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American Red Cross

March 13, 2019

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted via http://www.regulations.gov

Re: Docket No. FDA–2014-D-1814, "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion" Draft Guidance, December 2018

Dear Dockets Manager:

AABB, America's Blood Centers (ABC) and the American Red Cross (ARC) are jointly submitting comments to the Food and Drug Administration (FDA) on the December 2018 Draft Guidance, "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion services to Enhance the Safety and Availability of Platelets for Transfusion" (the 2018 Draft Guidance). Members of the AABB's Transfusion Transmitted Diseases Committee, and representatives from ARC and ABC have prepared these comments.

In April 2017, we provided comments to the FDA including additional important information intended to reinforce positions stated in our May 2016 comments. This information was intended to identify specific critical concerns important to both blood collection establishments and transfusion services and to alert FDA to adverse, unintended consequences expected to impact the blood supply and, ultimately, patient care. At the July 2018 Blood Products Advisory Committee (BPAC) meeting, the agency discussed the scientific evidence and operational considerations of all available strategies to control the risk of bacterial contamination of platelets with 5-day and 7-day dating, including testing strategies using culture-based devices, nonculture-based rapid bacterial detection devices, and the implementation of pathogen reduction technology (PRT). We presented a statement at the meeting, to assist FDA in evaluating the multiplicity of effective approaches that are available to enhance the safety of the blood supply. The allowance for multiple approaches balances the need to improve safety with economic and logistical considerations that may influence decision-making in different institutions.

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We have heard from diverse members that these 2018 Draft Guidance recommendations will challenge the blood community. Our comments in this document address complex issues in a manner that fully represents the diverse perspectives within our memberships. Many members are concerned that the contents of this draft guidance, while contributing to bacterial safety, may adversely affect platelet availability (in contrast to its title) due to increased outdates related to a shortened usable platelet shelf life inherent in some strategies, platelet loss inherent in enhanced culture-based options and an adverse effect on the ability to move platelets from hospital to hospital to maximize use and minimize outdating. We believe the agency is responsible for analyzing those concerns with a formal risk assessment before finalizing a Guidance and stand ready to facilitate that effort.

With the understanding that the docket remains open for a draft guidance, we will submit additional comments at a later date, if necessary.

We have the following comments on the 2018 Draft Guidance.

COMMENTS

COMMENTS 1 - 5 are general comments.

Comment 1: These general comments are consistent with our July 2018 Joint Statement before BPAC:

"While calibrating our efforts to enhance platelet bacterial safety is intrinsically difficult without an *a priori* threshold level of tolerable risk, we strongly endorse providing multiple options based on both demonstrable enhanced safety and operational considerations for collection facilities and hospitals across the US, dependent on their ability to implement one or more allowable interventions."

Comment 2: Timeframe for implementation

We support implementation of additional bacterial risk control strategies to enhance transfusion safety. However, we also recognize the many factors that could delay a fully current Good Manufacturing Practice (cGMP) compliant implementation for some facilities, including those captured in Comment 3, that may not be anticipated. Some members predict additional time will be needed for implementation, particularly if the immediate use of computer control of labeling functions is desired as a cGMP approach. Some members have suggested the agency consider an 18-month implementation, recognizing that many institutions will be able to move more quickly.

Comment 3: Impacts of implementation.

Our members shared a variety of comments on the impact of implementation on all stakeholders. They highlight changes in the relationship between hospital transfusion services and their blood suppliers inherent in this draft. More than any prior issue, the relationship between blood collection facilities and transfusion services is important to any risk mitigation strategy necessary to improve the bacterial safety of platelets while maintaining an adequate supply. Collection facilities have worked to provide ready to use components requiring no or minimal manufacturing steps to transfusion services. Some of the allowable strategies in this guidance depart from that model. Changes that include secondary testing, and at times serial secondary testing, changes in outdates and the resultant need for relabeling across a large proportion of a commonly used component are unprecedented challenges to many hospital transfusion services that are not paid adequate attention in the draft. Please consider the following comments that illustrate these concerns.

