Blood Products Advisory Committee Meeting
FDA White Oak Campus, Silver Spring, MD
July 18, 2018

Topic I: Strategies to control the risk of bacterial contamination in platelets for transfusion

Issue:

FDA is seeking advice from the Committee on the advantages and disadvantages of various strategies to control the risk of bacterial contamination in platelets, including the scientific evidence and the operational considerations involved.

Executive summary:

Bacterial sepsis due to contamination of platelets for transfusion remains a public health concern despite current interventions. Extension of dating of otherwise suitable platelets stored at room temperature (duration of storage beyond 5 days) depends on adequate measures to control or detect bacterial contamination prior to transfusion. Platelets are tested during their storage, at least one time for bacterial contamination, or treated with a device approved to reduce pathogens. In most cases, "primary testing" (bacterial culture) of apheresis or pre-storage pooled platelets is performed by the collection establishment prior to release of platelets to the transfusion service. Additional strategies exist to further decrease the risk of bacterial sepsis following the transfusion of platelets, including "secondary testing" (bacterial culture or rapid detection assay) at later times of storage, prior to transfusion.

The Committee will be asked to comment on the advantages and disadvantages of each of the various strategies to control the risk of bacterial contamination in platelets, including the scientific evidence and the operational considerations involved. The following strategies will be discussed for 5-day platelets: primary culture followed by secondary rapid testing within 24 hours prior to transfusion, primary culture followed by secondary culture on Day 3; minimal proportional sampling volume (MPSV); and pathogen reduction technology. The following strategies will be discussed for 7-day platelets: primary culture followed by secondary rapid testing within 24 hours prior to transfusion; primary culture followed by secondary culture on Day 4; and large volume delayed sampling (LVDS) culture-based testing.

I. Introduction

Approximately 2.4 million dose-equivalent platelet units are distributed and 2 million transfused annually.[1] The 2015 National Blood Collection and Utilization Survey reveals that platelet products in the U.S. are either obtained by apheresis (92%), or are derived from whole blood (8%).

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 of primary culture of platelets using analytically sensitive culture-based bacterial detection methods.[2-5]

Bacterial residual risk per transfused unit on the day of transfusion, despite primary culture, remains around 1/2300,[6] and fatal transfusion reactions from undetected contaminated platelet collections continue to occur. [7] The reported rates of septic transfusion reactions from platelets vary from 1/100,000 by passive surveillance to 1/10,000 by active surveillance when testing with primary culture alone.[5,8] Surveillance data on platelets stored up to 5 days have shown that 95-100% of platelet transfusion-related septic reactions.[2,5,9] and 100% of associated fatalities have occurred with transfusion of day 4 and day 5 stored platelets.[9]

In response to this persisting risk, FDA promulgated a regulation (21 CFR 606.145(a)) 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[1] 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 provided

[1] FDA issued its first draft guidance on the topic in December 2014. See Appendix A of this document for additional information.

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. The performance of secondary testing (i.e., following an early culture) of platelets has been implemented in some transfusion services. In addition, some blood establishments have implemented pathogen reduction of platelets.

Since the publication of the 2016 draft guidance document and receipt of comments, FDA became aware of additional strategies for bacterial detection using large volume with or without delayed sampling culture-based testing to potentially reduce the risk of bacterial contamination of platelets and permit extension of platelet dating up to 7 days. These additional culture-based strategies were discussed at a Blood Products Advisory Committee (BPAC) meeting in November 2017. In light of comments received at the November 2017 BPAC meeting and those received following the meeting, FDA is seeking advice from the Committee on all available strategies to control the risk of bacterial contamination of platelets with 5-day and 7-day dating, including bacterial testing strategies using culture-based devices, rapid bacterial detection devices, and the implementation of pathogen reduction technology.

A summary of FDA's efforts since 2012 to address the issue of bacterial contamination of platelets, and comments received by the Agency following publication of the 2016 draft guidance are included in Appendix A and B, respectively.

