified independent of the culture test system being used as the primary test. A possible exception would be to allow the use of a 3-4 mL sample for primary testing if secondary testing is mandated.

Rationale – We disagree with the agency’s conclusion, and would encourage a review of all of the available data. For example, Schmidt et al. Vox Sang 2007;92:15-21. The sensitivity of all culture tests is dependent upon the time between collection and sampling (because of bacterial proliferation) and the sampling volume (because of the probability of selecting an organism in the sample).

Section – III.

**CONSIDERATIONS FOR BACTERIAL TESTING OF PLATELETS BASED ON
EVALUATION OF THE AVAILABLE SCIENTIFIC DATA**

C. Considerations for Reassessing the Platelets Dating Period

2.

Recommendation – Regulation cited, 21 CFR 606.65(c), should be 606.65(e)

Rationale – Typographical error.

Section – V.

FDA RECOMMENDATIONS FOR PRIMARY TESTING OF PLATELETS

Under 21 CFR 606.140(a), establishments must perform tests to assure that platelet components are safe, pure, potent and effective (see also, 21 CFR 211.165(a)). Accordingly, every transfusable platelet product should be tested at least once prior to transfusion with an FDA cleared device intended for use in detecting bacteria in platelets for transfusion. The first test will be considered the primary test...

Request for clarification – Since a CFR section is cited along with the ‘should be’ modifier, it is unclear with the proposed wording whether or not this test is a rule requirement or a guideline recommendation.

Supporting Information – The following information is found in the **Introduction** to the draft guidance: “...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.” However, as noted above in the introductory paragraph to **Section V. Recommendations for Primary Testing of Platelets**, a regulation is cited and *should* is used.

Recommendation – “Transfusable” should be deleted and language in the final guidance should be reworded to state “Under 21 CFR 606.140(a), establishments must perform tests to assure that platelet components are safe, pure, potent and effective (see also, 21 CFR 211.165(a)). Accordingly, every platelet collection should be tested at least once prior to transfusion with an FDA approved/cleared device intended for use in detecting bacteria in platelets for transfusion. The first test will be considered the primary test...”

See also our comments/recommendations on use of FDA approved/cleared pathogen reduction devices.

Rationale – There must be clarity on the requirement for primary testing; i.e. whether it applies to each transfusable unit (e.g., 2 primary tests required for a double apheresis collection) versus to a collection (e.g., 1 primary test required on the pooled collected product from a double apheresis collection). We recommended “collection” in the reworded statement.

Section – V.

FDA RECOMMENDATIONS FOR PRIMARY TESTING OF PLATELETS

A. FDA Recommendations to Blood Collection Establishments

1. Apheresis Platelets

b.ii.

If the instructions for use of the bacterial detection device do not specify a minimal incubation period, release the products that have negative test results no earlier than 24 hours after culture inoculation. However, to ensure the availability of platelets, if you have measures in place to promptly alert the

transfusion service that the product has tested positive for bacterial contamination, you may release products that have negative test results no sooner than 12 hours after culture inoculation.

Recommendation – Reword to state “If the instructions for use of the bacterial detection device do not specify a minimal incubation period, release for distribution the products that have negative test results no earlier than 24 hours after culture inoculation. However, to ensure the availability of platelets, if you have measures in place to promptly alert the transfusion service that the product has tested positive for bacterial contamination, you may release for distribution products that have negative test results no sooner than 12 hours after culture inoculation.”

Rationale – “Release” should be further clarified so it is understood there are no restrictions on use of the product.

Section – V.

FDA RECOMMENDATIONS FOR PRIMARY TESTING OF PLATELETS

A. FDA Recommendations to Blood Collection Establishments

2. **Pre-storage Platelets**
3. **Single units of WBD platelets**

Recommendation – “If the instructions for use of the bacterial detection device do not specify a minimal incubation period, release for distribution the products that have negative test results no earlier than 24 hours after culture inoculation. However, to ensure the availability of platelets, if you have measures in place to promptly alert the transfusion service that the product has tested positive for bacterial contamination, you may release for distribution products that have negative test results no sooner than 12 hours after culture inoculation.”

Rationale – The same recommendations should apply to pre-storage platelets and single units of WBD platelets as apply to apheresis platelets

Section – V.

FDA RECOMMENDATIONS FOR PRIMARY TESTING OF PLATELETS

B. FDA Recommendations to Transfusion Services

2. Single units of WBD platelets intended for transfusion without prior pooling and not previously tested.
 - a.

We recommend sampling, no sooner than 24 hours after collection, the largest feasible sample volume consistent with the FDA-cleared device’s instructions for use (+ sampling margin) and inoculation into at least an aerobic culture medium

Recommendation – We recommend that a minimum sample volume be described.