- The new recommendations blur historically clear lines of responsibility for infectious disease blood product safety that have relied on the blood provider.
- Transfusion services have been free to adopt processes that served their unique needs and those of their patients and the community. Over time, many pursued operational models that rely on blood suppliers for essentially all (especially cGMP compliant) manufacturing processes. New responsibilities for compliance that pull transfusion services further into manufacturing processes introduce unprecedented complexity to the hospital.
- Some blood suppliers and hospitals report that transfusion services will find the implementation of rapid testing burdensome, especially in small to medium sized hospital customers with low platelet transfusion rates. The personnel, training, equipment, and information technology adjustments required for compliance can result in major expenditures for some transfusion services. For example, hospitals that have implemented secondary point of release testing or secondary culture have not yet had to deal with changing the expiration date of Single Donor Platelets. Many current blood establishment computer systems (BECS) are not able to handle multiple changes of expiration dates and the manual alternative, tie-tags, will not prevent the issuance of an expired or quarantined product as effectively as computer control, and the sheer volume of platelet units that will be affected is a challenge.
- The American Hospital Association has been contacted and is working to address the concerns about hospital preparedness. These include staffing, training, equipment, information technology adjustments, budget impacts, etc. Healthcare facilities often face difficulties justifying a request to administrators for the increased costs for competing patient safety recommendations. Some hospital members report a struggle to justify funding when competing with patient safety initiatives for much more common causes of morbidity and mortality, e.g. healthcare associated infections, medication errors, falls, patient identification errors, *et al*. Additionally, adequate planning, training, validation and implementation of changes to both quality systems and BECS must be completed after final recommendations are released. The cumulative impact may be daunting. A flexible approach and generous timeline for effective implementation is important, and these budgetary implications, by themselves, require consideration.

Comment 4: Discussion of options and methods.

We have consistently requested multiple, flexible options to achieve compliance across our membership.

- We found a broad range of perspectives on effectiveness of certain options, as well as very diverse opinions on the justification of these risk control strategies. In the final guidance, we request that the agency provide a robust discussion of the evidence base. The basis for strategies ultimately found adequate to mitigate risk for bacterial sepsis from contamination of platelets, and those rejected at this time, must be clear to fully inform our stakeholders.
- Reduction of the rates of septic transfusion reactions (STR) is the appropriate benchmark for this safety evaluation and the inclusion of STR data, as opposed to the surrogate of reactive test rates. Why enhanced primary culture cannot obviate the need for secondary testing for 5-day dating, and its attendant complexities is not clear and the agency should make it explicit why not.

Comment 5: Risk modeling

A group of members were concerned that the clinical effects from reductions in platelet supply due to elements of the guidance may exceed the decrement in STRs and ask the agency to provide modeling of such tradeoffs. Again, FDA is responsible for an explicit risk assessment model. Minimal elements to be considered include loss of a proportion of split apheresis products because of increased inocula for culture inherent in both enhanced primary culture and large volume delayed sampling, and the inability to move

products from hospital to hospital under consignment if cGMP compliance for rapid testing cannot be assured.

Understanding what constitutes "tolerable" risk, would assist with the divergent opinions across the industry and better support implementation efforts. The subject of tolerable is being explored by the Advisory Committee on Blood and Tissue Safety and Availability.

COMMENTS 6 - 9 on *Section III. Table 1 Summary Table of FDA's Recommendations*

Recommendations to control the risk of bacterial contamination in platelets		
Dating	*Method*	*Applicable components*
5-day storage	*Primary culture + secondary culture (no earlier than Day 3)*	• *Apheresis* • *Pre-storage pools*
	Primary culture + secondary rapid testing	• *Apheresis* • *Pre-storage pools*
	Pathogen Reduction Technology	• *Apheresis*[3]
7-day storage	*Primary culture + secondary culture (no earlier than Day 4)*	• *Apheresis*
	Primary culture + secondary rapid testing	• *Apheresis*
	Large volume delayed sampling[4]	• *Apheresis*

Comment 6: Omission of the Minimal Proportional Sampling Volume (MPSV) Option

Some blood suppliers believe the MPSV option should be included, as an acceptable enhanced primary culture in the final recommendations. What was the basis for eliminating this option when direct *clinical* comparisons to secondary testing are not available?

