TO THE EDITOR:

Implications of the US Food and Drug Administration draft guidance for mitigating septic reactions from platelet transfusions

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Introduction

In March 2016, the US Food and Drug Administration (FDA) issued the second draft guidance entitled “Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion.”¹ This draft guideline addresses the residual risk of bacterial contamination of platelet products, which may result in septic transfusion reactions.

Among blood products, platelet products are most frequently associated with septic transfusion reactions, as they are stored at room temperature. Since 2004, multiple steps have been implemented to decrease the risk of contamination. These include skin cleansing, diversion pouch, and bacterial screening. These steps have decreased the rate of septic reactions from a reported range of 10 to 400 to 7 to 25 per 1 000 000, and the rate of fatal septic reactions from a reported range of 2 to 63 to 2 to 12 per 1 000 000 apheresis platelet products transfused.² Thus, the overall risk has decreased by approximately two thirds.

In the last couple of years, additional steps to decrease risk of septic reactions have been FDA approved, including pathogen-reduction technologies (PRT) and point-of-issue (POI) (also known as point-of-release) testing capabilities. At the New York Blood Center (NYBC), the residual risk as reported from hospitals is septic reaction rate of 1 per 250 065.³ Recent data using prospective testing report 20 per 51 400 (1/2570) platelet products contaminated resulting in 4 per 51 400 (1/12 800) reactions (1 being fatal [1/51 400]).⁴ PRT decreases most bacteria load by >4 logs. Hemovigilance data have not reported septic transfusion cases with pathogen-reduced (PR) platelets.⁵ Prospective screening of apheresis platelets using the Pan Genera Detection (PGD) test (Verax Biomedical, Marlborough, MA), a POI test, demonstrated a residual bacterial contamination risk of 1 per 2302 (75% detected with PGD) apheresis platelets. The PGD has a false positive rate of 0.51% and a false negative rate of 1 in 9206.⁶ The FDA-reported fatality rates due to bacteria contamination of platelets (both pooled and apheresis) range from 1 to 4 per year from 2011 to 2015 in ~2.1 million annual platelets transfused.^{7,8} *Staphylococcus aureus* was the contaminant in the majority of contaminated apheresis platelets.

The FDA draft guidance asks for implementation of PRT, POI testing, or a second bacterial culture, or to shorten the shelf life of the platelet product from 5 to 3 days. Each of these methods has considerable logistical and clinical issues. In June 2016, during the open comment period, the NYBC, as well as other blood centers, including AABB (formerly known as the American Association of Blood Banks) and ABC (America's Blood Centers), expressed their opinions regarding the impact of implementing the draft guidance as written (<https://www.regulations.gov/docket?D=FDA-2014-D-1814>). We have recently submitted additional comments and have urged the FDA to reopen the comment period to encourage a broader community to remark. Options for meeting these new guidelines based upon days from collection are shown in Table 1. Once the guidance is finalized, there is a proposed 1-year implementation date.

Main points of draft guidance

As proposed in the draft guidance, platelet products will either need to be tested for bacterial contamination with an FDA-cleared device or treated with FDA-approved PRT system. The limits of detection of tests for bacterial contamination are shown in Table 2. Platelets that are primarily cultured, as is current practice, can be transfused through day 3 (compared with the current practice, which is day

Table 1. Platelet product shelf-life and draft guidance options

Day 0-3	Day 4-5	Day 6-7
Primary culture	POI	POI
Pathogen reduction	Pathogen reduction	

5). In order to use these platelets on days 4 to 7, an additional safety measure needs to be performed, such as an additional culture or POI testing. PR platelets can be used until day 5, as currently approved. To date, there is only 1 POI test that has the additional safety measure of FDA approval (PGD test) and only 1 FDA-approved PRT (INTERCEPT Blood System [IBS]; Cerus Corp, Concord, CA).

Alternatives not presented in draft guidance

The United Kingdom recently published their 5-year experience of delaying the time of primary culture and increasing the culture volume.⁹ In the United States, samples for culture are taken at 24 to 30 hours after collection (vs 36-48 hours in the United Kingdom). In the United States, samples are typically 8 mL in aerobic culture and from the primary platelet bag, which then may be split into 1 to 3 platelet products, whereas the United Kingdom uses 8 mL in aerobic and anaerobic culture for each product. These steps greatly increase the bacterial yield. They were able to decrease the number of clinically adverse bacterial transfusions by 90%; of the 1 239 029 platelet products screened, there were 4 false negatives (all *S aureus*). One of the false negatives resulted in a patient fatality. Notably, the United Kingdom has a strong transfusion event report system, SHOT (Serious Hazards of Transfusion). The risk of contamination is then calculated at 1 per 309 757 and fatality at 1 per 1 239 029 platelets transfused.

