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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION TO REFRAIN FROM ADMINISTRATIVE ACTION

A court will set aside an agency action when the action is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."[1]

The undersigned submits this Citizen Petition on behalf of Verax Biomedical Incorporated, ("Verax") pursuant to 21 C.F.R. § 10.25(a) requesting that the Commissioner of the Food and Drug Administration ("FDA") refrain from taking certain administrative action that, if unsupported by additional scientific evidence, will be found to be arbitrary, capricious, and an abuse of discretion.[2]

A. Action Requested

Verax requests that FDA:

(1) refrain from clearing, approving, recommending, or issuing a "safety measure" designation for Large Volume Delayed Sampling ("LVDS") as a single step bacterial culture technology for dating beyond Day 5 without first obtaining statistically conclusive data supporting the safety and effectiveness from clinical evidence on apheresis platelets demonstrating that the LVDS method is effective at preventing the transfusion of bacterially contaminated blood platelets beyond Day 5;

(2) refrain from clearing, approving, recommending, or issuing a "safety measure" designation for any other platelet contamination detection method, storage device or method, or pathogen reduction method without statistically conclusive data supporting the safety and effectiveness from clinical evidence on apheresis platelets demonstrating that the technology or methodology is effective at preventing the transfusion of bacterially contaminated blood platelets; and

(3) refrain from clearing, approving, recommending, or designating as a "safety measure" any technologies or methodologies without statistically conclusive data

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[1] 5 U.S.C. § 706(2)(A).

[2] *See Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Automobile Ins. Co.*, 463 U.S. 29, 41 (1983).

supporting the safety and effectiveness of the technologies or methodologies. The data must:

> (i) demonstrate the ability to identify and prevent the transfusion of at least 1:2,000 clinically-significant bacterially contaminated units on or **before** Day 5 (consistent with the clinical effectiveness of the two current technologies cleared with a "safety measure" designation when taken together with the required primary culture test);
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> (ii) demonstrate the ability to identify and prevent the transfusion of at least 1:750 clinically-significant bacterially contaminated platelet units for transfusion on or after Day 6 (consistent with the unit contamination rate identified by both the rapid test and the BacT/Alert insert on or after Day 6 on a primary culture negative cohort); and
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> (iii) confirm safety and effectiveness with an end-of-storage/at-issue study of 25,000+ units.

Verax further requests that FDA apply consistent regulatory standards and precedents in reviewing data in support of such products or expanded claims.

B. Statement of Grounds

1. Summary

FDA has repeatedly stated that blood platelets "are associated with a higher risk of sepsis and are related to more fatalities than any other transfusable blood component."[3]

To mitigate this safety issue, FDA has undertaken a seven-year guidance process that culminated in its issuance of the *Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion* Guidance for Industry in September 2019 ("Final Guidance"). The purpose of this guidance is to recommend certain bacterial risk mitigation measures that have been shown to significantly improve patient safety over current U.S. single culture testing practice.

However, FDA in the Final Guidance has arbitrarily included an LVDS methodology as a single step method for Day 5 platelet dating ***with no supporting analytic or clinical evidence.*** FDA further all but approved and recommended LVDS with Day 7 dating, despite evidence that LVDS is no safer or more effective than current U.S. primary culture practices, the inadequacy

[3] 81 Fed. Reg. 13,798, 13,799 (March 15, 2016) (notice of draft guidance availability); *see* FDA Center for Biologics Evaluation and Research, *Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion* 2 (Sept. 2019) (Final Guidance for Industry) [hereinafter *Final Guidance*] ("Room temperature stored platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component.").

of which is FDA's basis and rationale for the Final Guidance in the first place. As Dr. Michael Jacobs presented to FDA at the 2018 Blood Products Advisory Committee ("BPAC"), existing studies show only that LVDS is ***no safer*** than current (insufficient) U.S. "low volume" primary culture practices that led to this guidance in the first place.[4] To protect patient safety, FDA should not clear, approve, recommend, or designate with a "safety measure" any bacterial contamination detection or mitigation technologies or methodologies without statistically conclusive data supporting the safety and effectiveness of the technologies or methodologies.

2. Background Related to September 2019 Final Guidance

Under 21 C.F.R. § 606.145(a), blood collection establishments and transfusion services must use devices or methods cleared, approved, or otherwise found acceptable by FDA to ensure that they have adequately controlled the risk for bacterial contamination of platelets. Since 2012, FDA's Center for Biologics Evaluation and Research ("CBER") has held three BPAC meetings to address bacterial risk in blood platelet products, and related guidance for industry.[5]

At the second BPAC meeting, which took place on November 30, 2017, FDA sought to obtain recommendations regarding platelet contamination threat-reduction methodologies, including the large volume single culture methodologies of Minimal Proportional Sampling Volume ("MPSV") for five-day dating and LVDS for seven-day dating. Due to significant procedural missteps[6], FDA held a third and final BPAC meeting to again discuss bacterial testing strategies for blood platelet products in July 2018.

