Implementing 7 Day Platelet Dating with the Platelet PGD® Test

Paul D. Mintz, M.D., Chief Medical Officer, Verax Biomedical Incorporated

The Verax Biomedical Platelet Pan Genera Detection (PGD®) Test is a rapid, qualitative immunoassay for the detection of aerobic and anaerobic Gram-positive and Gram-negative bacteria in platelet components. It is the only device that has been cleared by the FDA as a "safety measure". Currently, the PGD test is the sole means for extending the expiration date of apheresis platelets in plasma for up to seven days when using approved containers.[1] An apheresis platelet may be transfused for up to 24 hours after a non-reactive test.[2]

Readers should note that platelets produced with pathogen-reduction technology or platelets only cultured with FDA-cleared devices are not approved for extending storage beyond five days. The efficacy of platelets stored for seven days is addressed in a separate White Paper (WP002) and has been shown to not be different than a platelet stored for five days. The PGD test also helps to assure the safety of transfused five-day dated platetlets.[1] This White Paper addresses the implementation of the PGD test in a hospital blood bank or transfusion service.

PGD TESTING FREQUENCY

It is important to note that platelets do not need to be repeatedly tested on storage days 4, 5, 6, and 7. They need only be tested once within 24 hours of transfusion. Both the March 2016 FDA Draft Guidance addressing bacterial risk control strategies to enhance the safety and availability of platelets for transfusion[1] and the Platelet PGD test package insert[2] make this clear. Hospital staff may identify those platelets likely to be used on a specific day and test only those. If a component is not transfused within 24 hours, it only needs to be retested within 24 hours of use. With this practice, experience at many institutions has shown that the vast majority of platelets are tested only one time, even if stored for 7 days.

TRAINING

Verax Biomedical Technical Support provides installation and customized on-site training by full-time employees of the company. Training is not sub-contracted. Training sessions last approximately 1.5-2 hours and can include up to four technologists per session. Train-the-trainer sessions and quizzes are also offered. Training checklists are provided. Color-coded, step-by-step, laminated work instructions describing how to run controls and how to process a platelet sample are given to the customer to use as a job aide.

Product for Verax training sessions is provided at no charge and any remaining product is left with the customer to assist in their validation process or training of remaining staff.

Familiarization panels are provided by Verax for use during training. The 10-member panel contains blind-coded tubes that contain different strains of bacteria or saline in each tube. Platelets from a non-reactive unit are added to each tube. The panel allows a new user to see what results may look like when testing a reactive platelet and also demonstrates varying line intensities as well as non-reactive results.

"Competency devices" are also provided as a training aid. These are mock devices showing reactive results of varying intensities to assist technologists in identifying reactive results and distinguishing them

from results from non-reactive samples. They may be used to assist in assessing competency throughout the year. Certificates of competency and/or train-the-trainer certificates are provided to everyone Verax trains.

Consultation on integrating PGD into laboratory workflow is available in advance of as well as after training.

VALIDATION

A bacteria panel is available from ZeptoMetrix, Buffalo, NY (http://www.zeptometrix.com/) (part number 0820000). This panel is a 12-member, frozen panel comprising 2 negatives, 5 Gram-positives and 5 Gram-negatives. When reconstituted with platelets, each tube contains sufficient volume for two tests. Platelet units used for reconstitution can be up to 7 days post-collection. The panel is also available from Fischer Scientific, Pittsburgh, PA (https://www.fishersci.com/us/en/home.html). These may be ordered as part number 22-156-706 or under the Zeptometrix part number.

QUALITY CONTROL

Platelet PGD Controls can be ordered directly from Fenwal Inc., a Fresenius Kabi company, Lake Zurich, IL (http://www.fenwalinc.com/Pages/Home.aspx) (part number P30C) or by calling 1-800-333-6925. There is a positive and a negative external control in the set. The Control vials contain sufficient volume to generate 30 positive and 30 negative test results.

An Internal Quality Control Plan (IQCP) template is available upon request from Verax to assist a customer in performing a risk assessment in order to run external controls less frequently than CLIA requirements (i.e., daily). Users are required to run external PGD Controls when they receive a new shipment, start a new lot, or train a new technologist and as specified in their own SOP. More information from CMS about IQCPs is available at https://www.cms.gov/regulations-and-guidance/legislation/CLIA/Individualized_Quality_Control_Plan_IQCP.html

In addition to performing periodic quality control testing, every PGD test device has internal "Procedural Control" windows on both ends of the device. These windows change color from yellow to a blue-purple to indicate that each test is valid.

