Blood Products Advisory Committee Meeting
FDA White Oak Campus, Silver Spring, MD
November 30 - December 1, 2017

Topic I: Options to further reduce the risk of bacterial contamination in platelets for transfusion

Issue:

FDA is seeking advice from the Committee whether the available scientific data support the adoption of certain newer strategies to a) control the risk of bacterial contamination in 5-day platelets; and b) to extend platelet dating beyond 5 days and up to 7 days.

Brief Summary:

Bacterial contamination of platelets remains a public health concern despite current interventions. Additionally, extension of dating (duration of storage beyond 5 days) of otherwise suitable platelets depends on control of bacterial contamination. Under current regulations, platelets are tested at least one time for bacterial contamination, or treated with a device approved to reduce pathogens. In most cases, "primary testing" (bacterial culture) is performed prior to release of platelets by the collection establishment. However, FDA has considered whether to require additional "secondary testing" (bacterial culture or rapid detection assay) by the transfusion service at later times of storage. FDA currently permits extension of dating based on secondary testing with a rapid assay labeled as a "safety measure."

Based on a review of recent data, the Committee will be asked to consider whether specific strategies of later and larger volume sampling of platelets for culture (relative to current practices) can provide adequate assurance of bacterial safety of 5 day and 7 day stored platelets in the absence of secondary testing.   The Committee also will be asked whether secondary testing by culture on day 4 of storage is sufficient to assure bacterial safety of platelets stored for 7 days without further testing more proximate to the time of issuance.

I.   Introduction

Platelet components 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).

In response to this persisting risk, FDA has promulgated a regulation (21 CFR 606.145) requiring that blood establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices, or other adequate and appropriate methods found acceptable for this purpose by FDA. Additionally, in March 2016, FDA published a draft guidance document titled: "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion." This draft guidance document provides recommendations to control the risk of bacterial contamination of room temperature stored platelets through the performance of pathogen reduction technology or bacterial testing of platelets intended for transfusion.

Currently, blood collection establishments perform one-time bacterial cultures, shortly after collection, on platelets obtained by apheresis and on pre-storage pooled platelets prepared from whole blood. Use of an FDA-approved pathogen reduction device soon after collection is less prevalent. Similarly, the performance of secondary testing (i.e. following an early culture) of platelets in transfusion services is not presently commonplace.

Since the publication of the draft guidance document and receipt of comments, FDA has become aware of additional strategies for bacterial detection that might reduce the risk of bacterial contamination of platelets and potentially permit extension of platelet dating up to 7 days. At this meeting, outcome data for current practices and for these additional strategies will be discussed, along with implications for the logistics of implementation.

II.   Current U.S. practices in platelet collection, utilization, storage dating, and bacterial testing

A. Collection and utilization

According to the 2015 National Blood Collection and Utilization Survey platelet products in the U.S. are either obtained by apheresis (92%), or are derived from whole blood (8%). Approximately 2.4 million dose-equivalent platelet units are distributed and 2 million transfused annually (Ref. 4).

B. Platelet dating

1. 5-day dating

   a.   Introduction

   Under 21 CFR 610.53(b), the dating period for platelets is 5 days from the day of collection, unless a different dating period is specified in the instructions for use of the blood collection, processing, or storage system approved or cleared for such use by FDA.

   For 5-day apheresis platelets, the requirements to control the bacterial contamination risk [21 CFR 606.145(a)] are currently met by either culturing the product at least 24 hours after collection, or pathogen-reducing it within 24 hours after collection, using respectively an FDA-cleared and an FDA-approved device (Ref. 5).

   b.   Bacterial testing of 5-day platelets

   The current methods for bacterial testing of platelet products are either culture-based or rapid tests. Bacterial testing is additionally classified as either primary or secondary. Primary testing is the initial testing of a platelet component, and is

conducted early in storage using a culture-based method. Secondary testing is any additional test performed closer to the time of transfusion to detect bacterial contamination not revealed by primary testing. Secondary testing is currently optional and conducted with a rapid test. Appendix A provides an overview of bacterial detection devices for platelets that currently are available in the U.S.