Rationale – The sensitivity of all culture tests is dependent upon the time between collection and sampling (because of bacterial proliferation) and the sampling volume (because of the probability of selecting an organism in the sample).

Section – V.

FDA RECOMMENDATIONS FOR PRIMARY TESTING OF PLATELETS

B. FDA Recommendations to Transfusion Services

2. Single units of WBD platelets intended for transfusion without prior pooling and not previously tested.
 - b.

We recommend using a rapid bacterial detection device cleared by FDA to detect the presence of bacteria in platelets for transfusion no sooner than 72 hours after collection. The product should be transfused within 4 hours of a negative rapid test result.

Recommendation – Recommend “no sooner than 72 hours after collection” be deleted.

Rationale – This is already in the manufacturer’s instructions.

Recommendation – Delete “The product should be transfused within 4 hours of a negative rapid test result.”

Rationale –A test result on a single WBD platelet should be good for the remaining life of the platelet. The shelf life of the product has not been compromised.

Section – VI.

ADDITIONAL CONSIDERATIONS FOR INVENTORY MANAGEMENT WITHOUT SECONDARY TESTING

In accordance with section III.C.1 of this document, transfusion services may also consider optimizing platelet inventory management to minimize, to the extent possible, the proportion of day 4 and day 5 platelets issued for transfusion

and,

VII.

ADDITIONAL CONSIDERATIONS FOR SECONDARY TESTING OF PLATELETS (i.e., FOR PLATELETS WITH PREVIOUS PRIMARY TESTING FOR BACTERIAL CONTAMINATION)

A. Additional Considerations for Transfusion Services

In addition to implementing inventory management to minimize the proportion of day 4 and day 5 platelets issued for transfusion (section VI of this document),

Recommendation – These statements should be deleted.

Rationale – As written, the agency is implying that day 4 and 5 platelets are unsafe, yet the agency is not mandating the use of safety measures on those days. This is a contradiction. The agency is creating undue pressure on hospitals to demand day 2 and day 3 platelets from blood centers and to return platelets not transfused on day 3. It is unlikely that blood centers will be able to meet such a demand. Unwillingness to transfuse platelets on day 4 and 5 may lead to undue wastage of products and a lack of availability.

Section – VII.

ADDITIONAL CONSIDERATIONS FOR SECONDARY TESTING OF PLATELETS (i.e., FOR PLATELETS WITH PREVIOUS PRIMARY TESTING FOR BACTERIAL CONTAMINATION)

A. Additional Considerations for Transfusion Services

1. b.

Culture on day 4, using a device cleared by FDA, for issuance 24 hours after the time of sampling on day 4, provided a negative result (is) obtained.

Request for Clarification – Please clarify in the final guidance document that the product undergoing secondary testing can remain in inventory, and available for transfusion, while awaiting the test result.

Rationale – As written, it is not clear that products can remain available for routine (non-secondary tested) inventory while awaiting the results of the 24 hour culture. Moving platelets in and out of available inventory (released, quarantined, released) is logistically difficult and will add to the complexity in the transfusion service.

Section – VII.

ADDITIONAL CONSIDERATIONS FOR SECONDARY TESTING OF PLATELETS (i.e., FOR PLATELETS WITH PREVIOUS PRIMARY TESTING FOR BACTERIAL CONTAMINATION)

A. Additional Considerations for Transfusion Services

2.

IMPORTANT NOTE

Currently, appropriately labeled bacterial detection devices and platelet storage containers for the extension of dating beyond day 5 are not available. The additional considerations to extend platelet dating beyond day 5 in this section may not be implemented until the availability of both:

- 1) Bacterial detection devices cleared by FDA and labeled as a “safety measure;”
and
- 2) Platelet storage containers cleared or approved by FDA for 7-day platelet storage and labeled with a requirement to test every product with a bacterial detection device cleared by FDA and labeled as a “safety measure.”

Recommendation – We recommend that the requirement for a “safety measure” claim be applied only to rapid/point of issue devices and that devices with analytic sensitivity equivalent to the currently approved device that has a “safety measure” claim be allowed that claim by default. Flexibility in this area and the availability of multiple options, will encourage adoption of secondary testing in the transfusion service.

This recommendation is applicable to each use FDA has made of the Important Note in the draft guidance, or reference to it.

Rationale – Bacterial detection devices cleared by FDA and labeled as a “safety measure;”

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 sensitivity of culture-based tests used to detect bacterial contamination in platelet products. In addition, we believe there is generally little incentive for the manufacturers to invest in this activity.

Rationale – Platelet storage containers cleared or approved by FDA for 7-day platelet storage and labeled with a requirement to test every product with a bacterial detection device cleared by FDA and labeled as a “safety measure.”