This Issue Summary describes studies on different strategies to mitigate the risk of bacterial contamination of platelets. The corresponding outcomes were generated in studies performed in different establishments, using different technologies and practices, and conducted in different time periods. Given these limitations, it is difficult to make direct comparisons between the outcomes of these strategies.

II. Platelet storage, dating, and bacterial testing in the U.S.

A. Platelet dating

1. Dating up to 5 days

Under 21 CFR 610.53(b), the dating period for platelets stored between 20 and 24 degrees centigrade 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.

2. Dating beyond 5 days and up to 7 days

Containers that store apheresis platelets for up to 7 days are available in the U.S. Currently, extension of dating beyond 5 days and up to 7 days is permitted 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" and,
2) The platelets are cultured at least 24 hours after collection with an FDA-cleared device, and secondary testing is performed with a device labeled as a "safety measure", proximate to the time of transfusion.

Thus, the concurrent use of cleared or approved platelet containers with cleared bacterial detection devices according to their instructions for use permits platelet dating up to 7 days.

B. Bacterial testing

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 can be conducted with a rapid test or culture. Appendix C provides an overview of bacterial detection devices for platelets that currently are available in the U.S. and their indications.

1. 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 at least 12 hours) before release to a transfusion service. Generally, the culture is incubated continuously for the duration of the product dating period to permit product retrieval if it turns positive. Physical retrieval of contaminated products is generally successful.[10]

Primary bacterial culture (mainly aerobic) has been performed by blood centers on nearly all apheresis platelet collections in the U.S. since 2004 when AABB Standard 5.1.5.1 was introduced. Since that time, blood banks and transfusion services have introduced methods to limit and detect bacterial contamination in all platelet components.[8,10] Studies of these practices have shown a risk reduction in reported septic transfusion reactions and related fatalities ranging from approximately 50% to 70% since their introduction.[4,11,12]

Anaerobic cultures are not performed routinely in most U.S. blood collection centers. While the additional use of an anaerobic culture medium may increase the bacterial detection rate, detect a broader spectrum of species, and decrease time to detection for certain organisms, it also increases the false positive rate, which can lead to discarding otherwise suitable products. The majority of organisms detected by the anaerobic culture are not associated with post transfusion sepsis.[13,14] However, severe and fatal septic transfusion reactions due to anaerobes have been reported,[3,15,16] suggesting the need to consider the routine use of both aerobic and anaerobic culture modalities.

Increasing the platelet sample volume for culture has been associated with an increase in detection of bacterial contamination in multiple studies.[17-20] This observation has been explained by Poisson distribution modeling showing that the likelihood of bacterial detection by culture is dependent on the sample volume as well as the concentration of bacteria in the sample, particularly at low levels of contamination. [21]

Various studies [13,19,20,22-24] have shown that the clinical sensitivity of the day 1 culture (≥24 hours) to detect contamination was <40%, despite the high analytical sensitivity of culture technologies. This low clinical sensitivity is thought to be 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 despite the early culture testing, potentially causing septic reactions in the recipient.

Bacterial tests are labeled as a "safety measure" when they show benefit for detection of bacterial contamination not revealed by previous bacterial testing. The use of a culture-based device labeled as a "safety measure" performed no earlier than Day 4 permits extension of platelet dating up to 7 days.

2. Rapid bacterial detection devices

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. These tests may be used alone such as on post-storage platelet pools, or as a secondary test following an initial primary culture on apheresis platelets and pre-storage pooled platelets.

A study by Jacobs et al, published in 2011, demonstrated that rapid testing, 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.[6] This finding provided support for

labeling a rapid testing device as a "safety measure." The use of a rapid test labeled as a "safety measure" performed within 24 hours prior to transfusion permits extension of platelet dating up to 7 days.