Impacts on patient care

Loss of inventory

The FDA operates in a zero-risk principle for blood safety but acknowledges the inherent risk of infectious disease. "The role of the FDA is to drive that risk to the lowest level reasonably achievable without unduly decreasing the availability of this life saving resource" (<https://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/>). The loss of inventory with this draft guidance is substantial. First, if hospitals and blood centers do not use a secondary safety measure test, platelets will expire after 3 days. This effectively means platelets will only have a little over 1 day to be transfused, because usually they cannot be released for at least 36 hours from collection while waiting results of the primary culture. The majority of platelet products are currently transfused on day 4 or 5. Second, the current FDA-approved POI test has a 0.5% false positive rate, which will result in substantial wastage. Lastly, the current FDA-approved PRT has substantial technological restrictions, which preclude our ability to treat all platelet products collected.

Pathogen reduction

The transfusion services rely on blood centers to provide products meeting all FDA requirements. Thus, many want PR platelets to meet the requirements of this draft guidance, as they are ill-prepared to implement secondary testing. Currently, the United States does not have the ability to inactivate bacteria using PRT for all platelet products. The IBS is only approved for the Amicus

(Fresenius Kabi, Lake Zurich, IL) apheresis single-donor platelet technology in platelet additive solution (PAS) and the Trima (TerumoBCT, Lakewood, CO) apheresis single-donor platelet technology in plasma. There is no PRT available for whole blood-derived single or pooled platelets. The inability to select from multiple options to protect platelets from bacterial contamination is critical. Associated with stringent process guard-bands, the PR method has platelet concentration and volume limitations resulting in limitation of the collections to which they are applicable. The NYBC has wholeheartedly attempted to implement the current PRT with our appropriate suppliers.

The NYBC currently has approximately 43 000 annual apheresis platelet collections that yield 81 700 platelet (termed apheresis platelets) products per year. Each collection can yield a single (termed single), two (termed double), or three (termed triple) platelet products depending on the number of platelets in the bag. The NYBC's split rate (meaning the average number of products from each collection) is ~2.1. Thirty-one percent of our products are collected as triples, 56% as doubles, and 13% as singles. Currently, the IBS only allows for single and double collections but does not have a system for PR treating triple collections. In addition, the IBS has narrow product guard-bands, meaning the platelet count and volume that is acceptable to process a product, that need to be met in order to be eligible for PR of single and double collections. The guard-bands require double apheresis platelet products to have a lower volume and higher platelet concentration than is typically collected at the NYBC. The machines estimate the number of platelets in the collection based on a preprocedure donor platelet count. However, the ability to predict the collection yield based on these numbers is not precise. The current Trima configuration at the NYBC is designed to collect at an average platelet concentration of $1.5 \times 10^9/\text{mL}$; this reduces the chances of a high concentration failure and allows for greater success in split rate. The PR guard-bands are much tighter and therefore exclude many products and increase the number of discards due to high-concentration products (Table 3). Without making any changes to our current collection configuration, 3% to 5% of the inventory meets the required guard-bands for IBS treatment.

Over the course of 10 weeks, 4 different collection configurations were implemented at 1 fixed site to determine our ability to increase the percentage of PRT products. The changes involved decreasing the collection volume for doubles and increasing the volume for single-apheresis platelet collections in order to target the IBS guard-bands. No changes were made to the configuration for triple-apheresis platelet collections. The settings were evaluated for their effect on the split rate and concentration failure rate, as well as the IBS success rate (products meeting the guard-bands). A baseline was established using collections data from 3 weeks prior to the first change. Notably, IBS platelets were not actually produced.

Table 2. Limits of detection for assays

Method	CFUs/mL
Culture	10^{1-2}
eBDS	10^{2-3}
Platelet Pan Genera	10^{3-5}
BacTx	10^{3-4}
Gram stain	10^6

CFUs, colony-forming units.

Table 3. Current and IBS product volume and yield

Acceptance criteria	Single collection	Double collection	Triple collection
Current product yield (platelet count)	$3.0\text{-}6.19 \times 10^{11}$	$6.2\text{-}9.29 \times 10^{11}$	$>9.3 \times 10^{11}$
Current product volume, mL	250-300	450-500	600-660
IBS product yield* (platelet count)	$3.4\text{-}6.19 \times 10^{11}$	$6.8\text{-}7.9 \times 10^{11}$	N/A
IBS product volume, mL	270-420	375-420	N/A

NA, not applicable.