PROFICIENCY TESTING

Proficiency testing material is available through the College of American Pathologists (CAP). CAP offers 2 different Proficiency Panels – a 2-member and a 5-member set (order code BDPV or BDPV5). The product description can be found and orders can be placed by searching the CAP web site (www.cap.org) for BDPV and BDPV5.

The catalog states:

- The Centers for Medicare and Medicaid Services (CMS) requires proficiency testing for bacterial detection in platelets.
- Survey BDPV is designed for donor centers/laboratories that are associated with a CMS-certified microbiology laboratory with the same CLIA number and are participating in an approved proficiency testing program for bacterial detection.

- Survey BDPV5 is designed for donor centers/laboratories that are performing bacterial detection for the purposes of platelet unit screening and are not associated with a CMS-certified microbiology laboratory with the same CLIA number

INFORMATION TECHNOLOGY

A system or process will need to be designed to implement outdate extension within 24 hours of PGD testing to allow for accurate relabeling and product release. Sites may need to configure their laboratory information system (LIS) to enable product code modification and relabeling using the new E-codes (see below) after testing is completed. Consideration must be taken to assure that all products outdate within 24 hours of testing and no later than at the end of Day 7.

REGISTRATION

The March 2016 draft guidance states that "except as provided in 21 CFR 607.65, all owners and operators of blood establishments that engage in the manufacture of blood products are required to register with FDA and list the blood products they manufacture, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act and the implementing regulations under 21 CFR 607.7(a)."[1] The FDA considers the use of a bacterial detection device to re-label any platelet product with a six- or seven-day expiration date as a manufacturing procedure requiring registration and product listing, as described in 21 CFR 607.3(d). Note that services that are irradiating blood components at present are already registered, as FDA considers blood component irradiation as manufacturing. Importantly, transfusion services that perform secondary testing on platelets with a five-day expiration date are **not** required to register and list for this testing because they are not extending the dating period of platelet components. It is the relabeling and extension of dating that are manufacturing steps requiring registration and listing. If an institution is already registered or licensed with the FDA, the only regulatory action they need to take is to amend/update the existing license/registration.

If a transfusion service is currently not registered with the FDA and chooses to extend platelet dating beyond 5 days, it must register with the FDA and update its product listing. Registering or updating an existing registration and product listing may be done online and is a very straightforward and quick process. FDA recommends that the service record that it is performing bacterial detection testing on platelet products in the "Other" field in the Products section of the registration form.

General information on the FDA registration process is available at:

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/BloodEstablishmentRegistration/default.htm

The log in to register is available at:
https://www.accessdata.fda.gov/scripts/cber/CFApps/Login/Index.cfm?CFID=14371273&CFTOKEN=3bf68105249a55d0-A85D0D0F-1372-5AE1-674338933A9DF71D

The registration form (Form 2830-Electronic Blood Establishment Registration and Product Listing Form) is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082389.pdf

Instructions for filling out Form 2830 are available at:

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/BloodEstablishmentRegistration/ucm055484.htm

AABB STANDARDS

The 30th edition of the AABB Standards for Blood Banks and Transfusion Services has incorporated permissibility for extending platelet storage beyond five days. Revised Standard 5.1.8A permits Apheresis Platelets Leukocytes Reduced to have a seven-day expiration if storage containers are cleared or approved by FDA for seven-day platelet storage and "labeled with requirements to test every product stored beyond five days with a bacteria detection device cleared by FDA and labeled as a "safety measure"."[3]

AABB Association Bulletin #16.05 also addresses this change.[4] The Bulletin states, "This revised expiration timeframe is consistent with the recent availability of FDA-cleared or -approved safety measures and collection/storage bags that allow for an outdate of seven days for Apheresis Platelets Leukocytes Reduced. Currently culture-based bacterial detection devices labeled as a "safety measure" for the extension of dating beyond Day 5 are not available. Facilities planning to extend the outdate for this component should contact their FDA consumer safety officer to ensure they are using the appropriate implementation route/reporting category."[4]

OPERATIONS

Verax Biomedical provides customers with draft SOPs as starting points to facilitate sites writing their own SOPs. Worksheet templates for non-reactive and reactive samples are also provided. PGD testing must occur within 24 hours prior to transfusion. For some services, testing during the night shift will be preferable so that PGD tested units expire at or near midnight. Other institutions have chosen to implement testing throughout the day to ensure units are always available and distribute the workload across shifts. Fifty (50) hospital transfusion services that utilize the Platelet PGD Test were selected randomly and contacted by Verax staff. All 50 implemented and performed PGD testing with existing staff. 98% said PGD testing was easier to perform or similar to other tests run in their laboratory.[5] To date, no institution performing PGD testing routinely has had to hire additional staff for this purpose. In fact, Dunbar et al. implemented testing of every platelet in inventory without the need for additional staffing.[6]