During that 2018 BPAC meeting, Committee members noted that attempts to improve patient safety by enhancing primary culture are confounded by limited and sometimes difficult-to-interpret data. Specifically, existing data on LVDS are controversial and, at best, suggest LVDS is no better than current primary culture practices in the U.S.,[7] which FDA has found insufficient for patient safety (and which led to the Final Guidance).

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[4] *See* Dr. Michael Jacobs, *Prevention of Bacterial Contamination of Platelets: Rapid testing on Day of Transfusion compared to Culture Approaches* at Slide 30 (July 2018) (Presentation to the 2018 BPAC) [hereinafter *Jacobs 2018 Slides*].

[5] *See, e.g.*, FDA Center for Biologics Evaluation and Research, *Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion* at 5, Docket No. FDA-2014-D-1814 (Mar. 2016) (Draft Guidance for Industry) [hereinafter *2016 Draft Guidance*].

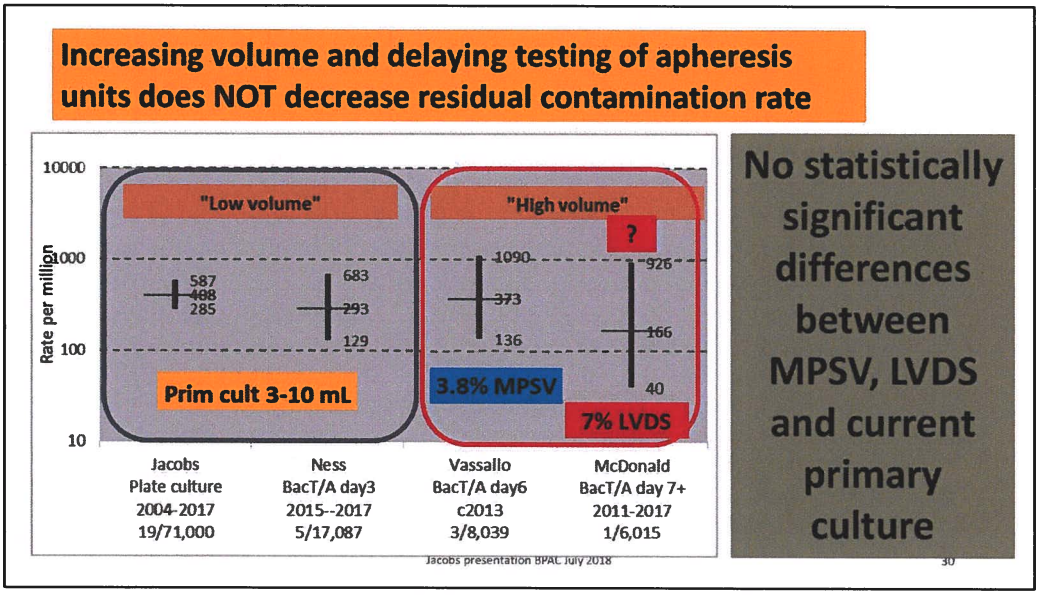
[6] As detailed in our March 2018 Citizen Petition, FDA exerted inappropriate influence on the BPAC during that November 2017 meeting, which it attempted to resolve by holding the third BPAC to reevaluate the available data on bacterial culture. *See* Anthony Pierce *et al.* on behalf of Verax Biomedical, Inc., *Petition to Revoke or Stay Administrative Action and Refrain from Further Action* (March 5, 2018) *available at* https://www.regulations.gov/docket?D=FDA-2018-P-1013.

[7] *See* Dr. Michael Jacobs, FDA Blood Products Advisory Committee, *Transcript at 126 (July 18, 2018) (testimony).*

For example, end-of-storage/at-issue data generated from the use of LVDS in England are from a very small study of just 6,015 units, composed of a mixture of apheresis platelets, as used in the U.S., and buffy coat-derived platelets, which are not licensed for use in the U.S. (and should be properly excluded before comparing to U.S. practices).[8] This detection rate suggests that LVDS, like primary culture in the U.S., fails to detect about half of all contaminated units. Even including the buffy coat-derived platelets, the very small sample size of this study has a very wide confidence interval—such that there is *no statistical difference* between the effectiveness data of LVDS versus current (insufficient) primary culture in the U.S.[9]

This point was highlighted in a slide presented by Dr. Michael Jacobs at the 2018 BPAC meeting, in which he compared the available bacterial screening effectiveness data of three different culture methodologies, primary culture (as currently conducted in the U.S.) and both MPSV and LVDS methodologies, demonstrating that there is no statistically significant difference in the effectiveness of these three different single-culture methodologies.[10]

Dr. Jacobs's slide presented at the 2018 BPAC[11]



Dr. Jacobs has identified an end-of-storage/at-issue culture study size of 25,000–50,000 samples as the minimum appropriate to prove safety.[12] This would be an appropriate benchmark

[8] Dr. Michael Jacobs, FDA 2018 Blood Products Advisory Committee, *Transcript* at 126 (July 18, 2018) (testimony); *Jacobs 2018 Slides* at 33.