*The IBS product yield range is tighter than the guard-bands cited by IBS package insert, which allows IBS PRT treatment of single apheresis platelet collections starting at 3.0×10^{11} . It also allows treatment of double apheresis platelet collections falling between 6.2 and 6.8×10^{11} . Assuming a 10% to 15% loss of platelets during the PRT process, the NYBC modified the IBS platelet yield range to ensure each component contains $\geq 3.0 \times 10^{11}$ platelets after IBS treatment per the FDA licensing requirement.

†Product volume is dependent on the IBS PRT processing kit to be used. There are 3 processing kits that can be used for single collections based on the volume and yield. One of them is also used for the double collections.

The baseline split rate for the collection site was 2.14 (Table 4). The impact on the split rate from the various configurations ranged from 1.68 to 1.88. The change in collection volume had a great impact on the platelet concentration, leading to as much as 16% failure in one of the configurations that was evaluated. The overall inventory that met the guard-bands ranged from 19% to 38%. The percentage of IBS-eligible products was inversely proportional to the split rate. The IBS success rate peaked at 56% for doubles and 89% for singles. After the evaluation period was over, analysis of the data showed that the best scenario yielded a split rate of 1.88, achieving only 30% of the total inventory to be eligible for IBS treatment.

With adherence to the manufacturer's guard-bands and through the NYBC's experience and modeling, if all of its collections are maximized

to required settings, we would only be able to IBS PRT 32% of the inventory and would lose 12% to 15% of total collections (~10 000 units). These data include only being able to PR 43% of double, 78% of single, and none of the triple collections. Since the NYBC does not typically produce an excess of platelets, assume arguendo that 81 700 is the required amount to meet current local demand. The NYBC would thus have to ramp up collections by 10 000 units or purchase the same amount on the market. This represents a greater than 10% increase in annual donations. Extrapolation across the entire industry results in a significant and likely unattainable collective ramp up in platelet donations. Similarly, for NYBC to purchase 10 000 units, those units need to be produced elsewhere. The market for platelets does not and likely cannot support that kind of incremental demand from a center like the NYBC, which will likely be mirrored by others. In other words, a conversion to PR is unmanageable given the present technology and present donation patterns. With additional FDA approvals and alternate technologies, this may mitigate the current technology limitations.

In the current environment, 100% PRT platelet supply is not attainable because of limitations on PRT and use of whole blood-derived platelets. In 2013, 1.2 million apheresis collection procedures yielded 2.2 million apheresis units in the United States.¹⁰ If all collections were optimized to meet the current IBS FDA-approved guard-bands using our data, then ~300 000 products would be lost and 600 000 IBS products would be available. With a national split rate of 1.8, then 160 000 more collections would need to be performed. Currently, there is no PRT available for whole blood-derived platelets, which numbered 164 000 apheresis equivalent units in 2013.¹⁰ Applying our numbers conservatively to the national platelet supply results in a substantial shortage of product and increase in donor collections (and resulting donor reactions) and thus has an impact on care.

Table 4. Effect of IBS PRT settings on platelet inventory and number of theoretical PRT products

Parameter	Time period					
	1	2	3	4	5	6
Length, d	21	12	14	20	40	30
Collection configuration	Original* (no PRT settings)	PRT1	PRT2	PRT3	PRT4	Normal
Number of donations	152	104	84	158	288	227
Number of products†	326*	187	155	272	540	469
Overall split rate	2.14*	1.79	1.85	1.72	1.88	2.07
Triple donations, %	46	48	30	30	33	32
Double donations, %	42	45	56	50	53	61
Single donations, %	12	7	14	20	14	7
Products discarded	1*	6	7	40	44	9
Discard rate, %	N/A	3	4	13	8	2
PRT products attempted from single and double collections	N/A	101	106	190	347	293
PRT units produced	N/A	35	59	79	160	23
PRT success rate, %	N/A	35	56	42	46	8
Overall PRT product inventory, %	N/A	19	38	29	30	5

PRT1 to PRT4 are collection configurations designed to target products that are eligible for PRT by IBS. The overall split rate is the number of products collected divided by number of collections. The products discarded/discard rate represents the products discarded due specifically to concentration failure (the TerumoBCT Platelet storage bag allows for maximum concentration of 2.1×10^9 /mL). The IBS PRT success rate is the percentage of products eligible for IBS PRT treatment from the attempted single and double donations (triple collections excluded). Overall IBS PRT product inventory is the percentage of entire apheresis platelet inventory eligible for IBS PRT.