The necessary changes to an institution's LIS may be performed by information technology staff as part of their routine support functions, so that there are likely no or minimal external costs associated with updating the LIS. There are no extra costs associated with implementing the necessary E-codes (see below). While FDA registration is required to relabel and extend platelet outdates, as described above, no variance application is necessary. Dunbar reported the outdate rate at her institution has decreased from 5% to 1% since the formal implementation of routine use of Day 6/7 platelets.[7]

Operational matters will be the subject of a future White Paper.

LABELING

Extending the expiration date of a blood component requires relabeling with the new expiration date and time. The use of the Platelet PGD test to extend platelet expiration and thereby require relabeling is a manufacturing step that also requires registration with the FDA, as noted above. The institution's circular of information should be updated to include an insert stating that Day 6 and Day 7 platelets have undergone rapid testing to enable outdate extension. One approach could be to use language such as: "All apheresis platelet products have been tested no earlier than 24 hours after collection using an FDA-cleared culture-based bacterial detection device. Platelets transfused on Day 6 or Day 7 have

undergone secondary testing as a safety measure within 24 hours of dispense to detect bacterial contamination."[7]

21CFR 606.121c(4)(i) states that the container label must include the expiration date, including the day, month, and year, and if the dating period for the product is 72 hours or less the hour of expiration. Further, The FDA draft guidance states that following secondary testing FDA recommends that a site maintain a labeling process that relays the following information and is integral to the container (e.g., on the container label or an attached tie-tag): the type of bacterial detection test that was performed (rapid or culture test) and the date and time the bacterial detection test was performed.

The new date and time may be handwritten. The Code of Federal Regulations does not require the outdate to be machine readable. The following information must be machine-readable: (A) A unique facility identifier; (B) Lot number relating to the donor; (C) Product code; and, (D) ABO and Rh of the donor. 21 CFR 606.121(c)(13)(iii).

The International Council for Commonality in Blood Banking Automation (ICCBBA - https://www.iccbba.org/home) Information Standard for Blood and Transplant (ISBT) 128 E-code database has not, until recently, contained codes specifically created for the extension of platelet component outdate times using rapid testing. Multiple hospitals have requested and have been provided day 6 and/or day 7 codes for irradiated and non-irradiated platelet units. These codes have been available in the ICCBBA database since August 1, 2016 and examples are listed below. Additional codes for products can be requested from ICCBBA. ICCBBA states that codes created from existing attributes are generally available within 1 month of request. The ICCBBA code request form is located at https://www.iccbba.org/subject-area/blood-transfusion/product-description-request-code-form-blood-actual.

Multiple product codes have been approved by ICCBBA for extension of dating. Below are examples of approved platelet product codes currently in use for this purpose. Please check with ICCBBA for the correct code usage for your institution.

IRRADIATED PLATELETS:

Day 6:
E8595 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|3rd container|Bacterial test
E8596 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|2nd container|Bacterial test
E8597 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|1st container|Bacterial test
E8598 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|Bacterial test

Day 7:
E8642 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|2nd container|Approx 300 E9 plts|Bacterial test
E8643 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|1st container|Approx 300 E9 plts|Bacterial test
E8644 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|Approx 300 E9 plts|Bacterial test
E8645 Apheresis PLATELETS|ACD-A/XX/20-24C|Irradiated|ResLeu:<5E6|3rd container|Approx 300 E9 plts|Bacterial test

Day 6:
E5073 = apheresis platelets, irradiated, leukoreduced, plts 3XE11, bacterially monitored
E5532 = apheresis platelets, irradiated, leukoreduced, plts 3XE11, bacterially monitored , 1st container
E5533 = apheresis platelets, irradiated, leukoreduced, plts 3XE11, bacterially monitored , 2nd container
E5534 = apheresis platelets, irradiated, leukoreduced, plts 3XE11, bacterially monitored , 3rd container

Day 7:
E5034 = apheresis platelets, irradiated, leukoreduced, bacterially monitored
E5035 = apheresis platelets, irradiated, leukoreduced, bacterially monitored , 1st container
E5036 = apheresis platelets, irradiated, leukoreduced, bacterially monitored , 2nd container
E5037 = apheresis platelets, irradiated, leukoreduced, bacterially monitored , 3rd container

NON-IRRADIATED PLATELETS:

Day 7:
E8815 – Apheresis PLATELETS|ACD-A/XX/20-24C/ResLeu:<5E6|Approx 300E9 plts|Bacterial test
E8816 - Apheresis PLATELETS|ACD-A/XX/20-24C/ResLeu:<5E6|1st container|Approx 300E9 plts|Bacterial test
E8817 - Apheresis PLATELETS|ACD-A/XX/20-24C/ResLeu:<5E6|2nd container|Approx 300E9 plts|Bacterial test
E8818 - Apheresis PLATELETS|ACD-A/XX/20-24C/ResLeu:<5E6|3rd container|Approx 300E9 plts|Bacterial test

Day 6 and Day 7:
E8761 Apheresis PLATELETS|ACD-A/XX/20-24C|ResLeu:<5E6|Bacterial test
E8762 Apheresis PLATELETS|ACD-A/XX/20-24C|ResLeu:<5E6|1st container|Bacterial test
E8763 Apheresis PLATELETS|ACD-A/XX/20-24C|ResLeu:<5E6|2nd container|Bacterial test
E8764 Apheresis PLATELETS|ACD-A/XX/20-24C|ResLeu:<5E6|3rd container|Bacterial test

Standardization of the labeling process has not yet been defined by organizations such as AABB.

Some hospitals have chosen to use the same product code for days 6 and 7 or different codes.

Some hospitals have elected not to change product codes at all. Rather, they add a label to each bag indicating they are extending the expiration date after testing with a safety measure and place a sticker on the bags with PGD tested Date and Time. They also change the outdate on the printed face labels.

PLASMA VOLUME REQUIREMENTS FOR EXTENDING PLATELET SHELF-LIFE

Platelets collected in Trima (Terumo BCT) bags and Amicus (Fresenius) bags have both received FDA approval to extend dating to 7 days. The efficacy of 7 day platelets is discussed in White Paper WP002.

Apheresis platelets in 100% plasma in Terumo BCT bags do not have a plasma volume requirement for extending storage through 7 days. Therefore, any apheresis platelet suspended in plasma in a Terumo storage container is eligible for dating extension to 7 days with safety measure testing.

The Fenwal Amicus Separator System allows for flexibility to adjust the storage fluid volume collected to maximize collection efficiency. For Platelets Pheresis, Leukocytes Reduced in 100% plasma collected with the Amicus, depending on the number of platelets in the container, a minimum storage fluid volume, including ACD, is required to support the platelets and to maintain a pH >6.2 in order to extend shelf-life through 7 days. Fresenius Kabi has developed a reference guide to help define if the component volume meets the minimum storage fluid volume requirement to qualify for extended storage through 7 days. This Guide is reproduced in Appendix 1 of this report.

In general, if the number of platelets in the unit is in the range of $3.0 – 4.7 \times 10^{11}$, AND the storage fluid volume of the unit is 255mL or higher, a platelet unit meets the volume qualification for a shelf-life of up to 7 days. Should a platelet unit contain a volume of less than 255mL, or contain fewer than 3.0×10^{11} or more than 4.7×10^{11} platelets, a table is provided in the Guide that specifies if the apheresis platelet unit meets the volume requirement for an extended shelf-life of up to 7 days.

The Fresenius and Terumo BCT bags that are cleared for 7-day storage are pictured in Appendix 2 of this report.

CUSTOMER SUPPORT

For technical support contact Verax Biomedical at vts@veraxbiomedical.com or call 508-688-2992 or 425-736-9392. To place an order an existing customer should contact Fenwal Customer Service at 800-333-6925.

SUMMARY AND CONCLUSION

Implementation of seven-day dating of apheresis platelets is readily feasible at this time. Favorable cost/benefit calculations have been reported, although each institution should perform its own analysis.[6] PGD testing provides cost-savings and enhances safety while reducing the platelet outdate rate, increasing inventory, improving management of rare components, and helping to assure therapeutic use of the donor's gift.

REFERENCES

1. US Food and Drug Administration. Bacterial Risk Control Strategies for 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. http://www.veraxbiomedical.com/pdf/US-PLatelet-PGD-Test.pdf

3. Standards for Blood Banks and Transfusion Services. 30th ed. 2016. AABB. Bethesda.

4. Regan D, Markowitz M. Changes to the 30th edition of Standards for Blood Banks and Transfusion Services. AABB Bulletin #16-05. Available at: http://www.aabb.org/programs/publications/bulletins/Documents/ab16-05.pdf

5. Hornbaker N, Rasmusson P, Lee W, Sanders J. Pan Genera Detection (PGD®) Testing for Bacteria in Platelets at 50 US Institutions. Transfusion 2012;52(S):206A.