Rationale: A complete discussion of the proposal for MPSV was submitted by Vitalant and will not be reiterated here.

- The prior BPAC vote supported inclusion of this option and current draft recommendations appear to reflect limited data presented at the July 2018 BPAC meeting, which did not include a formal vote. Inaccuracies have been noted by Vitalant in their comments from the presentation, as quoted from the FDA transcript, page 140:
  - Regarding the quote:
    "Changes to primary culture volumes and times have not improved detection rates."

    Statistically significant data generated at Vitalant presented at BPAC and published suggest that MPSV doubled detection rates over unenhanced primary culture (Transfusion 2017:57:2469-76). This incremental interdiction is indistinguishable from the corrected interdiction rate reported for secondary rapid testing (Transfusion 2011;51:2573-82).

  - Regarding the quote:

> "Secondary testing by a variety of methods has been proven to detect contaminated units missed by primary testing and considerably improve the safety of platelet transfusion, and FDA has given safety measure labels to two of these methods."

Given that FDA has not publicly shared a minimal acceptable level of increased safety it is difficult to compare the results from different mitigation methods. MPSV, doubled detection rates (from 0.9 to 1.83 per 10,000; $p<0.05$) and, while lower than those achieved in the Verax trial (3.26 per 10,000), a statistical test was not done to determine whether a significant difference between these interventions exists.

Comment 7. Enhanced primary culture (the use of "maximal" inocula in both of an aerobic and anaerobic culture bottle)

We support FDA's consideration of comments and data from multiple publications by ARC, which proposes that FDA allow blood establishments to perform enhanced primary culture testing using the upper limit of sample volume range for each an aerobic and an anaerobic culture strongly supporting the request for a 5-day shelf life, without a requirement for secondary testing. We refer FDA to those comments rather than risk misrepresenting their proposal.

Rationale: Again, we believe that all strategy options found acceptable to FDA should be included in final recommendations to best support the goals of the guidance and support implementation efforts.

Comment 8: Future applications for PRT and apheresis platelets

Footnote 3 (page 3, following Table 1) pertains to use of PRT with 5-day apheresis platelets and states:

> "*This strategy could apply to other platelet products in the future if appropriately labeled devices become available."*

This footnote should apply to all platelet products listed in the table to more easily permit the adoption of PRT as it becomes available for additional products.

Rationale: PRT use is likely to expand in the future. The recommendation should be in place for future use if manufacturers and blood collectors collect data and obtain FDA approvals for 7-day storage of whole blood-derived platelets and across cleared apheresis platforms.

Comment 9: Discrepancies in acceptable sampling times

Table 1 shows two minimum timeframes for secondary culture. For 5-day products, secondary culture is performed "no earlier than day 3." For 7-day platelets, recommendation III.D.1, secondary culture is recommended "no earlier than day 4." Please clarify the data supporting the difference in sampling time. While it is logical that a delay from day 3 to day 4 might increase detection of contamination from slow growing organisms, are there data that the increment in detection is worth additional complexity? Again, this is a question of tolerable risk thresholds.

Rationale: It is unclear why a primary culture of a product labeled for 7 days is adequate risk control for 4-5 days, while primary culture for a product labeled for 5 days is deemed adequate risk control for only 3-4 days.

COMMENTS 10 - 12 on *Section III.B. Primary Culture Testing*

Recommendation III.B. states:

This section provides information pertaining to recommendations for primary culture-based testing.

Culture-based primary testing should be performed no sooner than 24 hours after collection. Testing should include methods to identify both aerobic and anaerobic organisms. To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for each of the aerobic and anaerobic cultures. If you opt to sample a volume larger than the upper limit of the volume range described in the device's instructions for use for one culture, we recommend that the amount of the sample that is in excess of the upper limit volume recommended for use be inoculated into additional culture.

If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.

Comment 10: Aerobic and anaerobic culture

Regarding:
"Testing should include methods to identify both aerobic and anaerobic organisms."