NA, not applicable.

*Failures unknown for this time period. Split rate may be slightly lower.

†Concentration failures and discards excluded from number of products collected.

POI testing

Under the draft guidance, use of platelets beyond day 3 would require POI testing on platelet products. Such testing could be in the form of a cleared culture method starting on day 4 of the product or via an FDA-cleared POI test. Otherwise, platelets would need to be expired at the end of day 3. The NYBC distributes 17% of our platelet products on day 4 or 5, and the majority of platelet transfusions in the hospital are day 4 and 5 (74% of platelets transfused in one large randomized controlled trial were day 4 or 5).¹¹

Currently available POI tests are limited to the PDG test, which is the only test currently FDA cleared as safety measure, and the BacTx Bacterial Detection Kit for Platelets (Immunitics Inc., Boston, MA). Both POI tests can detect aerobic and anaerobic gram-positive and gram-negative bacteria. The PDG test is an immunoassay, and the BacTx assay is a colorimetric enzyme assay. Both are completed in ~1 hour and mitigate the risk of bacterial contamination for 24 hours from testing when the testing result is negative. Testing would be required on day 4 and again on day 5 (or toward the end of day 4) for units that remain in inventory after day 4. Both tests are required to be performed by clinical laboratory technologist, because they are considered moderate complexity tests by the Clinical Laboratory Improvement Amendments. Also given PGD has a false positive rate 0.51%, 1 in 196 products would be falsely discarded.⁶

As the draft guidance is written, the POI test needs to be repeated every 24 hours, while the culture test would be good for 48 hours. However, a culture method must be initiated on day 4 and the product held for 12 hour, thus losing ≥ 12 hours of transfusable life of the platelet, unless the culture method instruction states otherwise. Alternatively, POI testing can be timed so that little time exists when the platelet is unavailable.

Importantly, the draft guidance provided a pathway to extend the usable life of platelets for up to 7 days. The conditions for extension of platelet shelf life beyond day 5 are (1) the platelets must be collected in an FDA-cleared or approved container with labeling that allows storage for up to 7 days, and (2) the platelets must be tested for bacteria using a method labeled as a “safety measure” within the time specified by the testing manufacturer. This testing only extend the usable life of the unit for 24 hours after testing, but the test may be repeated if needed on day 6 to allow use on day 7. Notably, the FDA has not yet approved the use of PRT platelets for 7 days.

Clinical efficacy

Multiple randomized clinical trials (RCTs) have determined noninferiority between PR and standard platelets in hypoproliferative thrombocytopenic hematology/oncology patients. Hemovigilance data demonstrate a low rate of adverse events with PR platelets,¹² and some studies fail to demonstrate increased bleeding or worse clinical outcomes for patients treated with PR platelets.^{13,14} However, studies have shown an association between PR platelets and a reduction in 1- and 24-hour corrected count increments, increase in platelet refractoriness, decrease in time to next transfusion, and increase in platelet use.¹⁵⁻¹⁷ The most recent study demonstrated a 50% increase in platelets transfused and a 25% increase in red blood cells transfused in patients receiving INTERCEPT vs control platelets.¹⁶ The increase in platelet use will also impact the national platelet inventory.

Impact on transfusion services

Transfusion services have relied on their blood collection establishments to address the FDA’s manufacturing and safety recommendations. In

this draft guidance, transfusion services will have to implement unfunded testing and relabeling requirements.

In order to understand the implementation requirements, process, and timelines related to steps for additional blood safety. The NYBC’s transfusion service at Westchester County Medical Center is piloting secondary testing methods using the PDG test to extend the expiration of apheresis platelets beyond day 5. As described by Dunbar et al, implementation requires training, relabeling, product codes, new charges, FDA registration, validation, and computer system changes.¹⁸ The steps required for implementation vary depending on your registration and licensing status with the FDA. In our case, where the hospital service is FDA registered but not licensed, we needed to (1) create and implement an SOP for 7-day platelets, (2) determine product relabeling, and (3) amend our registration with the FDA. Testing is performed near the end of the day (~10:00 PM on day 5 and again on day 6, if needed) to maximize the shelf life of the units. Only those units (~10% of our inventory) that we anticipate will not be transfused before expiration are tested. The actual testing and validation of the testing is relatively straightforward. The largest obstacle for implementation of the POI testing is related to the computer information system. Information system issues include creation of new products (for extension beyond day 5 currently and perhaps beyond day 3 under the proposed guidance), and appropriate extension of expiration dates to no longer than 24 hours beyond the entry of a negative test result from the POI test. The solution to these issues will vary depending on your specific system but require full validation to ensure that products are not released without appropriate testing or beyond the 24-hour time allowed (or beyond midnight of day 7 for extended platelets or day 4 or 5 under the draft guidance).

