November 30, 2020

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2001 K Street NW
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Re: Citizen Petition [Docket Number: FDA-2019-P-5800]

Dear Mr. Pierce and Mr. Graver:

This letter responds to the Citizen Petition to Refrain from Administrative Action (Petition) received on December 6, 2019 that you submitted on behalf of Verax Biomedical Incorporated (Petitioner). The Petition requests that the Food and Drug Administration (FDA, the Agency, or we) refrain from taking certain administration action pursuant to 21 CFR 10.25(a)(2) in the form of a Citizen Petition filed pursuant to 21 CFR 10.30. For example, the Petition requests that FDA "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 platelet dating beyond day 5"—or "for any other platelet contamination detection method, storage device or method, or pathogen reduction method"—without obtaining "statistically conclusive data supporting the safety and effectiveness" of those technologies or methodologies. The Petition further proposes specific criteria for "clearing, approving, recommending, or designating as a 'safety measure'" any technologies or methodologies. In addition, the Petition requests that FDA "apply consistent regulatory standards and precedents in reviewing data in support of such products or expanded claims."

We appreciate the Petitioner reaching out to the Agency with their concerns and suggestions. FDA has extensively considered all the issues raised. We have reviewed the data and information referenced in the Petition as well as additional data and information relevant to the points raised in the Petition.

After careful review and consideration, the Petition is granted in part and denied in part, for the reasons set forth below.

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I. BACKGROUND

The actions requested by the Petitioner pertain to both "technologies" and "methodologies." FDA interprets that "technologies" as described by the Petitioner refer to devices, and "methodologies" to bacterial risk control strategies. These two categories involve distinct regulatory considerations. As described below, the standards for approval and clearance of devices differ from one another and from the considerations relevant to the adequacy of a bacterial risk control strategy.

A. Standards for Approval and Clearance of Devices

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval). Because the Petition specifically references clearance and approval, we focus below on the requirements for clearance of 510(k) submissions and approval of premarket approval applications (PMAs).

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is substantially equivalent (SE) to a legally marketed device.[1] Submitters must compare their device to a similar legally marketed device that is not subject to premarket approval to support their device's substantial equivalence.[2] The legally marketed device to which a device is compared for purposes of substantial equivalence is commonly known as the "predicate."[3]

For purposes of determining substantial equivalence, section 513(i)(1)(A) of the FD&C Act provides the following:

> "[S]ubstantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device –
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> (i) has the same technological characteristics as the predicate device, or
>
> (ii) –
>
> (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and

[1] See sections 510(k), 510(n), 513(f)(1), and 513(i) of the FD&C Act (21 U.S.C. §§ 360(k), 360(n), 360c(f)(1), and 360c(i)); see also 21 CFR 807.92(a)(3).

[2] Section 513(i) of the FD&C Act (21 U.S.C. 360c(i)); 21 CFR 807.92(a)(3).

[3] A device cannot be found to be SE to a predicate device that has been removed from the market on FDA's initiative or that has been determined by a judicial order to be misbranded or adulterated (section 513(i)(2) of the FD&C Act (21 U.S.C. 360c(i)(2))).

(II) does not raise different questions of safety and effectiveness than the predicate device.

The acceptability or level of data necessary to support an SE determination is product specific. For example, while FDA may rely upon descriptive information alone to make some SE determinations, performance data may be needed to address a variety of safety and effectiveness issues relevant to an SE determination in other situations and may be generated from different types of tests and studies. The data needed to support an SE determination may vary depending on the type of device under review and the differences between the device and the predicate. The evidence necessary to show substantial equivalence will generally increase as differences between the new device and the predicate device increase, if those differences significantly affect, or may significantly affect, safety or effectiveness.

Class III devices, the highest-risk class of devices, are subject to premarket approval under section 515 of the FD&C Act to demonstrate a reasonable assurance of safety and effectiveness.[4] Under section 513(a) of the FD&C Act, FDA determines whether PMAs provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.[5] The evidence to support approval of a PMA may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, among other factors.[6] Decisions as to whether a device meets the statutory standard of reasonable assurance of safety and effectiveness for its intended use are based on the totality of the valid scientific evidence, including any clinical and/or non-clinical testing.