Some members noted the background does not include an explanation for a requirement for aerobic and anaerobic cultures for primary but not secondary culture. Please clarify the goal of this recommendation to support effective implementation efforts.

Rationale: The 2018 Draft Guidance does not provide background information on the basis for this decision necessary to support compliance efforts.

Comment 11: Impact of recommending a 12-hour minimum incubation period.

Regarding:
"*If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours."*

Some members noted that this minimum incubation period may be too restrictive and have an unintended adverse impact, while other members routinely do this successfully. We suggest FDA guidance consider a minimum time period that explicitly includes incubation, labeling, and transportation that should elapse before transfusion. If such were to be allowed, blood establishments would be required to determine methods to document compliance.

Comment 12: Upper limit of sampling volume

Regarding:
"To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for each of the aerobic and anaerobic cultures."

In addition to recommending the upper limit of sample volume, we note FDA's intent to require sampling of each split product rather than sampling the mother bag prior to splitting the component. Please clarify the basis for the requirement to double standard volumes, regardless of mother bag volume.

Rationale: While we understand that variability in the level of contamination at inoculation means that one daughter may be contaminated and other(s) not when very low numbers of bacteria are involved, the clinical impact (number of STRs) of this phenomenon is likely minimal. The need to sample each daughter is operationally complex and the need to enter multiple bags separately may increase the probability of contamination from the process itself. It will increase the expense for kits (by requiring the integration of multiple sampling access sites—two for double and three for triples—instead of one on the mother bag), again with minimal clinical yield. Please justify this requirement in any risk modeling. Alternate strategies used to enhance the volume of primary culture, and thus achieve the same outcome, have been presented by ARC and Vitalant in their responses.

COMMENTS 13 - 21 on *Section III.C. 5-Day Platelet Storage*

Recommendation III.C.1. states:

> 1. ***Primary culture followed by secondary culture performed no earlier than Day 3***
>
> *This strategy applies to apheresis platelets and pre-storage pools and includes the following steps:*
>
> - *Initial primary culture (see section III.B of this guidance).*
> - *Secondary culture on Day 3 or Day 4.*
>
> *Secondary culture:*
> *To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for use, taken from the main collection, and inoculating the sample into an aerobic media. Use of an anaerobic culture, in addition to the aerobic culture, should be considered.*
>
> *If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend that you establish a minimum incubation time period in your Standard Operating Procedures (SOPs).*

Comment 13: Clarify sample volume for secondary culture

We suggest that the sample volume is most appropriately addressed in the package insert for the test system. We note that using the upper limit of the sample volume range permitted by the manufacturer equates to sampling approximately 10mL for an aerobic culture and 10mL for an anaerobic culture from each final storage container. Therefore, the total sample volume removed from original collection by primary plus secondary culture would be 80mL for a triple, 60mL for a double, and 40mL for a single, assuming aerobic and anaerobic cultures are used for both primary and secondary testing**.**

Rationale: Due to the large amount of volume loss incurred for bacterial contamination testing, this has potential to result in an increase of low yield platelets and a need for additional units. This risk also applies if only aerobic cultures are used for secondary testing.

Comment 14: Clarify sampling for secondary culture of split components

We request FDA clarify the goal for sampling of the "main collection" for secondary culture. It is unclear what bag is the "main collection." We have the following question:

- Does FDA consider the main collection to be the original collection container that is commonly referred to as the mother bag or parent bag? This container no longer exists after splitting and distribution, so this requirement is inconsistent with operations even in the unlikely event that the products are returned to an external supplier for secondary testing.

Rationale: Frequently, sampling of the mother/parent bag is not possible on day 3 or 4 because it is split into the separate components which are already distributed.

Comment 15: Clarify the platelet yield requirement following secondary culture.

If secondary culture is not performed by the Transfusion Service, please clarify if a platelet yield of $\geq 3 \times 10^{11}$ is required following secondary culture for blood center (re)labeling. We have the following questions if the yield is $\geq 3 \times 10^{11}$ at product creation prior to day 3. It seems inappropriate to hold the blood center to a higher performance standard than the Transfusion Service after secondary culture.

