

FDA DRAFT GUIDANCE: RECOMMENDATIONS FOR ADDRESSING BACTERIAL CONTAMINATION RISK IN PLATELETS AND PATHWAY FOR IMMEDIATE EXTENSION OF PLATELET DATING TO 7 DAYS

The presence of bacteria and bacterial toxins in platelet concentrates intended for transfusion has been a vexing and longstanding problem that continues to threaten patients and challenge physicians, scientists, and regulators to improve transfusion safety while preserving transfusion efficacy. This has been exemplified by the considerable variability throughout the past 35 years in the permissible length of storage for platelet concentrates intended for transfusion. A brief review of the history of the shifting requirements for platelet storage duration was presented in a previous White Paper addressing the safety and efficacy of seven-day platelets and readers are referred to this report for further details.

To address these issues, on March 14, 2016, FDA issued a revised draft guidance addressing bacterial detection testing to enhance the safety and availability of platelets for transfusion.¹ This draft guidance provides recommendations for managing platelet components during days four and five of storage and also provides one specific pathway for extending platelet storage for up to seven days. The draft guidance represents the current thinking of the Food and Drug Administration on this topic.

Importantly, a significant change in the draft guidance is that it does not include the option for transfusion services to make no changes to their existing practices, if they are not already following one of the strategies outlined. This “no change” option was included in the first draft guidance issued December 2014.

FDA RECOMMENDATIONS FOR TESTING DAY FOUR AND DAY FIVE PLATELETS

Surveillance data on platelets stored for up to five days have shown that 95 percent of platelet transfusion-related septic reactions and 100 percent of associated fatalities have occurred with transfusion of day four and day five stored platelets, with an almost even distribution between these two days.²

The FDA draft guidance, in Section VII, recommends implementing secondary testing of previously cultured apheresis platelets and pre-storage pooled platelets to enhance platelet safety through day five of storage in one of two ways:

1. A rapid test should be performed on day four or day five with an FDA-cleared rapid bacterial detection device within 24 hours prior to transfusion, or

2. A culture-based test should be performed on day four and the component should be released either after the incubation period specified in the testing device instructions for use, or at least 12 hours after sampling if the testing device has no specified incubation period and if the testing establishment has in place measures to promptly alert the receiving establishments should the distributed platelet product be subsequently identified as positive for bacterial contamination. If releasing the product during the culture incubation period, FDA recommends conducting a rapid test with an FDA-cleared rapid bacterial detection device.

Additionally, the draft guidance recommends that post-storage pools of whole blood-derived platelets should be tested using an FDA-cleared rapid bacterial detection device within four hours prior to transfusion, if the constituent single units were not previously tested.

PATHOGEN-REDUCED 5 DAY APHERESIS PLATELETS

The draft guidance also addresses pathogen-reduced (PR) apheresis platelets stating that they do not require testing for bacteria. This would mean that a hospital would need to shift from its current platelet inventory to Intercept-treated Platelets if it did not choose to test. It should be noted, however, that the FDA has previously disclosed that recovery and survival for Intercept Platelets have been reported to be statistically significantly inferior to control platelets with recovery decreased 15.5% and survival decreased 20% relative to untreated platelets.³ In addition, statistically significant differences favoring non-Intercept-treated platelets have been detected in platelet collection yield, the mean number of days of Grade 2 bleeding, mean days between platelet transfusions, mean number of platelet and red cell transfusions, the rate of refractoriness to platelet transfusions, and the mean 1- and 24-hr corrected count increments collectively implying reduced quality of Intercept Platelets. In vitro testing of Intercept Platelets has also demonstrated degraded performance.^{3,4,5,6} This degradation has been reflected in the need to perform more and more frequent transfusions of PR-treated platelets.³ These characteristics were summarized and published by the agency in the FDA Summary of Safety and Effectiveness Data (SSED) for the Intercept Blood System for Platelets.³ In addition, the FDA has required that a phase 4 study be completed due to the concern of an increased incidence of Acute Respiratory Distress Syndrome from PR platelets. Intercept treatment adds significant direct costs to product manufacturing.⁷

Pathogen reduction does not extend dating beyond five days at present, though the guidance contemplates that if it is ever approved for that indication, PR platelets should be retested with a “safety measure” on days 6-7 to extend their dating.

Excerpt from the FDA SSED for Intercept Platelets⁸

2.3 Analyses of Secondary Endpoints

The outcome of the following secondary endpoints were all statistically significant and against the Test platelets.