III. Strategies to reduce the risk of bacterial contamination in platelets for transfusion

The following strategies for 5-day and 7-day platelet dating will be discussed:

A. 5-day dating

1. Primary culture no earlier than 24 hours after collection, followed by secondary rapid testing within 24 hours of transfusion

This strategy entails an initial primary culture of the apheresis or prestorage pooled platelets followed by secondary testing with a rapid test. In a study published in 2011, 27,620 apheresis platelet units, that had been tested by primary culture and released as culture negative, were retested on the day of transfusion using a rapid bacterial detection test.[6] Nine of 27,620 (1/3069) doses were positive by this rapid test and confirmed as bacterially contaminated by culture. The false positive rate was 0.51%. A subset of the apheresis platelets (10,424 units) were tested with concurrent culture, resulting in 5 positive cultures, 3 of which were detected by the rapid test. Based on the two nonreactive rapid test cases, the false negative rate was calculated as $\geq$2/10,424 or $\geq$1/5,000. Of these two rapid test false negative cases, one resulted in a septic transfusion reaction which was detected by prospective surveillance. A third false negative (from the subset of 17,196 on which a confirmatory culture was performed only on positive rapid test results) was detected by passive surveillance, based on a retrospective culture of a unit that caused an allergic transfusion reaction. Based on the one definite septic transfusion reaction and the possible septic transfusion reaction, both with false negative rapid test results, the septic transfusion reaction rate associated with the use of the secondary rapid test on the day of transfusion following a negative primary culture is determined to be 1/27,620 to 1/13,810 in this study.

2. Primary culture no earlier than 24 hours after collection, followed by secondary culture on Day 3

This strategy includes an initial primary culture (8 mL in an aerobic bottle) of apheresis platelets followed by secondary culture (5 mL in an aerobic bottle) on day 3.

In a study describing this strategy, 23,044 apheresis platelets, previously found negative by Day 1 culture, were recultured on Day 3 over a 13-month study period.[25] The platelets were not subjected to any quarantine following Day 3 sampling. Five confirmed positives were detected as well as 3 indeterminates (defined as cases in which the product was unavailable for repeat confirmatory testing and/or platelets had already been transfused). All 5 true positive units were interdicted and not transfused. The 3 indeterminates were transfused and no septic reactions were reported. Overall, there were no septic transfusion reactions reported during the 13-month study period. In the preceding 13 months, during which primary culture alone was performed, 26,586 platelets were transfused with reports of 4 possible and 3 definite septic transfusion reactions (combined rate of 1/3798), including 1 fatality. The authors concluded that implementation of secondary bacterial culture on Day 3 was feasible in a hospital transfusion service and successfully detected contaminated platelets missed by primary culture.

3. Minimal Proportional Sampling Volume (MPSV)

This strategy entails sampling of ≥3.8% of the platelet collection volume, 24-36 hours after collection, for aerobic culture. Secondary testing is not performed.

This new strategy of minimal *proportional* sampling volume, in which the sampling volume used increases proportionally to the collection volume, has been implemented to decrease the sampling error and enhance bacterial detection, as a stand-alone strategy to ensure safety through Day 5 of storage.

This strategy was implemented in a blood collection establishment in which apheresis platelets were collected during two study periods using the same apheresis platform[26] In both periods, the 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. 188,389 and 159,098 apheresis collections were tested in the first and second periods, respectively. The true positive rate in the first period was 0.90/10,000 (17/188,389) and in the second period 1.83/10,000 (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. Concurrently, the false positive (FP) rate increased by close to four-fold, from 3.66/10,000 (69/188,389) to 15.05/10,000 (241/159,098). The indeterminate rate (defined as growth of an organism from the culture bottle, but platelet component unavailable for testing) increased from 0.37/10,000 to 0.63/10,000. There was one septic transfusion reaction per study period (1/188,389 and 1/159,098 respectively), and consequently, the septic transfusion reaction rate per collection, did not show a significant change.

The MPSV study did not culture platelets at the end of their 5-day dating; therefore, the residual bacterial contamination risk at the end of day 5 could not be established. However, in a separate surveillance study of 5-day expired units previously cultured using the MPSV strategy and then recultured on Day 7,[27] [28] the residual risk of bacterial contamination on Day 7 ranged from 3/8038 (1/2679) (only true positives) to 6/8038 (1/1340) (3 true positives, 1 indeterminate, 2 presumed septic reactions from transfusion of in-date co-components).