- How should blood centers document the pre-secondary sampling content if they choose not to label products until day 3?
- How should a blood center indicate to the Transfusion Service that a secondary culture has been performed if all units are labeled with a 5-day expiration?

Please clarify FDA's expectations on this because sampling for secondary testing of each split component will decrease the yield potentially requiring relabeling as a Low-Yield platelet unit.

Rationale: The guidance does not specify how transfusion services could perform secondary culture and accurately determine product yield after removal of samples. Blood establishments would need to label all platelet products with the yield to allow Transfusion Service to recalculate yield, or the transfusion service would need to determine the platelet yield, adding additional complexity. Such activities could be considered further manufacturing that would require the transfusion service to register as a blood establishment. Changing labeling specifications, such as labeling all products with platelet yield, would have broad operational impact.

To avoid product discard due to low yield, blood establishments would need to adjust split volumes to account for anticipated large volume sampling needed for secondary culture, further reducing platelet availability mainly by reducing the number of collections qualifying to produce triples and doubles.
It is also unclear whether routine monthly platelet yield quality control acceptance criteria could be met if secondary testing is implemented. Failure of routine monthly quality control would trigger unnecessary investigations for corrective action. It is unclear whether a separate platelet yield quality control data set for secondary-tested platelets that would avoid this issue is allowed in the draft guidance.

Comment 16: Determining expiration and inventory control

Please clarify the following questions which frame the challenges of differing processes and relationships between blood suppliers and their customers. In addition, these issues impact cost, product codes, and safety concerns that must be effectively addressed in the BECS before any final guidance can be implemented, as well as physical inventory management strategies to ensure proper secondary testing. We have the following questions:

- What is the true expiration of the product that is initially distributed by the blood collection establishment and what expiration should be printed on the label?
- How will diverse computer systems be required to handle the need to relabel after initial and subsequent secondary testing?

- If the FDA maintains that 5 days is the labeled expiration, how are cGMP requirements met for a product that may actually be considered "expired" or not acceptable for transfusion until secondary testing has been done, while the expiration date on the label indicates otherwise?
- What, if any, responsibility does the blood collection establishment have with respect to secondary testing requirements for a product that has been distributed and left its control? We believe they have none unless accepting the unit back into inventory for further testing or relocation to support patients and/or minimize waste of this critical product. It is likely that the requirements of this draft will eliminate or sharply reduce consignment practices and exacerbate shortages.
- If secondary testing (culture or rapid test) is performed by the transfusion service and the product is returned to a blood center supplier, can the blood center still label the platelets with a 5/7-day expiration (the center having no control if required secondary test was actually performed and performed correctly on day 3 or 4)?
- If secondary culture is not performed on day 3 or 4, will the platelet have to be discarded at the end of Day 4, or could a transfusion service do a rapid test on day 5 and still be able to use the platelets?

Please provide details to fully support compliance efforts.

Rationale: Although the FDA describes 5-day platelets in the guidance, it appears no platelet process except PRT and high volume delayed primary culture is valid for transfusion on day 5 without additional testing. Logistically and realistically, to avoid excessive delays and outdates (in the absence of delayed large volume culture as a safety measure or PRT), this testing will most commonly be performed by the transfusion service. As such, the performance, recording, and actions taken based upon the results of this testing are outside the control of the blood collection establishment. This creates uncertainty and will reduce the ability to redistribute urgently needed products across multiple transfusion services at need.

Comment 17: Risk study on implementation

The July 2018 BPAC meeting was intended to address scientific and operational considerations for 5-day and 7-day platelets. Some conclude that the 2018 Draft Guidance will not result in 5-day or 7-day platelets, given the complexity of the available options, because the absolute best-case scenario would be 4 days on "5-day platelet" and 4.5 days on a "7-day platelet."

Please clarify what, if any, consideration and analysis has been given by the agency to a risk study prior to promulgation of final guidance, as requested above, to address, minimally, additional product losses and restrictions on redistribution that could impact the adequacy of the platelet supply, the additional costs for implementation, the increased recruiting efforts to find additional platelet donors to make up for the reduced shelf life and loss of products, the burden placed on hospitals with additional product manipulation and management of dual inventories, and the risk for increased clerical errors.