    i. Culture-based devices

Culture-based devices have an analytical sensitivity (limit of detection) of ~ 1 CFU/mL, and are traditionally used early in the storage of platelets (primary testing) at the blood collection center. Most commonly, an 8 mL platelet sample is drawn at least 24 hours after collection, and inoculated into an aerobic culture medium. The product is held for a variable time (generally 12 to 24 hours) before release to a transfusion service. In some cases, the culture is incubated continuously for the duration of the product dating period to permit product recall if it turns positive. Physical retrieval of contaminated products distributed within 24 hours of sampling is generally successful.
Table 1 shows the bacterial detection and sepsis rates of 5-day stored apheresis platelets tested by primary culture under alternative scenarios.

The culture-based studies have shown that the sensitivity of the primary early culture conducted at least 24 hours after collection in detecting bacteria ranged only from 11 to 40% despite the high analytical sensitivity of culture technologies (Refs. 6, 7, 8, 9). This is due to the small bacterial load present at sampling time resulting in a high proportion of samples that do not contain bacteria (sampling error). Thus a bacterial residual risk exists on the day of transfusion in spite of the early culture testing, potentially causing septic reactions in the recipient.

    ii. Rapid bacterial detection tests

FDA-cleared rapid bacterial detection devices have an analytical sensitivity of 10^3-10^5 CFU/mL depending on the organisms and the testing devices, and are optimally used at

least 72 hours after collection. Use of these rapid tests on apheresis platelets is conducted in the transfusion service within 24 hours prior to transfusion, but is not currently commonplace.

Data in Table 2 show that the use of the PGD rapid test as a secondary test on the day of transfusion interdicted contaminations not revealed by the early culture at a rate of 1/3,069. This finding has qualified the device for labeling as a "safety measure." The table also reports the false negative rate and the sepsis rate associated with the use of the secondary rapid test.

In public comments to FDA's draft guidance documents issued in December 2014 and in March 2016, concerns were expressed regarding the logistical and operational challenges to implementing secondary rapid testing in transfusion services. It was also noted that the relatively high false positive rate (0.51 % with the PGD test) would lead to the discard of otherwise suitable products thus impacting platelet availability. Conversely, a number of blood establishments have reported on the successful implementation of secondary rapid testing within their transfusion services (Refs. 10, 11).

Table 1. Estimated Bacterial Detection and Sepsis Rates of Five Day Stored Apheresis Platelets Tested by Primary Culture Under Alternative Scenarios

	Primary testing by Aerobic Culture using BacT/ALERT (4-10 mL) or eBDS (3-4 mL) at $\geq$24h after Collection	Proposed Minimal Proportion Sampling Volume (see Section IV.A): $\geq$ 3.8% Sample for Aerobic Culture at $\geq$ 24-36h after Collection
Bacterial Detection Rate	1/3,965 – 1/8,960 (Refs. 12,13, 14, 15)	1/5,464
Bacterial Detection on Day of Transfusion	1/2,302 (Ref. 16)	Not available
Sepsis Rate	-1/59,000 to 220,000 per collection and by passive reporting) -1/10,000 (per component and by active reporting) (Refs. 1, , 15)	~ 1/159,098 (per collection and by passive reporting)

Table 2. Bacterial and Sepsis Rates of 5-day Apheresis Platelets Tested by Secondary Rapid Testing Following the Performance of a Primary Culture

Detection rate on Day of Transfusion (Days 2, 3, 4, or 5)	9/27,620 =1/3,069	
False Negative Rate	On Day of Transfusion (Days 2, 3, 4, or 5)	$\geq$ 3/27,620 = $\geq$ 1/9,200
	Limited to Day 5 Transfusion	$\geq$ 3/8,549 = $\geq$ 1/2, 850
Sepsis Rate (Passive reporting)	On Day of Transfusion (Days 2, 3, 4, or 5)	1/13,810 to 27,620
	Limited to Day 5 Transfusion	1/4,274 to 8,549

2. Dating beyond 5 days

Dating of apheresis platelets up to 7 days is currently available in the U.S. Extension is achieved if apheresis platelets are stored in a container cleared or approved by FDA for 7-day storage and:

1) The 7-day container is labeled with a requirement to test every product with a bacterial detection device cleared by FDA as a "safety measure test"[1] and,

2) The platelets are cultured at least 24 hours after collection with an FDA-cleared device, and secondarily retested with a bacterial detection test labeled as a "safety measure," proximate to the time of transfusion.