4. Pathogen Reduction

FDA has approved a psoralen/UV irradiation-based pathogen reduction device for use on certain apheresis platelets within 24 hours after collection.[29] 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.[29] However, Bacillus cereus spores have demonstrated resistance to this pathogen reduction process.

Published studies have shown that apheresis platelets spiked with either 100 CFUs or 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.[30] Another study looked at apheresis platelets, inoculated with 1 of 5 different bacterial strains at 3-53 CFU/unit and treated with the FDA approved pathogen reduction device 24 hours after collection. Two of the bacteria were fast-growing organisms (*Klebsiella pneumoniae* and *Streptococcus pyogenes*), and two were slow-growing organisms (*Escherichia coli* and *Staphylococcus epidermidis*). The fast-growing organisms had grown by 5-6 logs, and the slow-growing organisms by up to 2 logs in the 24 hours between inoculation and inactivation. There was no bacterial growth at day 2, 5 or 7 by bacterial culture.[31] An additional study spiked double platelet 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.[32] 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.

National hemovigilance reports from Europe on platelets treated with the FDA-approved pathogen reduction device indicate that transfusion of 214,293 five-day platelets in France, 167,200 combined five and seven-day platelets in Switzerland, and 227,797 combined five

and seven-day platelets in Belgium were associated with no confirmed septic transfusion reaction in the recipients.[33] However there were two reports of septic reactions categorized as "possibly related." In 2015, a septic transfusion reaction caused by *Klebsiella pneumoniae* following the transfusion of pathogen reduced apheresis platelets was reported from Switzerland, reported by the investigator as a probable STR, but assessed by the authors as "possibly related" due to the possibility of retrograde contamination. An additional case of a septic transfusion reaction was reported in 2016 to Cerus Hemovigilance from Belgium, due to *Staphylococcus haemolyticus*, assessed by the hospital physician as "probably" related to the platelet transfusion, but assessed by the authors as "possibly related" due to incomplete testing information available.[33]

B. 7-day dating

1. Primary culture no earlier than 24 hours after collection, followed by a secondary rapid test labeled as a "safety measure"

This strategy entails an initial primary culture (at minimum: 8 mL in an aerobic bottle) of the apheresis platelets followed by secondary testing with a rapid test labeled as a "safety measure". As previously referenced in section II.B.2, Jacobs et al showed that a rapid test, performed within 24 hours of transfusion, was able to detect contaminated units that were missed by primary culture early in storage. [6] This finding has provided support for labeling the rapid test for labeling as a "safety measure", and as such, allows the extension of dating in 24-hour increments up to 7 days for apheresis platelets stored in appropriately labeled 7-day storage containers (see section II.B.2).

2. Primary culture no earlier than 24 hours after collection, followed by a Day 4 Secondary Culture

This strategy entails an initial primary culture (8 mL inoculated into each of an aerobic bottle and an anaerobic bottle) followed by secondary culture (8 mL inoculated into each of an aerobic bottle and an anaerobic bottle) on day 4.

The Irish Blood Transfusion Service (IBTS) has implemented a strategy of re-culturing, on Day 4, platelets that were negative on Day 1 and intended to be extended to 7 days. [22,34] Day 1 testing was conducted with a sampling volume of approximately 8 mL inoculated into each of an aerobic and anaerobic culture medium, at least 12-24 hours after collection for apheresis platelets, and 36-48 hours after collection for buffy-coat platelets. There was no hold period after inoculation of the bottles and prior to release of the units. Day 4 culture sampling volume also approximated 8 mL and was inoculated into each of an aerobic and anaerobic culture medium. Day 4 negative units remained in the inventory for use through Day 7.