Secondary Endpoints with Statistically Significant Differences between Treatment Groups

Secondary Endpoints	Test (n=318)	Reference (n=327)	p value
Mean Days of Grade 2 bleeding	3.2	2.5	0.023
Mean Days between transfusion	1.9	2.4	< 0.001
Mean number of platelet transfusion per subject	8.4	6.2	< 0.001
Mean CI at 1 hour ($\times 10^9/L$)	21.4	34.1	< 0.001
Mean CCI at 1 hour ($\times 10^3/L$)	11.1	16.0	< 0.001
Mean CI at 24 hour ($\times 10^9/L$)	13.2	21.5	< 0.001
Mean CCI at 24 hours	6.7	10.1	< 0.001
Clinical platelet refractoriness (%)	21.4	7.0	< 0.001

FDA RECOMMENDATIONS FOR DAY SIX AND DAY SEVEN PLATELETS

The current Code of Federal Regulations contains the following in 21 CFR 610.53(c) for the permissible duration of platelet storage: “72 hours from time of collection of source blood, provided labeling recommends storage at 20 to 24 deg. C or between 1 and 6 deg. C, or as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluation and Research.” In reality, the directions for use of the cleared or approved devices determine the allowable storage duration. Also, supplies and reagents, including bacterial detection devices and platelet storage containers, must be used in a manner consistent with the instructions provided by the manufacturer (21 CFR 606.65(e)). Until recently, this is what has established the limit on platelet shelf life at five-days.

Due to recent FDA product clearances the current maximal dating period for platelets in the U.S. is now as long as seven days in certain storage containers as long as specific conditions are met. In this regard, the draft guidance, in Section VIII, outlines a single pathway for immediate implementation to extend the dating period of platelets for up to seven days for apheresis platelets that have undergone primary bacterial culture testing. This pathway is in fact currently available independent of final guidance. Dating may be extended if: 1) the platelets are

collected in FDA-cleared or approved seven-day platelet storage containers with labeling (i.e., package insert) that requires testing every product with a bacterial detection device cleared by FDA and labeled for use as a “safety measure” and 2) the platelets are subsequently individually tested for bacterial detection using a “safety measure”, according to its instructions for use. The only device labeled as a “safety measure” is the Verax PGD® test.

The draft guidance notes that the one-time use of an FDA-cleared rapid bacterial detection device labeled as a “safety measure” (i.e. the PGD® test) could support an extension of dating up to 24 hours following the test, and not exceeding the seven-day expiration date of leukocyte reduced apheresis platelets that had tested negative by early culture.

The FDA states that its current review practice is to permit labeling of tests for bacterial detection in platelets for transfusion as a “safety measure” when clinical studies have shown that there is a benefit for detection of contamination not revealed by previous bacterial testing and where clinical specificity was determined. As noted, to date only the PGD® test from Verax has been awarded the “safety measure” labeling claim, since the post-marketing study by Jacobs et al. definitively met these criteria.⁹

PGD Indications for Use relevant to 7-day platelet dating¹⁰

B. INDICATIONS FOR USE

The Platelet PGD Test is a rapid, qualitative immunoassay for the detection of aerobic and anaerobic Gram-positive and Gram-negative bacteria in

- leukocyte reduced apheresis platelets (LRAP) suspended in plasma, LRAP suspended in Platelet Additive Solution C (PAS-C) and plasma, and pre-storage pools of up to six (6) leukocyte reduced whole blood derived platelets suspended in plasma, within 24 hours prior to platelet transfusion as a safety measure following testing with a growth-based quality control test cleared by the FDA for platelet components and

Seven-day storage containers are available from TerumoBCT, Inc. and Fresenius Kabi USA LLC. The Amicus Separator System (Fresenius) was cleared by the FDA on 20 July 2015 (BK 150242)¹¹ through a labeling modification to revise the current statement in the AMICUS Operator’s Manual and the Apheresis Kits’ Instructions for Use for “Platelets Pheresis Leukocytes Reduced in 100% plasma” to permit seven-day storage. The PL2410 plastic container used for collection was previously cleared for storage of platelets for up to seven days under BK040059 (09/24/04)¹². The Trima Accel® System (TerumoBCT) labeling change was cleared on 29 July 2015 (BK150269)¹³ for “Platelets Pheresis, Leukocytes Reduced” to permit seven-day storage in 100% plasma. The ELP plastic container used for collection was previously cleared under BK040086 (03/15/2005)¹⁴. These storage containers represent virtually the entire US apheresis platelet inventory and have been broadly used since their FDA clearance and introduction. For each of the above clearances, platelet storage beyond five days requires the use of a bacterial detection device labeled for use as a “safety measure”. Note that the seven-day storage clearance for each manufacturer is for apheresis platelets in 100% plasma. Platelet additive solutions are not included in the clearances though it should be noted that these are estimated to represent no more than 5% of the US apheresis platelet inventory.