In the U.S. only a rapid bacterial detection device (the Verax PGD test) is cleared as a "safety measure" test and is used to extend dating to day 7 (Ref. 17).

Table 3 shows the bacterial detection, and sepsis rates of 7-day stored apheresis platelets tested by culture under alternative scenarios.

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[1] FDA's current review practice is to permit labeling of tests for bacterial detection in platelets for transfusion as a "safety measure" when either clinical studies have shown benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined, or analytical sensitivity studies have shown at least equivalence to a previously cleared device labeled as a 'safety measure.'

Table 3. Estimated Bacterial Detection and Sepsis Rates of Seven Day Stored Apheresis Platelets Tested by Culture Under Alternative Scenarios

	Proposed Secondary Culture on Day 4 (i.e. Following a Primary Culture) based on the IBTS approach-see Section IV.B.2	Proposed LVDS based on the U.K. NHSBT approach (7.0% sample for culture at ≥36-48h)-see Section IV.B1.b	LVDS based on Héma-Québec approach (20 ml at 48 hours)-see Section IV.B1.a
Bacterial Detection Rate	5/51041*=1/10208	1/4618	14/44,190 =1/3156
Bacterial Detection Rate after 7-day Outdate	0/2169	0/4515 (Apheresis + WBDP)	0/2216
Sepsis Rate	0/106,337 units collected**	0/960,470*** (three contaminated apheresis units were released but interdicted on visual inspection	No septic reactions reported (44,190 apheresis platelets collected, corresponding to ~ 66,000 apheresis platelet doses)

*Estimated quantity of donations retested at day 4, based on a 2016 rate of 48% retested.

** No septic reactions reported for 65,619 whole blood derived platelets collected

*** One septic reaction was documented after transfusion of a negatively screened pool of whole blood derived platelets (WBDP) out of a total of 278,559 screened pools.

3. Differences in bacterial contamination rates based on method of platelet preparation

Studies have shown that bacterial contamination rates may vary based on the method of platelet preparation. As noted in Table 1, bacterial detection rates in apheresis platelets at ≥ 24 hours after collection ranged from 1/3,965to 1/8,960 (Refs. 12,13, 14, 15, 18). In pre-storage pooled platelets the rates varied between 1/1,000 and 1/2,500 (Refs. 9 and 19). Furthermore, single units of whole blood derived platelets (WBDP), tested also ≥ 24 hours after collection, had a detection rate of 1/13,579 (Ref. 20). Post-storage pools of WBDP units tested after pooling and just prior to transfusion, showed a rate of approximately 1/418 (Ref. 21).

Recent publications raised the possibility that different bacterial detection rates could be associated with the use of different automated platforms for the collection of platelets. Independent blood collections centers demonstrated that the true positive bacterial detection rates, and the sepsis rate at one institution, were significantly different in platelets collected by two different automated technologies (Refs. 22, 15). This observation is consistent with the findings of a surveillance study on residual bacterial contamination rate on day 7 in apheresis platelets collected by the two technologies (Ref. 23). The explanation for the disparate contamination rates is not clear; however, it has been hypothesized that it could be related to the apheresis processing technology (Ref. 24).