Following the implementation of this strategy,[27] 106,337 apheresis units and 65,619 whole blood derived platelets units were collected and processed. The confirmed positive rate for apheresis platelets tested by primary culture was 29/106,337 (1/3667). There were 5/51,041 confirmed positives of apheresis platelets sampled on Day 4, for a bacterial detection rate of 1/10,208. There were no confirmed positives out of 2169 expired apheresis products on day 7, for a bacterial residual risk of 0/2169. There were no reported septic transfusion reactions associated with transfusion of about 50,000 apheresis and 15,000 pooled platelets.

3. Large Volume Delayed Sampling culture-based testing

This strategy entails the culture of a large volume of the platelet product (divided into an aerobic and anaerobic bottle) taken 36-48 hours after collection. Secondary testing is not performed.

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, could increase the bacterial yield.

Methods using large sampling volumes and delayed sampling have been implemented in Québec, Canada and England as measures to allow storage of platelets for up to 7 days.

a. Studies from Héma-Québec, Canada

In 2015, Héma-Québec in Canada implemented a large volume delayed sampling approach for testing apheresis and pooled platelets.[35] Sampling occurs at 48 hours after collection with a sampling volume of 20 mL, split evenly between aerobic and anaerobic media. Following the implementation of this strategy and through October 2017, 9,215 platelet pools and 44,190 apheresis platelet collections were cultured. The overall bacterial detection rate was 1/2543 (21/53,405). No septic reactions were reported during this time period (the historical rate is 3/276,866, ~1/93,000) and the culture at outdate of 2216 apheresis units and 588 pools was negative.[36]

b. Studies from the National Health Service Blood and Transplant (NHSBT) in England

McDonald *et al* described the introduction in 2011 of bacterial testing of apheresis and pools of whole blood derived platelets by the National Health Service Blood and Transplant (NHSBT).[14]

Prior to the introduction of bacterial screening, and in the period from 2006 to 2010, septic reactions in 10 patients were reported, including 3 fatalities. Additionally, there were 5 reported "near-miss" cases in which platelet components suspected of being contaminated by visual inspection prior to transfusion were interdicted.[14] The reported septic transfusion reaction rate was approximately 1/100,000 (10/1,087,322) and bacterial detection rate after 5-day expiration was 1/433.[14,37,38]

Beginning in 2011, platelet components were cultured at 36-48 hours after collection using a 16-mL sampling volume, inoculated evenly into an aerobic and anaerobic bottle.[14] There was a hold period of 6 hours prior to release, and negative-to-date results qualified the products for a 7-day storage. Results from processing 1,239,029 apheresis and pooled platelets between 2011 and 2015 were recently published. The true positive rate was ~1/3075 (apheresis and pooled collections), the false positive rate was ~1/521. Surveillance culture testing was conducted on expired 7-day platelets with a detection rate of 0/4515. There was 1 septic transfusion reaction associated with the transfusion of pooled platelets,[14] and 3 near-miss cases, all associated with contamination with *Staphylococcus aureus*.

Updated data on the NHSBT experience with LVDS from 2011 to 2017 was recently presented.[39] During that period over 1.8 million apheresis and whole blood derived platelet components were screened with an overall detection rate of 1/2500 (1/5000 for apheresis platelets). The overall false positive rate was about 1/250. [39] There were no reports of septic transfusion reaction beyond the case described above, but there was one additional near miss case in 2016 associated with *Serratia marcescens.* The reported overall septic transfusion reaction rate is about 1 in 1.8 million collections, and the false negative rate, taking into account the near misses, is 1/360,000 (0.0003%). Surveillance of platelets screened after 7-day expiry yielded 1 positive out of 6015 apheresis and pooled units tested (0.017%).