Three containers have been rigorously tested, reviewed by FDA and previously approved for functional capacity to store platelets through 7 days: Terumo BCT (BK040086), Fenwal Inc. (BK050038) and Haemonetics¹ (NB: The Haemonetics bag was cleared through an NDA amendment. Given the nature of available information on NDA approvals, we were unable to specifically reference this approval). The labeling change stipulated by FDA to add ‘safety measure’ testing should be rapid, require no testing or additional validation, an administrative approval, and should be actively solicited by FDA from the manufacturers. Again, we are concerned that the manufacturers may have little incentive for this investment because of conflicting interests (e.g., selling more collection sets to replace outdated products, perceived competitive posture against pathogen reduction technology).

(¹ Slichter SJ, Bolgiano D, Jones MK, Christoffel T, Corson J, Rose L, Foley J, Popovsky M, Baril LL, Corda T, Dincecco DM, Snyder EL. Viability and function of 8-day-stored apheresis platelets. *Transfusion* 2006;46:1763-9.)

Section – VII.

ADDITIONAL CONSIDERATIONS FOR SECONDARY TESTING OF PLATELETS (i.e., FOR PLATELETS WITH PREVIOUS PRIMARY TESTING FOR BACTERIAL CONTAMINATION)

A. Additional Considerations for Transfusion Services

2.

Perform secondary testing of apheresis platelets or single units of WBD platelets, using a device cleared by FDA, to extend the dating period beyond day 5 and through day 6 or day 7, after registering as a manufacturer as described in section XI of this document.

b. Culture on day 4 using a test cleared by FDA and labeled as a “safety measure” for issue with a 48-hour extension (through day 6) following a negative result 24 hours after the time of day 4 sampling, *or*

c. Culture on day 5 using a test cleared by FDA and labeled as a “safety measure” for issue with a 48-hour extension (through day 7) following a negative result 24 hours after the time of day 5 sampling

Recommendation – FDA should describe one use of secondary testing and make it a recommendation, rather than a consideration. Use of a secondary test (culture-based or a rapid test) on day 4 or day 5 should also be sufficient to extend the expiration date of the platelet product through day 7 if the transfusion service wishes to take advantage of the option. Products being tested can remain in active inventory so long as the original expiration date has not been exceeded.

We also propose an alternate mechanism to extend dating to day 7. Blood centers could choose to delay primary culturing of part of their inventory until day 4 or day 5. Primary culture screening performed on each split apheresis product on day 4 or 5 should allow for 7 day storage for the same reasons stated below.

With either scenario there should be no requirement for additional testing, for instance with a rapid test. See also our recommendations/ comments applicable to use of FDA approved/cleared pathogen reduction devices.

Rationale –As written, the requirement for reculture on day 5 to extend shelf life to day 7 is unduly restrictive.

We believe that a careful review of data available from the PASSPORT study (Dumont LJ, Kleinman S, Murphy JR, et al. Screening of single-donor apheresis platelets for bacterial contamination: the PASSPORT study results. TRANSFUSION 2010;50:589-99) and the PGD Study Group (Jacobs MR, Smith D, Heaton WA, et al and the PGD Study Group. Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test. TRANSFUSION 2011;51:2573-82) supports this use of secondary tests for extending platelet shelf life.

The United Kingdom has experience with delayed primary culturing that is favorable to 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.]

The FDA has concluded that a negative culture primary culture at 24 hours postcollection allows only for a 2-day relative safety period. The data on which to base this conclusion are sparse. Moreover, even if this is the case, reculturing at day 4 is a different scenario than primary culturing at day 1; as such, it is expected to provide a longer safety interval (i.e. 72 hours) for the following reasons:

- By day 4, bacterial growth kinetics are different in that organisms that may have been in a lag phase on day 1 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.
- In most cases, day 4 reculture will be done on units that have already been split. Thus the 8-10 mL 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.

Section – VII.

ADDITIONAL CONSIDERATIONS FOR SECONDARY TESTING OF PLATELETS (i.e., FOR PLATELETS WITH PREVIOUS PRIMARY TESTING FOR BACTERIAL CONTAMINATION)

B. Additional Considerations for Transfusion Services

3.

Transfusion services may opt not to conduct secondary testing.

Recommendation – Delete this statement.

See also our recommendations/ comments applicable to use of FDA approved/cleared pathogen reduction devices.

Rationale – The recommendation proposed to item 2 of this section is the rationale for our recommendation to this item: FDA should describe one use of secondary testing. Use of the secondary test (culture-based or a rapid test) on day 4 or day 5 should also be sufficient to extend the expiration date of the platelet product through day 7 if the transfusion service wishes to take advantage of the option.

Section – X.

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. The bacterial detection testing statement may be on a sticker or stamp that is applied to the inside or outside cover of the circular of information.

Recommendation – Item 3 should be rewritten as follows: “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.”

Rationale – Item 3 instruction as provided in the draft guidance is too prescriptive.

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