4. Anaerobic culture testing

In the U.S. most blood collection centers do not routinely perform anaerobic cultures because of the rarity of strict anaerobes associated with post transfusion sepsis. The use of an additional anaerobic culture medium increases the bacterial detection rate (Ref. 6), and can shorten detection time for certain facultative aerobes (Ref. 25). It also associated with a significant false positive rate (Ref. 26) leading to discard of otherwise suitable for transfusion products. Additionally, the majority of organisms detected by the anaerobic

medium culture are considered of limited clinical relevance such as the *Propionibacterium* and *Corynebacterium* species (Refs. 6, 26). Septic reactions with *Clostridium perfringens* have been described (Refs. 27 and 28), and it has been estimated that the risk of posttransfusion sepsis with anaerobic bacteria is 1 per 6 million components distributed for transfusion. (Ref. 27)

III. **FDA's recent efforts in reducing the risk of bacterial contamination of platelets**

    A. **Events leading to FDA's issuance of draft guidance in March 2016**

FDA discussed the issue of bacterial contamination of platelets at a BPAC meeting in September 2012. A summary of this meeting and recommendations is provided in Appendix C. Briefly, BPAC supported primary culture followed by secondary rapid testing on storage days 4 and 5 to reduce the risk of transfusion of bacterially contaminated platelets of 5-day platelets.   Following the BPAC meeting, FDA published a draft guidance document in December 2014 proposing recommendations for bacterial testing for platelet components for transfusion. Subsequently FDA cleared revised labeling of rapid bacterial detection tests and platelet containers to allow extension of platelet dating to 7 days; and in 2014, FDA approved a pathogen reduction technology for apheresis platelets stored for up to 5 days as a measure to reduce the risk of bacterial contamination of platelets. In addition, FDA finalized its donor eligibility rule (the rule became effective in May 2016) requiring measures to ensure bacterial testing in platelets (21 CFR 606.145(a)). In March 2016, FDA published a second draft guidance document which introduced the option to use an approved pathogen reduction device, and expanded options for the use of culture-based and rapid bacterial detection devices, and provided options to extend platelet dating (See: https://www.fda.gov/downloads/Guidances/Blood/UCM425952.pdf).   A table summarizing the options of this draft guidance is provided in Appendix D. Consistent with advice received from BPAC in 2012, FDA's draft guidance of March 2016 included a recommendation for secondary testing of platelets prior to issuance unless the platelets had been stored for three or fewer days, or had been treated with an approved pathogen reduction device.

B. Stakeholder comments to FDA's March 2016 draft guidance document on bacterial contamination:

FDA received public comments from blood establishments, transfusion services, and device manufacturers on the recommendations provided in the 2016 draft guidance document. The major concerns fell into the following categories:

1. FDA should provide multiple options to decrease the risk of platelet bacterial contamination. FDA was advised to consider the UK NHSBT or the Héma-Québec approach to extend dating based on enhanced primary testing with delayed culture and increased volume, in lieu of secondary testing.

2. Platelet inventory loss anticipated for several reasons:
    a. The manufacture of pathogen reduced platelets entails the need to adhere to specific manufacturing guard bands that are not feasible for all platelet products.
    b. There is a potential for increased outdating of platelets because of secondary testing on day 4 and 5.

3. Impact on Transfusion Services: increased manufacturing responsibilities for transfusion services.

4. Implementation timeframe: FDA was asked to consider a reasonable timeframe for implementation of the recommendations in the guidance to allow blood collection facilities and transfusion services ample time to implement the recommendation.

The comments, together with new available data, provide additional strategies for consideration before FDA issues additional guidance on this topic.

IV. Proposed considerations to reduce the risk of bacterial contamination in Platelets for transfusion

FDA is seeking the Committee's advice on three considerations. The first relates to 5-day storage of apheresis platelets, and the remaining two considerations pertain to 7-day storage of apheresis platelets. FDA is not seeking advice from the committee on secondary *rapid* testing, or on pathogen reduction.

A. Five-day storage of apheresis platelets: considerations for use of a single culture-based method (i.e. without secondary testing) for 5-day apheresis platelets, based on the Minimal Proportional Sampling Volume (MPSV) approach

The predominant current sampling practice for culture-based bacterial testing is to sample a fixed volume from an apheresis platelet collection regardless of the volume of the collection itself. This was the sampling method recommended by FDA in its December 2014 and March 2016 draft guidance documents.