In the U.K., the transfusion-related adverse events reported by the NHSBT as well as by the Scottish, Welsh, and Northern Ireland Blood Transfusion Services are included in the annual Serious Hazards of Transfusion (SHOT) report.[38] The Northern Ireland Blood Transfusion Services (NIBTS) has implemented a variation of LVDS (sampling at 48 hours the main apheresis collection rather than the individual split units) with a total of 3 near miss cases reported in 2014 and 2016.[40]

Points for consideration:

Section III has presented the available data on several bacterial contamination mitigation strategies. Bacterial culture studies have been conducted at different institutions in different countries. Therefore, it is difficult to compare rates between different institutions since culture practices may vary even when using the same device.[10,8] Challenges also arise comparing previous to newly implemented strategies in a given institution due to period effect. Detection rates are affected by multiple factors, including the sampling volume, bacterial concentration in the bag, aerobic or anaerobic culture conditions, and sampling of the main collection bag versus split components. Additionally, there may be differences in the underlying contamination rate in the donor population, and definitions and reporting mechanisms of septic transfusion reactions.

Additionally, 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.[28,41] A large blood collection center reported that the true positive bacterial detection and sepsis rates were significantly different when comparing two different automated collection technologies.[8]

Near miss cases have been reported with the use of LVDS strategy. Of note, the studies associated with the other strategies described in this issue summary have not reported on the rate of their near miss occurrences.

IV. Question for the Committee

1. Please comment on the advantages and disadvantages of each of the various strategies to control the risk of bacterial contamination in platelets, including the scientific evidence and the operational considerations involved.

Appendix A. FDA's recent efforts to address the risk of bacterial contamination of platelets

1. 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. In summary, BPAC supported primary culture followed by secondary rapid testing on storage days 4 and 5 to reduce the risk of transfusion of bacterial contamination 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, including secondary testing of platelets on day 4 and day 5 of storage.

Subsequently, FDA cleared revised labeling of a rapid bacterial detection test and platelet containers to allow extension of platelet dating to 7 days; and in late 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 the donor eligibility rule (the rule became effective in May 2016) requiring blood establishments and transfusion services to control the risk of bacterial contamination of platelets (21 CFR 606.145(a)). Considering these developments, 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). Consistent with advice received from BPAC in 2012, and the December 2014 draft guidance, FDA's draft guidance of March 2016 recommended secondary testing of platelets on day 4 and day 5 of storage.

Based on the extensive stakeholder comments and the availability of new data on additional strategies for bacterial detection in platelets, FDA brought the issue back to the BPAC in November 2017. The Committee discussed whether specific strategies of sampling platelets for culture – specifically, sampling platelets for culture later in a storage period and using a larger sampling volume relative to current practices can control the risk of bacterial contamination of 5 day and 7 day stored platelets as stand-alone tests. The committee also discussed whether secondary testing by culture on day 4 of storage can control the risk of

bacterial contamination of platelets stored for up to 7 days without further testing closer to the time of transfusion. The Committee voted in favor of each of these strategies at the meeting.

Appendix 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 manufactures on the recommendations provided in the 2016 draft guidance document. The major concerns fell into one of the following categories:

1. Alternative strategies:
    a. FDA should provide multiple options to protect platelets from bacterial contamination.
    b. Commenters advocated for alternative strategies, including the increasing the sampling volume of the primary culture to at least 3.8% of the collection volume, as well as strategies adopted internationally such as the NHSBT/Héma-Québec approach to extend dating based on enhanced primary testing with delayed culture and increased volume, in lieu of secondary testing, and the strategy of the Irish Blood Transfusion Service to extend dating based on a secondary culture on Day 4.

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.

5. Bacterial detection rates: sensitivity depends on multiple factors, including timing, volume of sampling, and collection platform used.

Appendix C. Devices currently available in the U.S.

METHODOLOGY	DEVICE	INDICATION	PLATELET PRODUCT TESTED
Culture-based bacterial detection devices	bioMerieux BacT/ALERT	• Detection of bacteria as a quality control (QC) test • Safety measure	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-3/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	Pre-storage and Post-storage WBDP pools suspended in plasma
Pathogen Reduction Device	Intercept Blood System for Platelets	To reduce the risk of transfusion-transmitted infection (TTI), including sepsis	Apheresis platelets suspended in plasma or platelet additive solution, depending on collection platform

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