

**BLOOD PRODUCTS ADVISORY COMMITTEE**  
**86th Meeting – March 9-10, 2006**  
**Gaithersburg, MD**

**Issue Summary**

**Topic I.** Rapid Tests for Detection of Bacterial Contamination of Platelets for Transfusion

**Issue:** Development of a regulatory pathway for review and clearance of rapid bacterial detection tests suitable for testing of platelets close to the time of their release for transfusion

**Background:**

Platelets are currently stored at room temperature up to 7 days. They are a good medium for bacterial growth and if the platelet product is contaminated during collection bacteria can proliferate from negligible levels to bacterial concentrations of  $10^{12}$  CFU/mL and greater (1). Highly contaminated units may not appear much different than uncontaminated units and are sometimes transfused to immunocompromised patients with grave results. The contamination rate is approximately 1/2500-5000 units (2, 3).

Regulatory history of bacterial detection devices

**2002** FDA clearance of two culture-based devices (BacT/ALERT, bioMerieux and BDS, Pall Corp) for quality control monitoring of the platelet collection process. The intended use of the devices was to test a small number of products collected on a monthly basis to assure that the collection process is in control.

**2004** FDA clearance of antibody detection system with automatic visual scan (Scansystem, HemoSystems)

**2004** The AABB institutes a new standard that requires all products to be tested by some kind of bacterial detection devices prior to release. The two culture-based devices FDA cleared devices became the methods of choice for apheresis platelets, whereas inferior methods such as pH determination, decrease of glucose by dipstick, and bacteria visualization by gram stain are used for whole blood derived products.

**2005** Gambro and Baxter submit QC data from AABB that demonstrates performance of the BacT/ALERT device for apheresis platelets. Gambro and Baxter gain FDA clearance for storage of platelets to 7 days if products are tested with BacT/ALERT bacterial detection device according to specific protocols.

**2005** FDA clears a Pool and Store Set with Pall eBDS culture-based system for 4-6 unit pools of leukocyte reduced whole blood derived platelets stored for up to 5 days (Pall Corp)

## **Discussion:**

### Comparison between culture-based and rapid test devices

Culture-based systems have good sensitivity for detecting bacteria in platelet products. The current estimate of sensitivity is at the range of 1-10 CFU/mL. However, some of these devices need up to 4 mL of sample of the product to be inoculated into a culture bottle and usually 2 bottles are recommended (4, 5). The products must be held for 24 hours **prior** to inoculation of the bottles. It also takes 24 hours before the device can declare a “negative” reading to date. In comparison rapid test devices usually require small volume of sample (< 1 mL) and have a fast turnaround time on the order of a few hours or less. The trade-off comes in their sensitivity, which so far, is in the range of 1,000-10,000 CFU/mL.

Platelets are most often contaminated either through an inadequate skin prep at phlebotomy or from asymptomatic transient bacteremia in the donor. The initial level of contamination of a transfusion product is very low, most likely at < 1 CFU/mL. Platelets are stored at room temperature which allows bacteria to proliferate to clinically dangerous levels over the course of storage. The culture-based devices are used on samples >24 hours old which allows bacteria to proliferate to levels detectable by the device. In contrast bacteria levels needed for detection by rapid test devices are more likely to be reached after 48-72 hours. There could to be a discrepancy of the safety of platelets tested by culture-based or rapid test devices based on device sensitivity.

Due to the differences in analytical sensitivity of rapid test and culture-based devices it is likely that sampling of platelet products will need to be done later in storage, probably at or beyond 48-72 hours. This difference could be written into the Instructions for Use of the device. It is unlikely that a sensitivity of 10,000 CFU/mL would allow equivalent use of the device to a culture-based device. If rapid test device was the only release test for a platelet product then bacterial levels of 1000-10,000 CFU/mL could be released as “negative”. A potential future use of the rapid test devices could be to confirm at the point of transfusion the initial negative results obtained by a culture-based devices on the transfusion units when these were released from the collection center.