A new concept of minimal *proportional* sampling volume, in which the sampling volume used increases proportionally to the collection volume, has been advocated in order to decrease the sampling error, enhance bacterial detection, and eliminate the need for secondary testing on days 4 or 5. Poisson distribution modeling has shown that, compared to fixed volume sampling, minimal proportional sampling of 3.8% would increase the likelihood of bacterial detection (Ref. 29). It was projected that the probability of bacterial detection would increase from 41% to 68% at 30 CFU/collection, and from 9% to 17% at 5 CFU/collection.

This concept was applied in a blood collection system in which apheresis platelets were collected during two study periods using the same platform. In both periods the primary collection was sampled for culture in an aerobic medium between 24 and 36 hours after collection, however in the first period the sampling volume was the standard 8-10 mL volume (representing, on average, about 1.8% of the volume of an apheresis platelet

collection) whereas in the second period a minimal 3.8% proportional sampling volume was used. In the first and second periods, 188,389 and 159,098 apheresis collections were tested respectively. The true positive rate in the first period was 0.009% (17/188,389) and in the second period 0.018 % (29/159,098). Therefore the switch to the minimal proportional sampling approach led to a statistically significant approximate doubling of the bacterial detection rate compared to the fixed volume sampling of 8-10 mL (Ref. 30). The false positive (FP) rate increased as well, by close to four-fold, from 0.037% to 0.15%, and this increase in FP rate with increase in sampling volume, is consistent with previous findings (Refs. 12, 26). The septic transfusion reaction rate per collection, however, did not show a significant change and was 1/188,389 per collection for the 8-10 mL fixed sampling volume, and 1/159,098 per collection for the 3.8% minimal proportional sampling volume (a corresponding septic transfusion reaction rate of 1/286, 376 per component).

Of note, a larger sampling volume consumes, proportionally, a larger portion of the therapeutic platelet dose; the authors have stated that collection target settings were adjusted in the second period to compensate for the increase in sample volume and to maintain the split rate.

The probability of detecting bacteria in a platelet sample is a function of the number of organisms in the sample, which itself is determined by the sample bacterial concentration and volume. Therefore, increasing the sampling volume beyond the traditional 8-10 mL, as stipulated in the MPSV approach, would be expected to increase the bacterial yield. Indeed, and as presented above, culturing of a 3.8% minimal sampling volume has led to a significant doubling of the detection rate compared to the use of an 8-10 mL sampling volume. However, the passively reported septic transfusion reaction rates associated with the two sampling strategies did not significantly differ. The MPSV study did not culture platelets at the end of their 5-day dating; therefore, the residual bacterial contamination rate at the end of day 5 could not be established.

Main advantages of the MPSV approach:

- Single culture test conducted at the blood collection center
- Obviates need for secondary testing
- Doubles bacterial detection

Main drawbacks of the MPSV approach:

- Platelet collection procedures adjusted to compensate for product loss from increased sampling volume
- Increase in false positive rate leading to discard of otherwise suitable products.
- Clinical benefit of the approach yet to be demonstrated

B. Seven-day apheresis platelets

1. Considerations for storage of apheresis platelets for up to 7 days based on a single culture using the Large Volume and Delayed Sampling approach (LVDS)

Large sampling volume signifies a volume larger than the traditional 8 mL sample, and delayed sampling occurs beyond the 24-36 hour period after collection of apheresis platelets. Delayed sampling would allow bacteria already present in the collection to proliferate further, and in conjunction with large volume sampling, would increase the bacterial yield. In Québec, Canada and in England, the implementation of a large volume and delayed sampling strategy has allowed the storage of platelets for up to 7 days without recourse to secondary testing.

a. Studies from Héma-Québec, Canada

In 2015, Héma-Québec in Canada implemented a LVDS approach for testing apheresis and pooled platelets (Ref. 31). Sampling occurs at 48 hours after collection with a sampling volume of 20 mL, split evenly between aerobic and anaerobic media. Culture of 9,215 platelets pools and 44,190 apheresis platelet collections reveals an overall