Congress has added several statutory provisions to the FD&C Act directing FDA to take a "least burdensome" approach to device premarket evaluation while maintaining the statutory requirements for clearance and approval.[7] As FDA has explained in guidance, the agency believes that least burdensome principles should be applied throughout the device total product lifecycle and intends to request the minimum information necessary to adequately address a device regulatory question or issue.[8]

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[4] See section 513(a)(1)(C) of the FD&C Act (21 U.S.C. § 360c(a)(1)(C)).

[5] See sections 513(a) and 515(d) of the FD&C Act (21 U.S.C. §§ 360c(a) and 360e(d)) and 21 CFR 860.7. FDA regulations provide that a reasonable assurance of safety occurs "when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use… outweigh any probable risks," and can be demonstrated by establishing "the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use." 21 CFR 860.7(d)(1). Further, 21 CFR 860.7(e)(1) states that a reasonable assurance of effectiveness occurs "when it can be determined, based upon valid scientific evidence… the use of the device for its intended uses and conditions of use… will provide clinically significant results."

[6] 21 CFR 860.7.

[7] See sections 513(a)(3)(D)(ii)-(iv), 513(i)(1)(D), and 515(c)(5) of the FD&C Act (21 U.S.C. §§ 360c(a)(3)(D)(ii)-(iv), 360c(i)(1)(D), and 360e(c)(5)).

[8] See FDA's final guidance, *The Least Burdensome Provisions: Concept and Principles* (February 5, 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

B. Considerations Regarding the Adequacy of Bacterial Risk Control Strategies

Room temperature stored platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component. The risk of bacterial contamination of platelets is a leading risk of infection from blood transfusion. In light of these risks, FDA has established regulations and issued guidance to address the control of bacterial contamination of platelets.

For example, under 21 CFR 610.53(b), the dating period (expiration date) for platelets with a storage temperature between 20 and 24 degrees Celsius is 5 days from the date of collection, unless a different dating period is specified in the instructions for use by the blood collection, processing and storage system approved or cleared for such use by FDA. In the United States, the current maximum dating period specified in such instructions for use, at the time of FDA clearance or approval, for platelets with a storage temperature between 20 and 24 degrees Celsius, is up to 7 days in the FDA-cleared or approved storage containers. Additionally, under 21 CFR 606.145(a), "[b]lood collection establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA."

In September 2019, FDA issued a final guidance document entitled *Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion* (Final Guidance).[9] The Final Guidance provides recommendations to control the risk of bacterial contamination of platelets, including bacterial risk control strategies that FDA considers acceptable to assure that the risk of bacterial contamination of platelets is adequately controlled (see 21 CFR 606.145(a)).[10] When considering whether to include a strategy in the Final Guidance, FDA took into consideration the totality of available evidence regarding the approach with careful assessment of the benefits and risks as they relate to the maintenance of a safe, effective, and adequate platelet supply. FDA recognized several stakeholders' comments that some flexibility was necessary for hospitals and blood establishments to maintain an adequate platelet supply, and we note that all of the strategies included in the Final Guidance represent an improvement in safety compared to historical practice.[11]

FDA's assessment regarding the adequacy of a bacterial risk control strategy is informed by scientific data, clinical experience, and scientific judgment. The recommendations in the Final

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[9] Guidance documents, which are not legally binding, represent the Agency's interpretation of, or policy on, a regulatory issue (21 CFR 10.115(b)).

[10] Considering the biology of bacterial contamination of platelets, FDA recognizes that no available technology or bacterial risk control strategy completely eliminates the risk of transfusion of bacterially contaminated platelets, including the Petitioner's device (Verax Platelet PGD Test) [1].

[11] Specifically, the historical practice of performing a single early, small volume platelet culture can fail to detect delayed growth of bacteria that may cause septic transfusion reactions, especially after prolonged storage of platelets. This was recognized by FDA in its issue summary for the July 2018 BPAC meeting [2] and is also referenced on pages 7 and 8 and footnote 18 of the Petition, where the studies of apheresis platelets cited by Petitioner included cultures no sooner than 12-24 hours after collection and volumes of 4-20 mL per collection, generally sampled only from the main collection rather than from each of the split components.