### Proposed regulatory plan for rapid bacterial detection tests:

#### **A. Clearance for a rapid test device with a Quality Control indication**

1. The sponsor would submit a 510k application with culture-based devices and manual culture as predicate devices.

2. The initial submission should be for Quality Control Indication as was done for culture-based devices.

3. The sponsor should establish analytical sensitivity of their device for detection of bacteria in particular platelet products (apheresis platelets, whole blood derived, pooled whole blood derived, non-leukoreduced, leukoreduced). This can be achieved with simple spiking study of single bacterial species into a single unit of platelets. The contaminated unit is then sampled 10 separate times and the sample is tested in the bacterial detection device. The limit of sensitivity is defined as the lowest concentration of bacteria (CFU/mL) that is positively identified in all ten samples (100%). For example if a concentration of  $10^3$  CFU/mL comes up positive 8/10 times and a concentration of  $10^4$  CFU/mL comes up positive 10/10 times the limit of detection is at  $10^4$  CFU/mL. The bacterial species to be tested should include all of those tested with the predicate devices, which currently is a list of 10 including both aerobic and anaerobic species.

4. The sponsor should then demonstrate equivalence of their device to a predicate device. We propose a spiking study with timed sampling for predicate and test device. Based on preliminary studies the rapid test device will be less sensitive than culture-based devices currently cleared for Q/C. Equivalence can be established by prolonging the sampling of a platelet product contaminated with low level of bacteria to allow for proliferation of bacteria in the unit to levels detectable by the rapid test device. A unit of platelets should be spiked with 1 CFU/mL. The contaminated unit should be sampled and tested by the rapid test and the predicate device each day after spiking to determine the time it takes to reach levels detectable by the rapid test device. At each sampling a manual culture should also be performed to determine the CFU/mL level. All 10 bacterial species should be tested so that the sampling time is not based on fast growing organisms. Based on results of the timing study, a sampling time point for a rapid bacterial detection test will be identified which will make the device equivalent to detection with a culture-based system.

#### **B. Clearance of a rapid test device as an adjunct test for platelet products already tested with a culture-based device.**

1. Like the predicate devices (Gambro and BacT/ALERT and Baxter and BacT/ALERT) the rapid test device should demonstrate, with collected Q/C data, that it detects contaminated clinical units. The size of this data set should be comparable to the set submitted with the culture-based devices (~450,000 units tested).

2. An adjunct test indication will also require a commitment to a post market study. A potential design of the study could utilize clinical units detected as “positive” by a culture-based device. The positive units would be repeatedly tested with the rapid test to determine the time when the rapid test also identifies these as positive.

#### **C. Clearance of a rapid test device with a release test indication.**

1. To obtain device clearance as a stand-alone release test using a rapid bacterial detection test the sponsor should collect and present data outlined for the Q/C and adjunct test indications to the FDA.

2. In addition, the sponsor would need to commit to a follow up post market study where products tested by the device and released as “No bacterial growth at the time of release” would be retested with a culture-based device at outdate to confirm the initial test results. Based on the reported contamination rate the size of the study would be approximately 50,000 apheresis units and/or 50,000 pooled whole blood derived platelet units. The goal of the study would be to demonstrate that platelet products tested with a rapid test would have residual contamination rate of 1/10,000 with a 95% upper confidence limit of 1/5,000.

### **Questions to the committee:**

- 1) Is the kinetic comparison (timed sampling spiking study) an appropriate design of an equivalency demonstration between culture-based and rapid test devices?
- 2) What should be the minimum sensitivity in CFU/mL for detection of a contaminated platelet unit at time of release?
- 3) FDA proposes three tiers of data requirements respectively to validate a Quality Control indication, an indication for Adjunctive Use as a Release Test; and a Release Test indication. Are the data requirements in FDA’s proposed regulatory scheme appropriate to support clearance of these devices for the stated indications?

### **References**

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