Use of a POI test for extension of platelet shelf life beyond day 5 only requires testing of a small part of a hospital inventory (in our case ~10%). However, a requirement for testing platelets for use beyond day 3 would require testing of a much larger percentage of inventory (74% in the PLADO trial¹¹). The time and effort required for inventory management, testing and labeling will be significant. Further, limiting platelet shelf life with such a requirement may require a transfusion service to increase overall inventory on hand as part of the inventory may be unavailable at times. This is because despite a well-planned testing workflow; there will likely be platelets unavailable (in expired status) awaiting results of POI testing. As such, inventory management will become more complex, requiring additional staff time and attention. Although in theory our transfusion information systems will manage this, we know that the systems available are not always well equipped for such demands and may require workarounds with manual steps. Even with good software management, the management of the physical inventory requires additional effort and attention to ensure that only legitimately in date products are releasable and released.

Future products

Fortunately, new tests and methods for PR are in RCTs, which will expand our capabilities to address this residual risk. Two additional PR systems have been approved outside of the United States. One system (Mirasol Pathogen Reduction Technology System; TerumoBCT, Lakewood, CO) is enrolling in a phase 3 RCT for FDA approval (Mirasol platelets in plasma clinical trial, or MIPLATE; <https://clinicaltrials.gov/ct2/show/NCT02964325?term=miplate&rank=1>). Additionally, the RCT evaluating clinical effects of platelet transfusion

products (the Pathogen Reduction Evaluation and Predictive Analytical Rating Score [PREPAREs] trial) was recently completed in Europe and Canada using Mirasol vs standard platelets.¹⁹ Lastly, the Evaluation of the Efficacy of Platelets Treated with Pathogen Reduction Process (Effipap) trial in France is a multicenter, double-blind RCT with the primary objective to evaluate noninferiority with regard to prevention and control of hemorrhage of PR platelets (both INTERCEPT and Mirasol systems) compared with platelet concentrates stored in PAS-C and platelet concentrates stored in plasma (historical arm) (<https://clinicaltrials.gov/ct2/show/NCT01789762>). All these RCTs include hypoproliferative thrombocytopenic patients.²⁰ Additionally, in the future, IBS may allow for triple collections. However given the 10% loss of platelets during processing, the collected platelet count would need to be $>10 \times 10^{11}$, which would need to be collected within 2 hours, which few donors would achieve.

Other future platelet products will not be stored at room temperature so will have mitigated the risk of bacterial reactions. These products include cryopreserved and lyophilized platelets, and cold storage platelets. A recent study used cryopreserved autologous platelets in HLA-alloimmunized patients with hematologic malignancies.²¹ In 9 patients who received 40 units, there were no adverse events or bleeding, and the count increment was $6 \times 10^9/L$. There is continued research and development on lyophilized platelets, which are currently being tested in animal models.²² Cold-stored platelets are FDA approved, but only with a 3-day shelf-life. More recent data showed that alternate storage, such as in platelet additive solution, can lengthen the shelf-life.^{23,24} Also the platelets are more hemostatically active, which could be of use in bleeding patients. Although cold-stored platelets are cleared more rapidly, these platelet products may be more suitable for actively bleeding patients, particularly trauma patients.

Other testing

Other bacterial detection platforms for use in platelet products are in development. These may be easier to use and/or more sensitive. These include the BactiFlow flow cytometric assay or nucleic acid test.²⁵ BactiFlow has a limit of detection of 150 CFU/mL with <1 hour result time.²⁶ Use of the BactiFlow detected 12 additional true positives (12/34 631; 1/2886) and 12 false positive (false positive rate of 0.03%).²⁷

Discussion and conclusion

Blood centers have made substantial strides against septic transfusion reactions due to platelet transfusions. Further risk can be reduced in a number of ways. There are exciting alternate technologies to further mitigate this risk. However, at this time, the current requirements of the draft guidance will cause substantial disruption on the platelet supply. Careful, stepwise implementation of technologies may allow additional risk reduction while limiting the effect on the supply of this critical resource. Given the risk of septic reactions in patients with hypoproliferative thrombocytopenia, these patients may warrant additional testing or PR products. However, many patients with hypoproliferative thrombocytopenia are on antibiotics due to accompanying neutropenia. In contrast, bleeding patients may best be served with our current products or cold platelets. Maybe it is time to best suit a product to the patient need.

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