[9] *See infra* Note 13 and accompanying slide in the text.

[10] *Jacobs 2018 Slides* at 30.

[11] *Id.*

[12] *See* Dr. Michael Jacobs, FDA 2017 Blood Products Advisory Committee, *Transcript at 132-133 (Nov. 30, 2017) (testimony).*

for an LVDS end-of-storage/at-issue culture study on apheresis platelets to determine whether it provides safe and effective storage to Day 7. These data do not currently exist.

Members of the 2018 BPAC discussed the significant limitations with LVDS due to concerns with the potential lag phase in growth both prior to and after testing, and the absence of adequate clinical or sufficient end-of-storage/at-issue culture data supporting the performance characteristics of this methodology.[13] Some BPAC members stated that testing very close to transfusion was superior to testing early in storage, because of the variability in the lag phase of different pathogens of interest.[14]

3. Final Guidance for Industry: Approved Technologies

FDA issued the Final Guidance on September 30, 2019. In the Final Guidance, FDA appropriately included primary culture followed by rapid testing for storage to Day 7, as sufficient data exist to support the patient safety improvement over current U.S. practice offered by this technology. It also included secondary culture on Day 3 for storage to Day 5 (supported by sufficient data), but further included secondary culture on Day 4 or later for Day 7 dating, which is not supported by the data in the product's own package insert.[15] Additionally, the Final Guidance included in its recommendations an approved pathogen reduction technology for storage to Day 5 consistent with (and limited to) uses supported by available safety data.

FDA appropriately *excluded* the single-step MPSV culture methodology to Day 5 from the guidance due to sufficient dispositive data indicating its lack of effectiveness compared to current U.S. practice.

Troublingly, the Final Guidance recommended LVDS as a single-step method for storage to Day 5 without any publicly available safety data. While this was requested as an approved pathway in comments to the final guidance, *no data* were produced supporting the safety or

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[13] *See e.g.,* Susan Leitman, *BPAC Member Discussion Transcript*, FDA 2018 Blood Products Advisory Committee 244 (July 18, 2018) ("I'm still . . . troubled by the residual contamination rate at the time of a secondary experimental culture with the large proportional volume tests."); *see also* Roger Lewis, *BPAC Member Discussion Transcript*, FDA 2018 Blood Products Advisory Committee 256 (July 18, 2018) ("This again just strikes me as something in which it is subject to false negatives due to the lag phase and that the lag phase is more of an issue with a longer period of storage.").

[14] *See* Roger Lewis, *BPAC Member Discussion Transcript*, FDA 2018 Blood Products Advisory Committee 209–10 (July 18, 2018).

[15] While the BacT/ALERT system for a culture on Day 3 or Day 4 following a negative primary culture had a similar success rate for identifying contaminated units through Day 5 as the PGD Test, we have significant concerns about the data for storage to Day 7, based on the Package Insert. The Package Insert for the BacT/ALERT BPA and BPN culture bottles for leukocyte-reduced apheresis platelets (BK170142) provide data that show culture on Days 3 or 4 had true positive rates of 0.03%, similar to the PDG Test. However, the package insert states that on "Day 6 or greater" it had a true positive rate of 0.14% with all cultures performed in platelets that had also previously been screened by a primary culture. This nearly five-fold greater bacterial contamination rate on Day 6 or greater means that cultures on Days 3 or 4 were missing most of the bacterially contaminated units and underscores the need for testing close to the time of transfusion, and raises significant patient safety concerns.

effectiveness of this methodology. Moreover, to our knowledge, there was never even a submission made with regard to this newly conceived and unproven methodology.

Even more concerning, save for a problematic footnote, the Final Guidance effectively signaled its approval of the use of LVDS as a single culture at 48 hours for Day 7 dating—a method that has not been shown to effectively prevent the transfusion of bacterially contaminated platelets—setting forth a path for LVDS to obtain a "safety measure" designation to Day 7 without requiring any additional clinical or sufficient analytic safety data.