Guidance reflect FDA's evaluation of available data, including published literature, international experience, public presentations at advisory committee meetings and other forums, and comments to the draft guidance (including those from the Petitioner). When developing the guidance, FDA held three Blood Products Advisory Committee (BPAC) meetings between 2012 and September 2019 to obtain advice from the committee and input from stakeholders. In particular, the July 2018 BPAC meeting discussed the scientific evidence and operational considerations of available strategies to control the risk of bacterial contamination of platelets with 5-day and 7-day dating, including bacterial testing strategies (using culture-based and rapid bacterial detection devices) and pathogen reduction technology.[12]

C. Description of Relevant Devices and Methodologies

Currently available bacterial detection devices intended for use in testing room temperature stored platelet products have been cleared under the 510(k) pathway and are either culture-based or rapid tests. Culture-based bacterial testing devices consist of media for bacterial growth onto which a sample from the platelet product is added. The FDA-cleared culture-based devices have shown high analytical sensitivity and can detect bacterial content as low as 1 colony forming unit (CFU) per mL. Historically, sampling occurred 24 hours after collection and involved 4 to 8 mL of the platelet product sampled from the main collection, but now sampling may occur at later timepoints and with larger volumes, depending on the testing strategy used[13,14]. Large volume delayed sampling (LVDS) involves sampling a larger volume of the platelet product no sooner than 36 to 48 hours after collection, which enhances bacterial detection compared to earlier, smaller volume culture. Culture results are obtained within hours.

Rapid testing devices rely on direct detection of bacterial components, and sample about 0.5-1 mL of the platelet product with a read-out obtained within 60 minutes. FDA-cleared rapid testing devices have shown relatively lower analytical sensitivity than culture-based devices (e.g., $8.2x10^3$-$8.6x10^5$ CFU/mL for the Verax Platelet PGD Test, depending on the organism [3]), but are performed closer to the time of transfusion (e.g., within 24 hours). For apheresis

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[12] The Petitioner claims that the 2018 BPAC was held "[d]ue to significant procedural missteps…" (Petition, page 3) and that "FDA exerted inappropriate influence" on the BPAC in the 2017 meeting (Petition, footnote 6). We disagree and note that the November 2017 BPAC was held to discuss and obtain advice about certain newer strategies to control the risk of bacterial contamination of platelets and to extend dating, whereas the July 2018 BPAC was held so that the committee could discuss and provide advice regarding all available strategies to control the risk of bacterial contamination of platelets with 5-day and 7-day dating, including bacterial testing using culture-based devices and rapid bacterial detection devices and implementation of pathogen reduction technology.

[13] FDA's Final Guidance does not recommend the use of primary culture at 24 hours *alone* as a bacterial risk control strategy for 5 days of storage. For cultures performed no sooner than 24 hours, the guidance recommends a minimum sample volume of 16 mL split into aerobic and anaerobic media and sampled from the main collection, and additional testing should be performed after day 3.

[14] A given culture-based testing device with the same technological characteristics could potentially be used in several different risk control strategies. For example, cultures performed no sooner than 24 hours as an initial step in a two-step strategy, and cultures performed as part of a large volume delayed sampling strategy could potentially involve the same testing devices and growth conditions but would differ in the timing of when the cultures are performed following collection. Although analytical sensitivity of the given device would be identical, delaying the sampling would result in improved clinical sensitivity of the testing strategy (see additional discussion in sections II.A and II.C).

platelet products, the rapid tests are indicated for use following initial testing with a culture-based test.

Pathogen reduction devices are regulated as Class III devices subject to PMA, and the currently approved device (i.e., INTERCEPT Blood System for Platelets) uses a photochemical approach for inactivation of bacteria and other pathogens.

Certain bacterial testing devices may be cleared with an indication for use as a "safety measure" when used as part of a bacterial risk control strategy. This reflects that (1) clinical studies have shown benefit for detection of bacterial contamination not revealed by previous bacterial testing; (2) the bacterial testing devices have analytical sensitivity at least equivalent to a previously cleared "safety measure" device; or (3) the bacterial testing devices qualify by other methods found acceptable to FDA. The Final Guidance states that bacterial testing to extend dating of platelets beyond day 5 and up to day 7 should be performed with devices labeled as a safety measure.