Rationale: A clarification will inform our members, support effective implementation, and support our extended advocacy elsewhere in the federal bureaucracy.

Comment 18: Safety measure claim for secondary culture of 5-day platelets

In the expanded explanations requested in earlier comments, please also clarify if safety measure claim is, or is not, required for secondary culture of 5-day platelets.

Rationale: We are aware that a safety measure is necessary to extend expiration beyond 5 days. However, we continue to receive questions such as "Why does a secondary culture method for 7-day platelets require the assay to have 'safety measure' labeling, but this requirement is not mentioned for secondary culture of 5-day platelets?"

Comment 19: Secondary culture - limiting the platelet supply

One member expressed concern regarding an unintended consequence of recommending secondary culture no earlier than day 3 for a 5-Day platelet which may result in reducing platelet use to 3 or 4 days for products shipped prior to performing a secondary culture. The guidance allows transfusion services the option of 1) rapid tests or 2) secondary culture methods prior to transfusion, although culture methods may be too costly and complex for implementation in transfusion services, which may result in pressure to allow return of platelets to the blood center for re-culture. The delays, cost, and inconvenience inherent in shipping products back to the blood center for additional testing for day 4 or 5 platelets could result in hospitals restricting transfusion of nominally "5-Day" platelets to those stored for less than or equal to 3 or 4 days, impacting the overall supply and resulting in decreased platelet availability.

Rationale: If the hospital does choose to return a product to the blood center for secondary culture, the blood center would have limited time to perform secondary culturing and the rework required to ensure the product is labeled appropriately such that any remaining shelf life is not sufficient to distribute the 5-day platelet to another customer for transfusion. This will result in blood centers not accepting returns and can adversely affect supply.

Recommendation III.C.2. states:

> ***2. Primary culture followed by secondary rapid testing***
>
> *This strategy applies to apheresis platelets and pre-storage pools, and includes the following steps:*
>
> - *Initial primary culture (see section III.B. of this guidance).*
> - *Secondary testing with a rapid test.*

Comment 20: Secondary testing after enhanced primary testing

The agency has not established that requiring secondary rapid testing after *enhanced primary culture* is clinically justified, i.e. there will be significant operational complexity and decreased platelet availability due to more false positives from anaerobic bottles plus rapid tests without clear evidence that the incremental decrement on STRs is sufficient.

Rationale: Secondary rapid testing on day 4 or 5 has a defined role for platelets tested by primary culture using an 8-10 mL sample volume. What data support FDA's assumption that it is clinically superior to perform secondary rapid testing when enhanced primary culture uses a 16-20 mL "large volume" sample volume split equally into aerobic and anaerobic culture media, as recommended in this Draft Guidance? In the absence of head to head comparative trials of the various strategies, this does not seem to be evidence based. As requested above, we believe FDA should consider it acceptable to allow blood establishments to perform enhanced primary culture using the upper limit of sample volume range for each of an aerobic and anaerobic bottle to support a 5-day shelf life, without a requirement for secondary testing.

Recommendation III.C.3. states:

> ***3. Pathogen reduction***

This strategy applies to apheresis platelets. Platelets that have been treated by pathogen reduction need no further measures because pathogen reduction technology adequately controls the risk of bacterial contamination of platelets.

Comment 21: We support the expansion of PRT as a nearly definitive solution to the problem of bacterial contamination and sepsis, recognizing that the available process is not yet suitable for the entire platelet supply. This option provides hospitals with a ready-to-use, safe platelet product supported by a substantial body of surveillance from systems superior to those in the United States.

Rationale: As stated in our April 2017 Comments and July 2018 Statement to BPAC we continue to urge the manufacturer and FDA to "collaborate aggressively in pursuit of expanding guard bands and providing data for the treatment of triple collections." This option provides a simple solution for transfusion services preferring to avoid additional testing.