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bacterial detection rate of 1/2,543 (21/53,405) which represents approximately a four-fold increase compared to an earlier protocol using and 8-10 mL sample at 24 hours after collection. No septic reactions were reported since the implementation of the LVDS strategy (the historical rate is 3/276,866, ~1/93,000), and the culture at outdate of 2216 apheresis units and 588 pools was negative. Table 2 shows testing results of the apheresis platelets.

b. Studies from the United Kingdom

In 2011, the UK National Health Service Blood and Transplant (NHSBT) introduced screening of all platelet components for bacteria (Ref. 26). The testing protocol consists of sampling, at 36 to 48 hours after collection, a total of 16 mL from each platelet component (including splits from double or triple apheresis collections) into both aerobic and anaerobic culture media. After a 6-hour incubation period, negative-to-date results qualify the products for a 7-day storage period following collection.

Table 3 shows the bacterial detection and sepsis rates associated with the implementation of this strategy for apheresis platelets. Additionally, three apheresis platelet components that were culture-negative on screening showed clumping on visual inspection prior to transfusion and were discarded. Also, there was one septic reaction after transfusion of a negatively screened pool of buffy coat derived platelets out of a total of 278,559 screened pools. *Staphylococcus aureus* was implicated in all 4 cases.

Main advantages of the LVDS strategy:
- Single bacterial test conducted at the blood collection center, obviating a secondary test
- Enhanced availability of platelets with 7-day dating
- No reported septic reaction after the transfusion of about 1 million apheresis units

Main drawbacks of the LVDS strategy:

- Loss of therapeutic product
- Increase of number of culture bottles to be processed
- Delay in sampling time means transfusing older platelets
- High false positive rate

2. Considerations for storage of apheresis platelets for up to 7 days based on a primary culture early in storage, followed by a secondary culture on day 4

Considering that transfusion-associated septic reactions and related fatalities rise on days 4 and 5 of storage (Ref. 32), 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," would 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 late in storage.

The Irish Blood Transfusion Service (IBTS) has implemented a strategy of re-culturing, on Day 4, platelets that were negative on Day 1 (Ref. 7) and intended to be extended to 7 days. Day 1 testing was conducted with a sampling volume of 7.5 mL inoculated into each of an aerobic and anaerobic culture medium, at least 13 and 30 hours after collection for apheresis platelets, and buffy-coat platelets, respectively. Day 4 negative units remained in the inventory through Day 7. Day 4 sampling volume was 7.5 mL inoculated into each of an aerobic and anaerobic culture medium. Processing of 12,823 apheresis and 30,407 buffy-coat platelets with this testing strategy was associated with no septic transfusion reaction in the recipients (Ref. 7).

Table 3 includes the bacterial detection and sepsis rates following the implementation of this strategy for apheresis platelets between 2005 and 2016 during which 106,337 apheresis units and 65,619 whole blood derived platelet units were collected and

processed (Ref. 33). No septic reactions were reported and no bacterially contaminated units were detected at outdate.

Main advantages of the IBTS approach:

- Improved availability of platelets with storage to 7 days
- No documented STRs

Main drawback of the IBTS approach:

- In the U.S. the day 4 culture would need to be conducted by the transfusion service unless shipped back to a cooperating testing center

V. Questions for the Committee

FDA is seeking the Committee's advice on the following questions related to the proposed additional bacterial mitigation strategies described in Sections IVA, IV B1, and IV B2:

1. Do the available data support 5-day storage of apheresis platelets without secondary testing if platelets are cultured no sooner than 36 hours post collection with a sampling volume of at least 3.8% of the collection?

2. Do the available data support the following measures to extend dating to day 7?

   a. Culture of apheresis platelets sampled no sooner than 48 hours after collection using a test volume of at least 7% without secondary testing.

   b. Repeat culture on Day 4 (Note: This would require using a device cleared by FDA and labeled as a "safety measure.")

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Appendix A.   Bacterial detection devices currently available in the U.S.