Curiously, the Final Guidance details the methodology for use of LVDS to Day 7 in advance of such method being cleared with a "safety measure" designation and without the requisite data for such a clearance. Data should dictate what constitutes effective culture methodologies (time and volume) for a new methodology to be approved, cleared, recommended, or designated as a "safety measure." Instead, FDA has dictated the methodology without data to inform whether its procedures in fact provide effective patient safety. **Clearing, approving, recommending, or designating as a "safety measure" such a methodology without conclusive data on its safety and effectiveness would be arbitrary, capricious, and an abuse of discretion.**

4. <u>Final Guidance Uses Wrong Standard for Comparing Safety Claims</u>

Despite the concerns raised at the July 2018 BPAC meeting, the Final Guidance sets forth means by which FDA could grant a "safety measure" designation to LVDS or other technologies without sufficient supporting evidence, which could put patient safety at risk.

The Final Guidance states that "[b]acterial testing to extend dating beyond Day 5 up to Day 7 should be performed with devices labeled with LVDS as an acceptable safety measure."[16] Then—*in a footnote*—mentions LVDS has not been cleared with a safety measure designation, so the methodology cannot be used (yet).

However, in the very next footnote, FDA states that that LVDS (or any other technology) may be permitted to make safety measure claims for Day 7 dating based solely on "analytical" performance characteristics that are scientifically insufficient to demonstrate that the method is safe or effective at preventing the transfusion of bacterially contaminated platelets.

Specifically, FDA states that bacterial testing devices may obtain a "safety measure" designation when one of the following conditions applies:

> (1) clinical studies have shown benefit for detection of bacterial contamination not revealed by previous bacterial testing;

[16] *Final Guidance* at 6.

(2) the bacterial testing device has **analytical sensitivity** at least equivalent to a previously cleared "safety measure" device; or
(3) the bacterial testing device qualifies by other methods found acceptable to FDA.[17]

The first condition (clinical studies) and the third condition (FDA's discretion) are standards that *could* be appropriately applied by FDA. For example, there is an extensive body of literature that has shown that current bacterial contamination detection technologies and methodologies are able to identify 1:2,000 contaminated platelets by Day 5 (primary culture followed by either secondary culture or rapid test), and 1:750 contaminated platelet units missed by primary culture but identified by secondary culture or rapid test on Day 6 or Day 7. If FDA confirmed equivalent safety and effectiveness of technologies or methodologies through appropriate means to a level of statistical significance, and confirmed effectiveness with a 25,000+ end-of-storage/at-issue culture study, these conditions could be appropriately applied. However, FDA must hold any other technology or methodology to conclusively meet at least these standards for detection to ensure patient safety.

However, the second condition—"analytical sensitivity"—raises serious concerns regarding patient safety, as it applies entirely the wrong standard. Adopting the definitions from FDA (from the quote, below), *analytical sensitivity* is identified as the ability to detect bacteria present in the sample taken and tested, while *clinical sensitivity* is defined (for these purposes) as the ability to accurately predict whether dangerous levels of bacterial contamination will be present in the platelet bag at the time of transfusion. It is the latter—clinical sensitivity—that is important to patient safety, and can only be truly determined with end-of-storage/at-issue culture data.

FDA has demonstrated it understands the difference between these two standards. According to FDA:

> Various studies[18] have shown that the ***clinical* sensitivity** of the day 1 culture (≥24 hours) to detect contamination was <40%,

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[17] *Final Guidance* at 6, n.3 (emphasis added).

[18] FDA cited to: Dumont LJ, Kleinman S, Murphy JR, *et al.* Screening of single-donor apheresis platelets for bacterial contamination: the PASSPORT study results. Transfusion. 2010;50(3):589-599; Jenkins C, Ramirez-Arcos S, Goldman M, Devine DV. Bacterial contamination in platelets: incremental improvements drive down but do not eliminate risk. Transfusion. 2011;51(12):2555-2565; Souza S, Bravo M, Poulin T, *et al.* Improving the performance of culture-based bacterial screening by increasing the sample volume from 4 mL to 8 mL in aerobic culture bottles. Transfusion. 2012;52(7):1576-1582; Murphy WG, Foley M, Doherty C, *et al.* Screening platelet concentrates for bacterial contamination: low numbers of bacteria and slow growth in contaminated units mandate an alternative approach to product safety. Vox Sang. 2008;95(1):13-19; Pearce S, Rowe GP, Field SP. Screening of platelets for bacterial contamination at the Welsh Blood Service. Transfus Med. 2011;21(1):25-32; Yomtovian RA, Jacobs, M. R., Westra, J., *et al.* Detection of platelet bacterial contamination of apheresis and pre-storage pooled Whole Blood Derived Platelets units at blood centers prior to release and at a hospital transfusion service at time of issue. Transfusion. 2011;51(s):197A.