II. DISCUSSION

As noted, the Petition includes several requests relating to "clearing, approving, recommending, or issuing a 'safety measure' designation for" various technologies and methodologies. Each request is discussed below.

A. Single-Step Large Volume Delayed Sampling Methodology for Dating Beyond Day 5

The Petitioner requests that FDA "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." We interpret this as a request that FDA refrain from the following until obtaining the specified data: (1) clearing or approving a device seeking an indication for use as a safety measure for LVDS as a single step approach for dating beyond 5, and (2) recommending in guidance a bacterial risk control strategy involving LVDS as a single step approach for dating beyond day 5.

FDA's 510(k) clearance determinations are based on whether the device to be marketed is substantially equivalent to a legally marketed device that is not subject to premarket approval,[15] and the acceptability or level of data necessary to support an SE determination is product specific. In addition, under section 513(a) of the FD&C Act, FDA determines whether PMAs provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,"

[15] See sections 510(k), 510(n), 513(f)(1), and 513(i) of the FD&C Act (21 U.S.C. §§ 360(k), 360(n), 360c(f)(1), and 360c(i)); see also 21 CFR 807.92(a)(3).

among other relevant factors. As explained in section I above, the evidence required to support this determination may vary according to the characteristics of the device, its conditions of use, and the extent of experience with its use, among other factors.[16] FDA does not believe it would be appropriate to require submission of the particular type of clinical evidence specified in the Petition in order to support clearance or approval of any device to be labeled as a safety measure when used with the LVDS methodology described in the Final Guidance.

Similarly, FDA disagrees that data of the type specified in this request is the only way to establish the adequacy of a bacterial risk control strategy. As explained, FDA's recommendations in the Final Guidance regarding specific bacterial risk control strategies are based on the strategies that FDA considers adequate to assure that the risk of bacterial contamination of platelets is adequately controlled (see 21 CFR 606.145(a)). In assessing the adequacy of a bacterial risk control strategy, FDA considers the totality of available evidence. This involves consideration of multiple lines of evidence (e.g., rates of detection of bacterial contamination, clinical rates of septic transfusion reactions, and supportive end-of-storage culture data). For additional discussion regarding variables that may inform the assessment of a bacterial risk control strategy, see section II.C., below.

Additionally, to the extent Petitioner is implying that data from clinical evidence do not demonstrate that LVDS as a single-step method is effective at preventing the transfusion of bacterially contaminated blood platelets beyond day 5, we disagree. FDA has considered all available data with respect to LVDS, including those presented publicly at BPAC [4], from Hema-Quebec in Canada (using sampling no sooner than 48 hours after collection) [2, 5, 6] and the National Health Service Blood and Transplant (NHSBT) in the United Kingdom (using sampling at 36 to 48 hours after collection) [7]. FDA's assessment of the adequacy of LVDS in controlling the risk of bacterial contamination of platelets is based on several lines of evidence, including the rates of detection of bacterial contamination, clinical rates of septic transfusion reactions, and supportive end-of-storage culture data.

> *Contamination detection rates*
> Available data demonstrate that both single-step LVDS strategies described in the Final Guidance (i.e., LVDS no sooner than 36 hours for labeling with a 5-day expiration and LVDS no sooner than 48 hours for labeling with an expiration of up to 7 days) increase the detection rate of bacterially contaminated components when compared to the historical practice of smaller volume cultures no sooner than 24 hours after collection [2, 5, 7, 8]. For example, McDonald et al observed a contamination rate of 2 per 10,000 with 36 to 48-hour LVDS [2, 4, 7]. This detection rate is increased when compared to collections performed on the same apheresis collection platform and tested with smaller volume cultures no sooner than 24 hours after collection, where Eder at al observed a detection rate of 1 per 10,000 [9], consistent with other surveillance studies [8]. With 48-hr LVDS on the same apheresis collection platform, Delage et al observed a detection rate of 3-4 per 10,000 [2, 5]. Even when excluding *C. acnes,* LVDS showed an increase in true positives from 1 to 2 per 10,000 compared to the same establishment's historical data with a single, earlier, smaller volume culture [6]. FDA notes that the detection rate of bacterially contaminated units is necessarily a function of the initial contamination rate

[16] See 21 CFR 860.7(c)(2).

of the sampled platelet components. This contamination rate is a product of several factors including donor arm disinfection [10], collection methods [8], and collection devices [9].