COMMENTS 22 - 25 on *Section III.D. 7-Day Platelet Storage*

D. Storage may be extended beyond 5 days if:

- *The platelets are stored in a container cleared or approved by FDA for 7-day storage, and*
- *Individual platelet units are subsequently tested for bacterial detection using a bacterial detection device cleared by FDA and labeled for use as a "safety measure."* [7]

The following strategies are recommended for storage of platelets of up to 7 days:

Recommendation III.D.1. states:

1. Primary culture followed by a secondary culture with a device labeled as a "safety measure" performed no earlier than Day 4

This strategy applies to apheresis platelets, and includes the following steps:

- *Initial primary culture (see section III.B. of this guidance).*
- *Secondary culture no earlier than Day 4, using a device labeled as a "safety measure."*

Secondary culture:

To maximize the sensitivity of the culture, we recommend use of the upper limit of the sample volume range permitted by the device's instructions for use, inoculated into both an aerobic culture and an anaerobic culture.

If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.

Comment 22: Clarification requested

Our comments are similar to those described in Comments 13-20 for 5-day platelets. Please clarify details for: sample volumes, sampling of split components, yield requirements following secondary cultures,

timeframe for incubation prior to transfusion, expiration and inventory control, and considerations on the limitation of the platelet supply.

Rationale: Expanded explanations will support effective implementation with cGMP compliance.

Recommendation III.D.3 states:

> ***3. Large volume delayed sampling*** [8]
>
> *This strategy applies to apheresis platelets, and includes the following steps:*
>
> - *A single culture performed using a culture-based bacterial detection device no sooner than 48 hours after collection with a sampling volume of at least 16 mL, inoculated evenly into an aerobic culture and an anaerobic culture.*
> - *Each apheresis unit should be sampled for culture. If the apheresis product is split, each split product should be sampled.*
> - *If the instructions for use of the bacterial detection device specify a minimum incubation period, you should release platelet products consistent with the incubation period specified. If the instructions for use of the bacterial detection device do not specify a minimum incubation period, we recommend a minimum incubation period of 12 hours.*

Comment 23: Clarify language

Clarify language in the guidance referring to "a single culture" be performed and "Each apheresis unit should be sampled for culture. If the apheresis product is split, each split product should be sampled." We suggest the use of consistent terms to ensure clarity.

Further, we believe that prestorage pooled platelets from platelet rich plasma may quickly become a "component of the past" if the guidance as drafted is finalized. That is, there is no option for 7d storage for these components, as there is for apheresis. The three options for 7d storage of apheresis platelets (in a cleared storage container) should be included. Please recall that more than 9% of platelet doses in U.S. are from whole blood according to the National Blood Collection & Utilization Survey, so this aspect of the draft guidance demands consideration.

Rationale: This language is inconsistent with the implied instruction to obtain separate inocula from each separated component. The word "unit" is used for the first time in this recommendation and is open to interpretation as the collective unit (whole collection) versus each separated individual unit of a split apheresis collection. We reiterate that sampling the mother product of an apheresis product destined to be split should be reconsidered as noted above.

Comment 24: Reconsider minimum timeframe for sampling

We recommend a 36-hour delay for sampling as adequate to detect contamination.

Rationale: This is consistent with the data presented at the November 2017 and July 2018 BPAC meetings and published by the United Kingdom National Health Service Blood and Transplant who sampled at no sooner than 36 hours and which included clinical outcomes.

Comment 25: Reconsider the impact of a minimum incubation period of 12 hours

Similar to Comment 11, we suggest providing for shipment of product under quarantine for release if the culture remains negative at 12 hours to maximize the timeline for culture and distribution.

Rationale: Again, similar to Comment 11, this is consistent with information presented at the November 2017 and July 2018 BPAC meetings.

Comments 26 - 28 on *Section III.G. Labeling*

Recommendation III.G.1.a. states:

1. Labels on the Container

a. The container labels must comply with 21 CFR 606.121 and 21 CFR 610.60. Blood collection establishments and transfusion services, as appropriate, must also follow the general requirements for labeling operations described in 21 CFR 606.120.

Comment 26: Platelet ISBT-128 E-codes

The container label must accurately and consistently reflect the expiration dating of the product at all times and so it seems inadequate to use one product code for products with different expiration dates.