> **despite the high *analytical* sensitivity** of culture technologies. This low clinical sensitivity is thought to be due to the small bacterial load present at sampling time, resulting in a high proportion of samples that do not contain bacteria (sampling error). **Thus, a bacterial residual risk exists on the day of transfusion despite the early culture testing, potentially causing septic reactions in the recipient.**[19]

Whether a bacterial testing device has "analytical sensitivity at least equivalent to a previously cleared 'safety measure' device" is largely ***irrelevant*** to the question of whether the bacterial testing device is effective in determining whether a blood platelet product will be dangerously contaminated days after collection (clinical sensitivity).

It would be arbitrary, capricious, and an abuse of FDA's discretion for FDA—after itself citing half a dozen studies that demonstrated that bacterial culture, despite its high analytical sensitivity, misses more than half of all contaminated platelet units[20] (very low clinical sensitivity)—to then grant a safety measure designation to that very same bacterial culture technology to Day 7 without proof of its clinical sensitivity as demonstrated by a sufficiently large end-of-storage/at-issue culture study (i.e. 25,000+ tests).

By analogy, consider gauging whether a patient will have a fever on Saturday by using two different testing methods. First, you use a standard thermometer to take the patient's temperature on Monday. Although a standard thermometer provides the patient's precise temperature—and is accordingly very *analytically* sensitive—this precision is unlikely to be helpful in determining whether the patient will have a fever five days later. Second, you use a thermometer that signals—within half of a degree—whether a patient has a fever with just a blinking light, and use it to test the patient on Saturday. Although the second testing device has a *lower analytical* sensitivity than the standard thermometer, it will be much more effective at predicting whether the patient will have a fever on Saturday. Thus, despite its lower analytical sensitivity, this second method will have much higher clinical sensitivity—and that is the measure that actually affects patient safety.

Whether a bacterial culture test at 48 hours after collection is more sensitive than other technologies in determining the precise level of existing bacteria *in that sample* at the time of testing is largely unrelated to its ability to predict the level of bacteria growth (and, as a result, whether the platelets are safe for transfusion) three, five, or seven days after collection.

In the interest of patient safety, we urge FDA to require sponsors of any product, methodology, or combination of methods intended to serve as a safety measure—including

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[19] FDA, *Blood Products Advisory Committee Meeting July 18, 2018 Issue Summary: Strategies to control the risk of bacterial contamination in platelets for transfusion* at page 6 (emphasis added).

[20] *See infra* note 18.

LVDS—to produce data sufficient to prove safety and effectiveness at preventing the transfusion of bacterially contaminated platelets through sufficiently robust end-of-storage/at-issue data.

5. <u>FDA Should Not Act Without Sufficient Scientific Data</u>

FDA should only accept scientific evidence that meets three fundamental criteria before approving, clearing, recommending, or designating as a "safety measure" any technology or methodology, including with a "safety measure" designation. The scientific evidence must: (i) demonstrate effective bacterial contamination detection and interdiction rates commensurate with existing two-step technologies of at least 1:2,000 clinically significant contaminated units for transfusion to Day 5; (ii) demonstrate the ability to successfully identify and interdict at least 1:750 contaminated units from being transfused at Day 6 or Day 7 (if cleared for Day 6 or Day 7 storage); and (iii) confirm clinical effectiveness with an at-issue/end-of-storage study of at least 25,000+ units.

i. ***Effective Bacterial Detection Rate of at Least 1:2,000 clinically significant bacterially contaminated units***

Currently, both technologies/methodologies cleared with a "safety measure" designation (primary culture followed by rapid test or secondary culture) have demonstrated at least a 1:2,000 rate of identifying and interdicting clinically significant[21] bacterially contaminated apheresis platelet units on or before Day 5. This is the minimum level of effectiveness that should be demonstrated by any other technology attempting to show equivalent safety and effectiveness for dating to Day 5.

ii. ***Day 6 and Day 7 Safety and Effectiveness Data***

Any technology or methodology that seeks a "safety measure" designation for Day 6 or Day 7 dating should, in addition to demonstrating its ability to identify bacterially contaminated units earlier in storage, also provide sufficient data that show it can actually identify and interdict at least 1:750 contaminated units through Day 6 and Day 7 to a level of statistical significance. Its effectiveness should also be confirmed with an at-issue/outdate study of 25,000+ units on Day 6 and Day 7, consistent with the safety and effectiveness data from currently cleared technologies.[22]

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[21] Excluding non-clinically significant anaerobes that do not grow to dangerous levels or pose a human safety risk, even if identified in platelet units. As they pose no safety threat, such anaerobes are routinely excluded from effectiveness data. *See* McDonald C, Allen J, Brailsford S, *et al. Bacterial screening of platelet components by National Health Service Blood and Transplant, an effective risk reduction measure*. Transfusion 2017;57;1122–1131.