BACTERIAL TESTING METHODOLOGY	DEVICE	INDICATION	PLATELET PRODUCT TESTED
Culture-based bacterial detection devices	bioMerieux BacT/ALERT	Detection of bacteria as a quality control (QC) test	Apheresis platelets
		Detection of bacteria as a quality control (QC) test	Pools of single units of Whole Blood Derived Platelets (WBDP)
		Detection of bacteria as a quality control (QC) test	Single units of WBDP
	Haemonetics eBDS	Detection of bacteria as a quality control (QC) test	Apheresis platelets suspended in plasma
		Detection of bacteria as a quality control (QC) test	WBDP suspended in plasma
Rapid bacterial detection devices	Verax PGD test	Safety measure	Apheresis platelets suspended in plasma or PAS-C/plasma
			Pre-storage pools suspended in plasma
		Detection of bacteria	Post-storage WBDP pools suspended in plasma
			Single units of WBDP suspended in plasma
	Immunetics BacTx	Detection of bacteria as a quality control (QC) test	Apheresis platelets suspended in plasma

		Detection of bacteria as a quality control (QC) test	Post-storage WBDP pools suspended in plasma

Appendix B.   Pathogen reduction technology

FDA has approved a psoralen/UV irradiation-based pathogen reduction method for use on certain apheresis platelets within 24 hours after collection (Ref. 1).   The disposable kit, including the platelet storage containers of the FDA-approved pathogen reduction system, is currently validated to maintain the quality and efficacy of the treated platelets through 5 days of storage.

The approved pathogen reduction device has demonstrated effectiveness against a range of Gram-positive, Gram-negative, aerobic, anaerobic and spirochete bacteria (Ref. 1).

Studies have shown that apheresis platelets spiked each with 100 CFUs and 1000 CFUs of 8 clinically relevant bacterial organisms and treated 12 hours after collection with the FDA approved pathogen reduction device were culture negative at 5 and 7 days post treatment (Ref. 2). In a separate experiment buffy-coat platelets were each spiked with 12 clinically relevant bacterial organisms and treated 2 hours after achieving the bacterial load levels of 10^3 CFU/mL, and 10^5 CFU/mL. Following treatment at 10^3 CFU/mL the platelets were found to be culture negative at days 5 and 7 for all organisms except *Bacillus cereus* on both days. Following treatment at 10^5 CFU/mL, the platelets were culture negative at day 5 for all organisms except *Bacillus cereus* and *Serratia marcescens*, and culture negative at day 7 for all organisms except *Bacillus cereus*, *Serratia marcescens,* and *Pseudomonas aeruginosa* (Ref. 3).

National hemovigilance data from Europe for platelets treated with the FDA-approved pathogen reduction device show that transfusion of 214,293 five-day platelets in France, and of 167,200 combined five and seven-day platelets in Switzerland were associated with no confirmed septic transfusion reaction in the recipients (Ref. 4). In 2015, a

possible to probable septic transfusion reaction from Switzerland, caused by *Klebsiella pneumoniae,* was reported to FDA's Manufacturer and User Facility Device Experience Database (MAUDE) following the transfusion of an apheresis platelets treated with the FDA approved pathogen reduction method.

PRT References:

1. Intercept Blood System for Platelets Package Insert accessible at https://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/premarketapprovalspmas/ucm427488.htm

2. Schmidt M, Hourfar MK, Sireis W et al, 2015 Evaluation of the effectiveness of a pathogen inactivation technology against clinically relevant transfusion-transmitted bacterial strains, Transfusion 55: 2104-2112.

Appendix C. Summary and Recommendations of BPAC in 2012 on Considerations for Options to Further Reduce the Risk of Bacterial Contamination in Platelets

FDA sought the advice of the Committee on strategies to reduce the risk of bacterial contamination in Platelet. Dr. Salim Haddad from the FDA presented an overview of the risk of bacterial contamination of Platelet, discussed the currently available tests to detect bacterial contamination in Platelets and proposed several testing options to reduce the risk of transfusion of contaminated Platelets. Dr. Michael Jacobs from Case Western Reserve University discussed the microbiology of Platelets and presented the results of studies using a rapid test. William Murphy then presented data on the Irish Blood Transfusion Service's experience testing platelets for bacterial contamination. Dr. Larry Dumont from Dartmouth and Dr. Mark Yazer from the Institute for Transfusion Medicine in Pittsburgh then provided the Committee the perspectives of transfusion services and described their institutions' experiences with testing platelets for bacterial contamination.