Rationale: The labeling requirements lack clarity and enough detail to understand labeling of platelets throughout the dating period. Given that current platelet ISBT-128 E-codes define 5-day platelets products, are the use of new E-codes going to be required based on the variety of expiration dates for a given product to capture and many options? Some examples of the potential need for additional E-codes include:

- If the collection facility chooses to perform secondary testing, the guidance lacks recommendations for labeling that may be required to adequately manage product inventories through the various stages of testing. As described in our comment above, new product codes will be required to adequately manage product inventories, especially with regard to expiry.
- When a collection facility does not to perform secondary testing on apheresis platelets, transfusion services would bear the responsibility to manage inventory, perform the secondary testing with the recommended timeframes and clearly label the products. The guidance lacks detail and recommendations to change the container label or for the use of tie tags, a manual process with GMP implications, as an extension of the container label.
- If the blood establishment elects to perform secondary testing ("further manufacturing") on day 4 or day 5 for the purpose of extending the expiration date (to 5 days or 7 days respectively), the platelet container will need to be relabeled with a new product code which is consistent with the applicable new expiration date. Since a 5-day (or 7-day) product has an additional "labeling claim", it seems logical that platelets dated for 5 days or 7 days would require unique product codes. These new E-codes should be specific for the dating period of the product and established as industry standards.

Comment 27: Loss of consignment and inventory sharing due to labeling concerns

As previously noted, the lack of clearly defined labeling requirements for expiration dating, specific labeling for category of bacterial testing performed and differing paths for 5-day and 7-day dating will lead to an overly complex and burdensome path to compliance for many hospitals and impair the ability of collection facilities to rotate inventory among hospitals to maximize the therapeutic value of a critical blood component and minimize wasteful outdating. The impact of the guidance on platelet availability is critical to understand.

Rationale: A lack of clarity for labeling requirements will lead to a declining willingness to participate in inventory sharing between blood centers and from hospital to hospital. Loss of participation in a consignment model can lead to a reduction in available inventory and product outdating.

Recommendation III.G1.b. states:

1. Labels on the Container

b. The container labels must include the expiration date and time, if applicable, of the product based on bacterial detection testing (21 CFR 606.121(c)(4)(i)).

Recommendation III.G.1.c. states:

1. Labels on the Container

c. If secondary testing of platelets is performed consistent with this guidance, and the expiration date is extended to 6 or 7 days based on the bacterial testing performed, the blood establishment or transfusion service that performed the secondary testing must update the container label to reflect the new expiration date (21 CFR 606.121(c)(4)(i)).

Comment 28: Updating the container label and use of tie-tags

Please clarify FDA's expectations for updating the label and the expiration date after secondary testing. Specifically, greater details will assist with compliance efforts. For example, does this recommendation apply to tie tags or only the container label as specified? Proper labeling is a primary focus of blood safety and inventory management.

Rational: The March 2016 Draft Guidance provided detailed labeling recommendations, including the option for use of a tie tag for secondary testing. There is no recommendation in the 2018 Draft Guidance for how to distinguish a platelet that has or has not had secondary testing. The website for the International Council for Commonality in Blood Banking Automation lists product codes for 5- and 7-day platelets, but none of these codes addresses the issues of secondary testing. The agency must be clear about its expectations about the need for unique product codes that identify the possible combinations of secondarily tested platelets with their appropriate expiration dates, and that identify platelets manufactured using the high-volume delayed strategy.

Thank you for the opportunity to offer these comments. We look forward to continuing to work with the FDA on patient and donor safety initiatives. Questions concerning these comments may be directed to scarayiannis@aabb.org.

AABB is an international, not-for-profit association representing individuals and institutions involved in the fields of transfusion medicine and cellular therapies. The association is committed to improving health through the development and delivery of standards, accreditation and educational programs that focus on optimizing patient and donor care and safety. AABB membership includes physicians, nurses, scientists, researchers, administrators, medical technologists and other health care providers. AABB members are located in more than 80 countries and AABB accredits institutions in over 50 countries.

Founded in 1962, ABC is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the U.S., and a

quarter of the Canadian blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The ARC shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Sincerely,

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