[22] *See* BK170142 Package Insert BacT/ALERT BPA at 8, *available at* https://www.fda.gov/media/111052/download; Mintz PD, Sanders J, Blair J, Rasmussen P. Confirmed Positive Bacterial Detection in Platelet Concentrates by a Rapid Test after Negative Primary Culture. Transfusion 2019;59:66A. AABB Annual Meeting. October 2019.

iii. ***At least a 25,000+ unit end-of-storage/at-issue study on apheresis platelets to confirm safety and effectiveness at identifying and intercepting bacterially contaminated units before transfusion***

This is consistent with both technologies that currently have a "safety measure" designation for Day 7 dating, including the PGD Test and the BacT/ALERT system. This is also the minimum study size for a statistically significant study as identified by Dr. Jacobs at the 2017 BPAC meeting.[23]

6. <u>Clinical Outcomes for Transfusing Platelets to Day 6 or Day 7: Key Patient Safety Differences Between the PGD Test and Secondary Culture</u>

Both the PGD Test and secondary culture have data that identifies very similar contamination rates that increase throughout platelet storage. That rate is about 1:3,000 dangerously contaminated units for Day 3 and 4 for secondary culture and Days 3, 4, and 5 for the PGD Test (both following primary culture), which, cumulatively with the 1:5,000 units captured by primary culture, achieve a 1:2,000 bacterial contamination identification rate. [24]

However, the longer the time between testing and transfusion, the more opportunity undetected bacteria have to acclimate and grow. Both the PGD Test and the BacT/ALERT system have data demonstrating a much higher contamination rate on Day 6 and Day 7, when about 1:750 units are dangerously contaminated (based on Day 6 or Day 7 PGD Tests and the BacT/ALERT package insert), compared to Day 3, 4, 5 (about 1:3,000).[25]

Crucially, the patient safety outcomes are dramatically different. The PGD Test is actually used on the day of transfusion, so it is both identifying ***and interdicting*** those approximately 1:750 contaminated units that were missed by primary culture. On the other hand, secondary culture (which could also identify those units if done on Day 6 or Day 7), is cleared for testing on Day 4 for Day 7 dating, when it only catches about 1:3,000 units, even though more than 75% of contaminated units detected at Day 6 or Day 7 are missed by the Day 4 culture, raising concerns around the effectiveness of secondary culture on Day 4 to identify which units will be safe to transfuse on Day 6 or Day 7, despite its "safety measure" designation.

FDA should ensure that any subsequent technology be held to the same or better safety and effectiveness standards as demonstrated by the PGD Test at actually interdicting bacterially

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[23] *See* Dr. Michael Jacobs, FDA 2017 Blood Products Advisory Committee, *Transcript at 133-34 (Nov. 30, 2017) (testimony).*

[24] 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.

[25] *See* BK170142 Package Insert BacT/ALERT BPA at 8, *available at* https://www.fda.gov/media/111052/download; Mintz PD, Sanders J, Blair J, Rasmussen P. Confirmed Positive Bacterial Detection in Platelet Concentrates by a Rapid Test after Negative Primary Culture. Transfusion 2019;59:66A. AABB Annual Meeting. October 2019.

contaminated units at Day 6 or Day 7 prior to its being cleared, approved, recommended, or designated as a "safety measure" for transfusion after Day 5 of storage.

7. Currently Available LVDS Data are Insufficient, Problematic, and Incomplete

Data on LVDS is insufficient, problematic, and incomplete. There are no peer reviewed, publicly available data from either pre-market or post-market studies on LVDS sufficient to prove either patient safety or risk mitigation profiles that are any more effective than current U.S. primary culture practice.[26]

LVDS proponents cite a published report by McDonald *et al.* that demonstrates only that LVDS is an improvement over ***past* practices in England, which *did not include any* bacterial culture testing or any similar mitigation activity**.[27] These data are not comparable to the current U.S. platelet safety practices, which already include applying early bacterial culture testing to effectively all apheresis platelets in the U.S. platelet inventory. Furthermore, the McDonald *et al.* article relies on passively reported incidents, which FDA itself has noted are likely to "grossly underreport[] septic transfusion reactions."[28]

Additionally, the UK only attributes transfusion-transmitted infection cases to LVDS screening failures under very narrow circumstances, which likely contributed to the low number of adverse events described in the English LVDS study.