6. Dunbar NM, Dumont LJ, Szczepiorkowski ZM. How do we implement Day 6 and Day 7 platelets at a hospital-based transfusion service? Transfusion 2016; 56:1262-1266.

7. Dunbar N. AABB Audioconference handout. April 27, 2016.

Appendix 1

FRESENIUS KABI

Platelets Pheresis, Leukocytes Reduced stored in 100% plasma manufactured with the Fenwal Amicus Separator may qualify for an extended shelf-life of up to 7 days.

A check of the platelet unit volume allows the end user to quickly determine if a Platelet Pheresis, Leukocytes Reduced unit stored in 100% plasma qualifies for an extended shelf-life of up to 7 days, provided it tests negative with a bacterial detection device cleared as a safety measure as described in the draft version of the Bacterial Testing draft guidance by FDA.[1]

In general, if the *Number of Platelets* in the unit is in the range of **$3.0 – 4.7 \times 10^{11}$**, **AND** the *Minimum Storage Fluid Volume* of the unit is **255mL or higher**, a platelet unit meets the volume qualification for a shelf-life of up to 7 days* (**Table 1**). Should a platelet unit contain a volume of less than 255mL, or contain less than 3.0×10^{11} or more than 4.7×10^{11} platelets, refer to **Table 2** to determine if the apheresis platelet unit meets the volume requirement for an extended shelf-life of up to 7 days*.

Table 1:

Number of Platelets ($\times 10^{11}$)	Minimum Storage Fluid Volume (mL) Including ACD pH ≥ 6.2	Meet Criteria
< 3.0	-	Refer to Table 2
3.0 – 4.7	**≥ 255mL**	**Acceptable**
3.0 – 4.7	< 255mL	Refer to Table 2
> 4.7	-	Refer to Table 2

Example 1: If a platelet unit manufactured with the Fenwal Amicus Separator contains 3.7×10^{11} platelets and has a volume of 243ml (*minimum* storage fluid volume required for 7 day storage is **239mL**, see Table 1), the shelf-life of the unit can be extended to 7 days if tested negative with a bacterial detection device cleared as a safety measure, since the minimum storage fluid volume requirement of 239mL is met.

Example 2: If a platelet unit manufactured with the Fenwal Amicus Separator contains 3.4×10^{11} platelets and has a volume of 221mL (minimum storage fluid volume required for 7 day storage is **230mL** see Table 1), this unit does not qualify for an extended shelf-life of up to 7 days, and is limited to a shelf-life of up to 5 days

[1] Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion, Draft 03/2016, available online at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf (last visited July 28, 2016).

Appendix 1 (continued)

TABLE 2: Amicus Platelets Pheresis, Leukocytes Reduced stored in 100% plasma minimum storage fluid volume to extend shelf-life of up to 7 days*

Number of Platelets ($\times 10^{11}$)	Minimum Storage Fluid Volume (mL) Including ACD pH ≥ 6.2	Number of Platelets ($\times 10^{11}$)	Minimum Storage Fluid Volume (mL) Including ACD pH ≥ 6.2
2.3	180	4.4	252
2.4	185	4.5	253
2.5	191	4.6	254
2.6	196	4.7	255
2.7	201	4.8	370
2.8	205	4.9	382
2.9	210	5.0	382
3.0	214	5.1	392
3.1	219	5.2	392
3.2	222	5.3	402
3.3	226	5.4	402
3.4	230	5.5	410
3.5	233	5.6	410
3.6	236	5.7	420
3.7	239	5.8	420
3.8	241	5.9	428
3.9	244	6.0	428
4.0	246	6.1	438
4.1	248	6.2	438
4.2	250	6.3	444
4.3	251	6.4	444

* Platelets Pheresis, Leukocytes Reduced may be stored in the platelet storage container(s) for up to 7 days at 20°C to 24°C with continuous agitation. The Amicus platelet storage container is cleared to store Platelets Pheresis, Leukocytes Reduced in 100% plasma for up to 7 days. Additionally, for platelet units stored past 5 days and through 7 days, every product must be tested with a bacterial detection device cleared by FDA and labeled as a "safety measure."

References:

- Amicus Separator Operator's Manual Section A.5

Appendix 2

How to Identify Terumo Trima and Fenwal Amicus Storage Containers

- **Terumo Trima**

Shoulders are squared

Clamp is dark blue

Port to spike is on right

- **Fenwal Amicus**

Shoulders are rounded

Port to spike is in center

Clamp is light blue