Septic transfusion reaction rates

In addition to contamination detection rates, clinical experience with 36 to 48-hour LVDS (as implemented by NHSBT[17]) found 1 confirmed septic transfusion reaction in more than 1.9 million transfused platelet components (0 in 1.3 million apheresis components) [4], and with 48-hour LVDS, as implemented by Hema-Quebec [2, 6], 0 reactions in close to 100,000 transfused components. These rates demonstrate the improved safety of LVDS when compared to historical practice of smaller volume cultures performed 24 hours after collection where bacterial transfusion transmitted infection rates of 5-20 per 1,000,000 have been observed in the United States [9, 12, 13] under passive hemovigilance. FDA notes that these septic transfusion reaction rates are also improved compared to the study by Jacobs et al which found a septic reaction rate of 1 in 27,620 units after primary culture followed by secondary rapid testing using the Petitioner's device (Verax Platelet PGD Test) [14]. FDA also notes that a recent report from Canadian Blood Services[15], although not considered at the time of publication of the Final Guidance and not available at the time of receipt of the current Petition, found a 3-fold decrease in septic transfusion reactions after implementation of 36 to 48-hour LVDS compared to their historical practice of smaller volume cultures performed 24 hours after collection, despite an increase in storage duration from 5 to 7 days.

End-of-storage culture data

Available end-of-storage culture data with 48-hour LVDS showed 0 positives in 3,185 components cultured at outdate (7 days) as compared to the same establishment's historical rate of 5 in 9,165 from 2005-2014 (0.055%) at 5-day outdate [6]. End-of-storage culture data with 36 to 48-hr LVDS[18] found 1 contaminated component in 6,217 screened components [4]. FDA notes that both end-of-storage culture rates compare favorably with the rate of culture positive units previously found nonreactive by the Petitioner's device (Verax Platelet PGD Test) which showed 2 culture positive units in a subset of 10,424 nonreactive units that were concurrently cultured [14]. The slide from Dr. Jacobs[19] (included on page 4 of the Petition) refers to "[n]o statistically significant

[17] The Petitioner claims that "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" (Petition, p. 11). Data from NHSBT, under the mandatory SHOT hemovigilance scheme [11], represent one of the largest available hemovigilance data sets collected under mandated reporting, which is important to capture rare events. As discussed above, the reported rate of septic transfusion reactions supports the clinical effectiveness of the LVDS approach when compared to historical reaction rates using early testing, even when considering the potential for underreporting, as other hemovigilance programs [9, 12, 13] are subject to the same limitations of passive reporting.

[18] End-of-storage culture data with 36 to 48-hr LVDS likely represent a worst-case scenario as the end-of-storage culture data were obtained after a 7-day outdate. The Final Guidance recommends LVDS no sooner than 36 hours as a single-step strategy for platelet storage of up to 5 days.

[19] The Petition cites in multiple instances the presentation from Dr. Michael Jacobs at the 2018 BPAC. FDA wishes to clarify that Dr. Jacobs is not a member of the committee. He spoke on behalf of Verax Biomedical and Immunetics and disclosed that he had "every conflict [of interest] imaginable"[4].

> difference between MPSV, LVDS and current primary culture." But a lack of statistically significant difference does not equate with no difference. The end-of-storage culture positivity rate for units tested by LVDS (166/million) was the lowest compared to the other testing methodologies referenced on the slide. However, the sample size of the described studies may not have been large enough to document a *statistically significant* difference between LVDS and the other methodologies. Overall, FDA finds the available end-of-storage culture data with LVDS to support its adequacy as a strategy for control of bacterial contamination. FDA also notes that end-of-storage culture positivity, upon which the slide appears to be solely based, is only one of several types of evidence that can support a bacterial risk control strategy. In addition, end-of-storage culture positivity does not necessarily reflect units that would result in clinically significant reactions. Accordingly, there are no statistical criteria that necessarily must be met with end-of-storage cultures to determine the adequacy of a bacterial risk control strategy or to clear or approve a bacterial detection device.