The UK SHOT hemovigilance protocol likely underreports septic transfusion reactions, both because it is a passive reporting system, and also because it has overly exacting criteria for attributing sepsis to a transfusion.[29] Almost none of the hundreds of suspected septic transfusion reactions that have been investigated under this protocol are ultimately confirmed as septic transfusion reactions, not because there is no causal effect, but most likely because the imputability criteria cannot be met even if the transfusion caused the septic reaction. The UK reporting system for attributing bacterial transmission from a blood component state that bacterial cultures from the patient's blood must match cultures obtained from the blood component bag and/or from the donor.[30] As in the U.S., the potentially contaminated component bags are often discarded or destroyed (and not available for culture confirmation) by the time symptoms of sepsis are apparent and are recognized as possibly caused by the transfusion. Confirmation from the source donor is equally unlikely, as the source may have been a transient

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[26] We further note that there is also no cleared Premarket Notification with Indications for Use that addresses a change in culture testing strategy or protocol.

[27] Carl McDonald *et al.*, *Bacterial screening of platelet components by National Health Service Blood and Transplant, an effective risk reduction measure*, 57 Transfusion 1122 (May 2017).

[28] *2016 Draft Guidance* at 30.

[29] *See* UK Medicines and Healthcare Products Regulatory Agency, Serious Hazards of Transfusion (SHOT) Report at 156 (2018) available at https://www.shotuk.org/wp-content/uploads/myimages/20.-Transfusion-Transmitted-Infections-TTI.pdf.

[30] *See* S. Narayan (Ed) D Poles *et al.* on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2018 Annual SHOT Report 156–57 (2019).

skin contaminant or represent a low level, transient, asymptomatic bacteremia. The SHOT reports do not detail how many contaminated bags are cultured or donors are in fact tested.

Attending physicians in the UK have reported many cases of suspected transfusion sepsis that have failed to meet the strict imputability criteria required by the UK system. In fact, the total number of cases investigated as a result of clinician reports since the introduction of the LVDS protocols in the UK through 2018 is 717, with only one case definitively attributed to the transfusion. These data and the known false-negative "near misses" also reported in the SHOT reports strongly suggest that additional cases of bacterial sepsis have occurred as the result of platelet transfusions under the LVDS protocol, but are not being accurately categorized due to the overly stringent imputability criteria. These results support a conclusion that the risk of bacterial sepsis following transfusion of platelets cultured with the LVDS protocol is higher, and possibly considerably higher, than reported.

Even without considering those data, LVDS has an identical confirmed-positive bacterial contamination rate as the LVDS data *FDA had previously* ***considered and rejected*** *in its 2016 Draft Guidance*.[31] Indeed, subsequent to the issuance of the 2016 Draft Guidance, McDonald *et al.*[32] published a full-length report updating the data which were used by FDA to justify asking the BPAC to consider LVDS for seven-day platelet storage as an acceptable procedure without secondary testing. In that report, the authors describe primary culture screening 960,470 apheresis platelet components using the LVDS methodology with a confirmed positive rate of 0.02% (about 1:5,000), which is identical to the LVDS detection rate FDA considered—**and rejected**—in FDA's 2016 Draft Guidance, which had a sample size of 822,603 and an identical confirmed positive rate of 0.02% (about 1:5,000).[33] This is almost identical to the confirmed positive rate of primary culture in the U.S., and demonstrates no improvement over current U.S. primary culture practices. **It would be arbitrary, capricious, and an abuse of discretion for FDA—in a guidance document designed to improve patient safety—to endorse a culture technology no safer than current (insufficient) practices**.

8. <u>All Technologies and Methodologies Should Be Held to the Same Patient Safety and Scientific Data Standards</u>

Every platelet safety technology or methodology should be required to provide sufficient scientific data at least meeting the criteria in Section 5 of this Citizen Petition (*FDA Should Not Act Without Sufficient Scientific Data*) to demonstrate both its effectiveness and benefit to patient safety in the U.S. before it is approved, cleared, recommended, or designated as a "safety measure."

We note that FDA held a BPAC meeting on November 20, 2019, to evaluate cold storage of platelets, and to discuss the clinical studies needed to support the indications for use of cold stored platelet products stored beyond 3 days. This is certainly an appropriate discussion, but it

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[31] *See 2016 Draft Guidance* at 31.

[32] McDonald, *supra* note 9.

[33] McDonald, *supra* note 9 at 1124; *2016 Draft Guidance* at 31.

is critical to patient safety that FDA require sufficiently robust studies to gather both safety and effectiveness data which do not currently exist for extended storage for this product, and any such studies meet at a minimum the requirements in Section 5 of this Citizen Petition (*FDA Should Not Act Without Sufficient Scientific Data*).