In the draft guidance the FDA states that culture-based bacterial detection devices labeled as a “safety measure” for the extension of dating beyond day five are not currently available. In addition, FDA states that pathogen reduction systems may not be used to store platelets beyond day five at this time. Also, currently no platelet storage containers have been cleared or approved by FDA to store pre-storage pooled platelets for up to seven days. Shelf-life of this product is limited to five days. Additionally, post-storage platelet pools must be transfused within four hours so no extension of dating is possible. Rapid tests are not cleared at present for testing single units of whole blood-derived platelets.

The guidance also states that apheresis platelets remaining in inventory on day four and day five that are intended for extended storage through day seven, may be shipped to a blood collection establishment for secondary testing using a “safety measure” test (i.e. the PGD[®] test) and then re-issued to transfusion services provided the product was collected in an FDA-cleared or approved seven-day platelet storage container.

SUMMARY AND DISCUSSION

In its revised draft guidance released March 14 2016, the FDA has outlined its recommendations for reducing the risk of bacterial contamination in all platelet types currently transfused in the United States. Further, it has removed the option included in the first version of the draft guidance for transfusion services to make no change in their practices if they are not at present in compliance with the recommendations in the revised draft.

Most significantly, these recommendations focus upon implementing measures to reduce the risk of bacterial contamination of day four and day five platelets and offers two options for doing so. One option is to test a day four or day five platelet with a rapid test within 24 hours of transfusion with the added opportunity to extend platelet dating to seven days with a “safety measure” test. At present, the PGD[®] Test is the only test that satisfies both of these criteria. Use of the test to enhance patient safety on Day 4 and Day 5 platelets as well as to extend dating to day seven will likely result in savings which will more than cover all testing costs. The other option is the use of five day dated pathogen reduced platelets that are not tested for bacteria. Converting to pathogen reduced platelets will likely incur significant added cost, reflected not only in the treatment process itself but also the need for increased platelet transfusions.

Ultimately, the choice between these two approaches extends beyond simple economics; it is a choice between two fundamentally different approaches with significantly different implications for the management of patient risk. Pathogen reduction alters and degrades all platelets in order to inactivate the approximately one platelet unit out of every 2,000 to 3,000 that is actually contaminated with significant titers of bacteria. Rapid Testing (e.g. testing with PGD[®]) simply discards contaminated units without any degradation of the function or efficacy of the transfused platelet inventory itself.

While draft guidance is not binding, it is a strong and useful signal of what final guidance is likely to contain.

¹ US Food and Drug Administration. Bacterial Detection Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf>

² Benjamin, Richard, Blood Products Advisory Committee, September 21, 2012, transcripts accessible at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM325690.pdf>

³ Summary of Safety and Effectiveness Data (SSED) for Pathogen Reduction System for Platelets. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM431243.pdf>

⁴ McCullough J1, Vesole DH, Benjamin RJ, et al. Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. *Blood* 2004;104(5):1534-1541

⁵ Snyder E, Raife T, Lin L, et al. Recovery and life span of 111indium-radiolabeled platelets treated with pathogen inactivation with amotosalen HCl (S-59) and ultraviolet A light. *Transfusion* 2004;44:1732-1740

⁶ Ramsey G. Hemostatic efficacy of pathogen-inactivated blood components. *Semin Thromb Hemost* 2016;42:172-182

⁷ Webert KE, Cserti CM, Hannon J, et al. Proceedings of a Consensus Conference: pathogen inactivation-making decisions about new technologies. *Transfus Med Rev.* 2008; 22:1-34.

⁸ SSED. *Op. cit.*

⁹ Jacobs MR, Smith D, Heaton WA et al. Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test. *Transfusion* 2011;51:2573-2582

¹⁰ <http://www.veraxbiomedical.com/pdf/US-PLatelet-PGD-Test.pdf>

¹¹ Premarket Notification BK150242 clearance information. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm458040.htm>

¹² Premarket Notification BK040059 clearance information. Available at: <http://www.fda.gov/downloads/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/substantiallyequivalent510kdeviceinformation/ucm069849.pdf>

¹³ Premarket Notification BK150269 clearance information. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm458349.htm>

¹⁴ Premarket Notification BK040086 clearance information. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm076628.htm>