In summary, the 48-hour LVDS strategy recommended in the Final Guidance is supported by studies showing the ability of this method to further mitigate the risk of bacterial contamination of platelets compared to historical practice and clinical data supporting the safety of storage up to 7 days. Based on currently available information, FDA considers the 48-hour LVDS strategy adequate to control the risk of bacterial contamination of platelets beyond day 5 (see 21 CFR 606.145(a); 21 CFR 610.53(b)).

While the Petitioner claims that LVDS data are "controversial," the above-referenced data are publicly available and—with the exception of the recent report from Canadian Blood Services—have been presented publicly before BPAC prior to the current Petition, wherein the committee also recognized the improved safety of these strategies compared to historical practice. For example, Dr. Roger Lewis stated that "it has been demonstrated that this [LVDS] decreases the risk of contamination at the time of transfusion." Additionally, Dr. Jefferson Jones stated that "the data coming from NHSBT is some of the largest data that we have, and given the rarity of the event, having as much as data as has been accumulated in the UK, I think this strategy is more convincing" [4].[20]

B. Other Methodologies

[20] We note that the Petition selectively references BPAC comments that were critical of LVDS, some of which the Petitioner appears to have misinterpreted. For example, the Petition states that "[m]embers of the 2018 BPAC discussed the significant limitations with LVDS due to concerns with the potential lag phase…" and quotes Dr. Susan Leitman in footnote 13 ("I'm still…troubled by the residual contamination rate…"). However, this comment from Dr. Leitman was made during discussion of minimum proportional sampling volume [4], a strategy that samples components between 24 and 36 hours after collection and that was not included in the Final Guidance recommendations. The Petitioner also notes the following comment from Dr. Roger Lewis during discussion of LVDS: "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." This comment was part of a discussion that included LVDS no sooner than 36 hours after collection. To address the concerns reflected by this comment, the Final Guidance recommends LVDS no sooner than 36 hours as a single-step strategy only for platelet storage up to 5 days, whereas for platelet storage up to 7 days, the Final Guidance recommends LVDS no sooner than 48 hours as a single-step strategy.

The Petition also requests that FDA "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." For the reasons already explained in Section II.A above and further addressed in Section II.C, we disagree that the specified clinical data would always be necessary to satisfy the requirements for clearance of a 510(k) or approval of a PMA for a device seeking an indication for use as a safety measure, or to establish the adequacy of a bacterial risk control strategy.

We also note that the Petition raises specific concerns regarding certain of these "other" bacterial risk control strategies. For example, the Final Guidance recommends secondary culture performed no sooner than day 4 following collection for labeling with an expiration of up to 7 days. The Petition raises concerns about the effectiveness of secondary culture on day 4 for dating beyond day 5 (Petition, Page 10)[21]. Data supporting a secondary culture no sooner than day 4 for storage of platelets up to day 7, as performed by the Irish Blood Transfusion Service, were presented at the 2017 and 2018 BPAC meetings and demonstrate that secondary culture on day 4 is able to detect contaminated components previously found to be negative on primary culture. Testing of these components after 7-day outdate found 0 positives in 2,169 expired platelet components and there were no reported septic transfusion reactions associated with approximately 50,000 apheresis components [16]. Based on the data reviewed, FDA considers the strategy adequate to control the risk of bacterial contamination of platelets beyond day 5 (see 21 CFR 606.145(a); 21 CFR 610.53(b)).

Additionally, the Petition asserts that FDA "arbitrarily included an LVDS methodology as a single step method for Day 5 platelet dating with no supporting analytic or clinical evidence" (Petition, Page 2) and that the "Final Guidance recommended LVDS as a single-step method for storage to Day 5 without any publicly available safety data" (Petition, Page 5). This is inaccurate. The above-referenced clinical evidence from NHSBT in the United Kingdom (using LVDS at 36 to 48 hours after collection for storage up to 7 days) [7] were considered by FDA when evaluating this strategy. In addition, this information was presented and discussed publicly at the BPAC meetings [4]. These data support that LVDS performed 36 to 48 hours after collection increases detection of bacterial contamination in platelet components and lowers rates of septic reactions at the time of transfusion compared to historical practice of lower volume cultures performed 24 hours following collection. Based on the data reviewed, FDA considers the strategy adequate to control the risk of bacterial contamination of platelets (see 21 CFR 606.145(a)) and therefore appropriate for inclusion in the Final Guidance.