We also note that there is a clinical trial underway on platelet recovery and survival on seven-day stored pathogen inactivated platelets in plasma.[34] While, again, this is an important investigation, the study design raises significant concerns: according to ClinicalTrials.gov, it has no FDA pre-specified quantitative primary outcome measures for success, as have been used in previous platelet studies. As Dr. Scott Murphy rather famously explained, not setting an absolute benchmark "creates a 'slippery slope,' where successive innovations are approved on the basis of providing (almost) the same recovery and survival as the previous one until a clinically inadequate system could finally be the end result." As a resolution, he proposed "the application of an absolute criterion for acceptance of a platelet system based on a comparison of the 'test' system not with a previously approved one but the subject's own 'fresh' platelets. . . ."[35] This insight led to the ultimate adoption of the "Murphy Criteria,"[36] a set of FDA criteria for radiolabeled recovery and survival of platelets, which FDA has, until now, applied to judge both success and failure of platelet studies.[37] Not only does the lack of specified outcomes return to the "slippery slope," but FDA could arbitrarily declare *any* outcome a success, and must very carefully apply its discretion in interpreting the results of this study.

9. Conclusion: FDA Must Require LVDS and New or Modified Technologies and Methodologies to Produce Sufficient Scientific Data

To protect patient safety, FDA should not lower its data and scientific evidence standards for bacterial risk control methods. FDA should not clear, approve, recommend, or designate as a "safety measure" *any* bacterial testing or inactivation technology for 5-day dating without proof of its ability to interdict contaminated platelets at a rate of 1:2000 or for 7-day dating without proof of its ability to interdict contaminated platelets at a rate of 1:750. Acting without

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[34] *In Vivo Study to Assess the Recovery and Survival of Radiolabeled Autologous INTERCEPT Apheresis Platelet Components Suspended in 100% Plasma Stored for up to 7 Days* (2019) *available at* https://clinicaltrials.gov/ct2/show/NCT04022889.

[35] James P. AuBuchon *et al.*, *Preliminary validation of a new standard of efficacy for stored platelets*, 44 Transfusion 36, 37 (Jan 2004).

[36] Scott Murphy, *The case for a new approach for documenting platelet viability* 46 Transfusion 49S ("It is also proposed to have the fresh control collected, labeled, and infused on the same day as the test product is infused. I have proposed that test PLT recovery be at least 66 percent of control and survival be at least 50 percent of control.").

[37] *See* Larry J. Dumont *et al.*, In vitro and in vivo quality of leukoreduced apheresis platelets stored in a new platelet additive solution, 53 Transfusion 972 (May 2013) ("APs stored in PAS with 35% plasma carryover maintained pH over 5 days of storage **and met current FDA criteria for radiolabeled recovery and survival**." (emphasis added)); Sherrill Slichter *et al.*, *Extended storage of platelet-rich plasma-prepared platelet concentrates in plasma or Plasmalyte* 50 Transfusion 2199, 2203 (Oct. 2010) ("PLT survivals as a percentage of fresh PLT survivals met Murphy's guideline of 50% or more of fresh after 7 days of storage . . . but only met the FDA's guideline of 58% after 6 days of storage . . . .").

conclusive safety data would undo the seven years of work FDA just completed to reduce the single greatest infectious threat to patient safety from blood product transfusion in the U.S.

It would not only put patient lives and health at risk, but would also create an uneven and unfair playing field among bacterial testing devices or inactivation technologies. Whether it is LVDS, pathogen reduction technologies, cold storage, or new culture methodologies, each technology or methodology must be required to demonstrate the same level of patient safety and effectiveness through sufficient scientific evidence before FDA approves, clears, recommends, or designates as a "safety measure" such technology or methodology.

Verax has demonstrated conclusively that the PGD Test may be practically implemented and improves patient safety by mitigating risk from bacterially contaminated platelets. Moreover, the clearance of the PGD Test, and all of its subsequent 510(k) clearances, have enabled the collection of post-market data on the residual risk of early culture and, more importantly, demonstrated the technology's effectiveness as a solution to improve patient safety by interdicting highly contaminated units released as "early culture negative."

Verax requests that the sufficient scientific data requirements set forth in this Citizen Petition apply to any method for which an indication as a "safety measure" is desired. FDA can and must protect patient health by only allowing for the use of bacterial contamination testing methods that are proven effective with sufficient supporting clinical or end-of-storage/at-issue culture data.

C. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. §§ 25.30, 25.31, and 25.34.

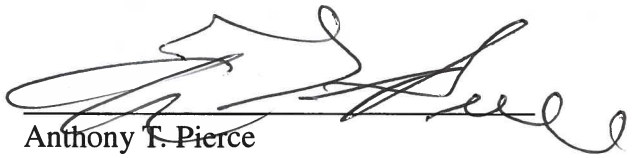
D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), information regarding economic impact is only to be provided when requested by the Commissioner following review of the petition. Verax will provide this information if so requested.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



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