Eleven presentations were made during the Open Public Hearing. Representatives from blood collectors, transfusion services, device manufacturers, and patient and family members provided their perspectives on testing strategies for bacterial contamination in Platelets.

The Committee addressed the following questions:

Q1: Does the Committee find that additional measures are necessary to decrease to decrease the current risk of transfusion of bacterially-contaminated platelet products?

Vote: 18 yes votes, 0 no votes.

Q2: Is the reduction in platelet product shelf-life from 5 to 4 days, and early culture, sufficient to obviate the need for additional testing?

Vote: 18 no votes, 0 yes votes.

Q3(a): For Platelets limited to 5 days of storage, do the available data support a strategy to culture platelets after the first 24 hours of storage and then retest just once with a rapid test on the day of transfusion?

Vote: 16 yes votes, 1 no vote, 1 abstention

The Committee supported an option to perform a rapid bacterial test on day of issue for day 4 and day 5 platelets.

Q3(b): Should the same strategy as described in Q3(a) be applied to day 3 (72 hours post collection) Platelets?

Vote: 5 yes votes, 5 no votes, 7 abstentions

The Committee also discussed the following issues:

• The Committee expressed concern about extension of dating Platelets to 7 days, even if the Platelets are re-cultured on day 3 or 4. However, FDA clarified that platelet containers for 7-day storage have been cleared by the Agency based on efficacy studies. The current concern with platelet extension to 7 days pertains to safety from bacterial contamination.

• Several members favored a re-culture over a rapid test as an additional safety measure.

• The Committee discussed the potential benefit of increasing the volume of the inoculum used in the culture based tests.

• Some members expressed concern regarding the logistics of testing at the transfusion service, commenting on the increased burden testing would place on transfusion service staff. Other members commented that required testing at the transfusion service may limit the availability of Platelets when needed urgently.

• Some members commented that the end users should understand the risks associated with Platelet transfusion.

• Other members commented that health care providers should be encouraged to report adverse reactions, such as febrile reactions, to ensure rapid medical intervention.

• The Committee also recommended that FDA should address pooling of whole blood-derived platelets at issue as a separate matter since there is no up-front bacterial culture.

Appendix D. FDA recommendations in draft bacterial contamination guidance of March 2016

Recommendations to Blood Collection Establishments	**A. Apheresis Platelets**

	1. Pathogen reduction:
	
	  Apheresis platelets should only be pathogen-reduced using an FDA-approved pathogen reduction device.
	
	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 additional 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 the distributed platelet product is subsequently identified as

	positive for bacterial contamination.

Recommendations to Blood Collection Establishments (continued)	**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: please 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.

	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: please see paragraph A.2.b in this table
	    3. FDA-cleared rapid bacterial detection devices
	    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	Apheresis 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 apheresis platelets are collected in FDA-cleared 7-day platelet storage containers.
Recommendations to Transfusion Services for Platelets Stored through Day 5	**A. Pathogen- Reduced Apheresis Platelets:** No Further Measures
	B. Apheresis 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.
	C. Pre-storage pooled platelets previously cultured: Please follow recommendations in B2a and B2b above in this section.
	D. 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.

	E. 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.

Recommendations for Transfusion Services and Blood Collection Establishments for Extending Dating Beyond Day 5 and up to Day 7	**A. Recommendations to Transfusion Services**
	
	Perform secondary testing of apheresis platelets previously cultured or PRT-treated, or of single units of WBD platelets 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" day 4 with a 48-hour extension through day 6 if negative result at least 24 hours after sampling; or

	c. Perform testing using a culture-based bacterial detection device labeled as a "safety measure" 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.