C. Specific Criteria Proposed by Petitioner

[21] FDA notes a prior communication received from Petitioner stating the following: "We feel that the use of culture as a secondary test does provide a meaningful incremental improvement in safety and its use is justified and should be included in guidance – whether that is a secondary culture on day 3 for 5-day dating or day 4 for 7-day dating"[17].

The Petition requests that FDA "refrain from clearing, approving, recommending, or designating as a 'safety measure' any technologies or methodologies without statistically conclusive data supporting the safety and effectiveness of the technologies or methodologies." The Petition further specifies that "[t]he 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);

(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

(iii) confirm safety and effectiveness with an end-of-storage/at-issue study of 25,000+ units"

We disagree that these data would always be necessary to satisfy the requirements for clearance of a 510(k) or approval of a PMA for a device seeking an indication for use as a safety measure, or to establish the adequacy of a bacterial risk control strategy. For example, a new rapid test with analytical sensitivity at least equivalent to the Petitioner's device (Verax Platelet PGD Test) could be cleared with an indication for use as a safety measure, without submitting the data described by Petitioner, when also indicated as a secondary rapid test in a two-step strategy, provided that the device otherwise meets the standard of substantial equivalence. In this case, analytical sensitivity refers to the smallest amount of bacteria present in the platelet sample that the device can accurately measure. Where the new rapid test has the same or better analytical performance, we would expect clinical performance of the device, when used as part of the same two-step strategy, to be at least equivalent to the clinical performance of Petitioner's device (the predicate) based on existing data regarding the clinical performance of devices used in that strategy.

The Final Guidance discusses labeling of a device as a safety measure when "the bacterial testing devices have analytical sensitivity at least equivalent to a previously cleared 'safety measure' device." Petitioner asserts that analytical sensitivity performance characteristics alone "are scientifically insufficient to demonstrate that the method is safe or effective at preventing the transfusion of bacterially contaminated platelets" and that this consideration regarding analytical sensitivity "raises serious concerns regarding patient safety, as it applies entirely the wrong standard" (Petition, p. 6-7). According to Petitioner, it is clinical sensitivity rather than analytical sensitivity that is important to patient safety. To clarify, as explained above in section I.A., the 510(k) review process involves a comparison of a device to a predicate, rather than an independent demonstration of the device's safety and effectiveness, as is required for approval of a PMA. Thus, in the 510(k) context, FDA generally relies, in part, on its prior safety and effectiveness determination for the classification of the device type and its prior substantial equivalence determinations for the predicate device(s). In addition, the considerations described in the Final Guidance, including analytical sensitivity, are assessed in the context of the risk

control strategy in which the device is intended for use. The risk control strategies included in the Final Guidance are based on clinical data supporting the adequacy of the strategy for bacterial risk control, including clinical sensitivity.[22] Therefore, analytical sensitivity is not considered in isolation and FDA recognizes that clinical sensitivity is important to establishing the effectiveness of a bacterial risk control strategy. For example, the analytical sensitivity of Petitioner's device (Verax Platelet PGD Test, $8.2x10^3$-$8.6x10^5$ CFU/mL, depending on the organism[3]), which is indicated as a secondary rapid test, would not be an acceptable comparator of analytical sensitivity for culture-based devices that would be used for LVDS strategies, which typically have much higher analytical sensitivity (as low as 1 CFU/mL). However, as noted above, an alternative rapid test with analytical sensitivity at least equivalent to the Petitioner's device (Verax Platelet PGD Test) could potentially be cleared with an indication for use as a safety measure when indicated as a secondary rapid test.

We note that different factors can contribute to bacterial detection rates (these factors are discussed in section II.A. above and include donor arm disinfection, collection methods, endogenous donor bacterial risk, storage conditions, and collection devices). Additionally, there are various potential approaches to bacterial risk control (e.g., pathogen reduction). Given these variables, FDA does not currently believe that it would be appropriate to mandate a single approach for establishing the adequacy of a bacterial risk control strategy or for clearance or approval of a device with an indication for use as a safety measure. As such, FDA does not agree that *a priori* specification of a detection rate (i.e., "the ability to identify and prevent the transfusion of at least 1:2,000 clinically-significant bacterially contaminated units on or before Day 5" or "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"[23]) is warranted.

Similarly, FDA does not agree that mandating "an end-of-storage/at-issue study of 25,000+ units" is warranted. While end-of-storage culture studies can be informative, they are only one of several types of evidence that may be relevant to device clearance or approval, or to the adequacy of a bacterial risk control strategy. As noted, when evaluating the strategies recommended in the Final Guidance, FDA considered all available data, including septic reaction rates and contamination detection rates. End-of-storage culture positivity does not necessarily reflect units that would result in clinically significant reactions, and such studies are not necessarily needed to assess the ability of a strategy to assure that that bacterial risk is adequately controlled, or for a device to satisfy standards for approval or clearance.

Additionally, the 25,000+ sample size of the post-marketing study that Verax conducted that supported clearance of the Verax Platelet PGD test with an indication for use as a safety measure

[22] As discussed in section II.A. above, clinical studies of the 48-hour LVDS strategy recommended in the Final Guidance support the clinical sensitivity of this strategy and its ability to further mitigate the risk of bacterial contamination of platelets compared to historical practice of a single earlier, smaller volume culture, as well as the safety of storage up to 7 days.

[23] Considering that culture-based devices would be expected to detect a much higher proportion than 1 of 750 contaminated units, FDA interprets that the sponsor is referring to an overall detection in rate of 1 *contaminated unit* in 750 *total units.*

was informed by the device's analytical sensitivity and the design of the study. This is documented by the Principal Investigator of the study, Dr. Michael Jacobs, in his published article on the study [18] and at the BPAC September 2012 meeting on "Considerations for Strategies to Further Reduce the Risk of Bacterial Contamination in Platelets" ("The statistical design was that, based on this limit of 10^5 CFU per ml being clinically significant, and based on that being the sensitivity of the test, that we should be able to pick up about 438 cases per million, roughly 1 in 2200").[24] Thus, it may be appropriate for a different bacterial detection device with a different analytical sensitivity, and using a different study design, to use a different study size.[25]

D. Application of Consistent Standards and Precedents

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

FDA already applies consistent and appropriate standards in reviewing data related to bacterial risk control strategies and device premarket submissions and, accordingly, grants this request. We note, however, that when discussing application of the same standards to all technologies and methodologies, the Petition states that "[e]very platelet safety technology or methodology should be required to provide sufficient scientific data at least meeting the criteria in Section 5 of this Petition [outlining the proposed criteria described above in section III.C.]…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.'" To be clear, for the reasons described earlier, FDA does not believe that mandating such criteria is warranted.

III. CONCLUSION

For the reasons described above, the Agency is granting your request regarding application of consistent regulatory standards and precedents, and the Agency is denying the other requests set forth in the Petition.

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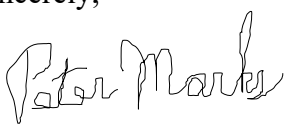
[24] See pages 48-49 of the September 21, 2012 BPAC meeting transcript. BPAC meeting materials are available on FDA's website at https://www.fda.gov/advisory-committees/blood-products-advisory-committee/meeting-materials-blood-products-advisory-committee.

[25] We note that the Petition asserts that "[i]t 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 (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)." To be clear, the referenced studies used a mix of growth conditions, sampling times (no sooner than 12 to 24 hours), and sample volumes 4 to 20 mL. See n. 12. To the extent Petitioner contends that the findings from those studies apply equally well to other bacterial risk control strategies such as LVDS, Petitioner is mistaken. As explained, in Section I.C., LVDS, particularly as recommended in the Final Guidance, involves sampling a larger volume of the platelet product at a later timepoint than in those studies. We have also explained in this response that analytical sensitivity is not considered in isolation to support FDA's decisions to clear a device with an indication for use as a safety measure.

We appreciate your concerns and appreciate you contacting us concerning this matter.

Sincerely,



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