

Blood Products Advisory Committee Meeting
December 12, 2002

Issue Summary: (1 of 3 for the BPAC Bacterial contamination topic)
Quality Control (QC) Measures for Aseptic Collection and Processing of Platelets and Platelets Pheresis

Background:

Although blood collection and processing procedures are intended to produce non-infectious blood components, bacterial contamination still may occur. Surveillance studies have found rates of contamination as high as 0.4% in single donor platelets, although rates at or below 0.2% are more reported. The causes include occult bacteremia in the donor, inadequate or contaminated skin preparation at the phlebotomy site, coring of a skin plug by the phlebotomy needle, and breaches of the closed system from equipment defects or mishandling. Platelet products are more likely than other labile components to be associated with sepsis due to their storage at room temperature, which is permissive of bacterial growth. For the same reason, bacterial cultures of platelets provide the best indication of the rate of contamination, provided that the sample for culture is obtained on a suitable sample volume and at a suitable time post-collection.

A variety of procedures may be used to obtain a valid platelet sample for bacterial culture. Aseptic techniques are required in order to minimize the risk of false positive cultures due to contamination at the time of sampling or upon inoculation in culture. Additionally, it is prudent to retain a sample that can be used for repeat culture to validate a positive result. Large volume samples removed from a several unit platelet pool or single donor apheresis unit can be cultured any time post-collection. However small volume samples (e.g. 2-5 ml removed from a single whole blood unit) should be obtained only after a 24-48 hour delay post-collection. The delayed sampling of a small volume permits bacterial growth to a level that subsequent assays will reliably detect, thereby overcoming sampling errors at low contamination levels.

High-Throughput Sampling Using a Sterile Connecting Device (SCD)

Sampling solely for quality control purposes can be accomplished by an aseptic, but open method (e.g. needle aspiration) for units at the time of issue (i.e. for use within four hours) or on outdated units. Conversely, sampling of platelets for the purpose of establishing a criterion for issuance of platelets as "culture negative to date" based on a negative result of bacterial cultures requires that the integrity of the closed system should be maintained. This is because platelets may continue to be stored for a variable period after sampling and before use. Suitable methods of sampling in this case would include the use of integral satellite containers, or stripping, refilling, and then pinching off duplicate pigtailed. Sampling also may be done into collection containers via the use of sterile connecting devices.

The FDA Guidance for Industry (Use of Sterile Connecting Devices in Blood Bank Practice, November, 2000) (1) describes an SCD as a functionally closed system for component preparation. However, given the room temperature storage of platelet preparations, current regulations do not permit extension of the 4 hour outdate for pooled random donor platelets pending submission of supporting data to ensure that sterility is not compromised by multiple SCD connections. While published US data support the sterility of SCD procedures when combined with visual inspection of the welded joint(2,3), a single European study described a 1.4% product contamination rate when an SCD was used to obtain samples for culture (4).

Recent clearance of two semi-automated culture systems for QC of platelet components has generated momentum within industry to culture in-date apheresis products followed by either product quarantine for a defined culture interval, or recall of a culture-positive distributed product. In part due to the absence of published data supporting SCD for sampling from in-date products, FDA has previously taken the position that the cleared culture systems should carry special labeling prohibiting their use as pre-release screening tests, due to a) possible risk of increased extrinsic contamination from SCD sampling and b) absence of data for the cleared devices when used for pre-release testing c) concern about off-label use of platelets older than the current 5 day shelf life (5). Similar concerns regarding extrinsic contamination may also exist if SCD procedures are used to collect a culture sample from many (or all) platelet products prior to release for transfusion. The Committee will hear a summary of available data on this issue.

Quality Control Strategies

The goal of quality control testing for bacterial contamination should be to assure that blood collection and processing procedures conform to defined standards. Statistically-based sampling of platelets for culture (or analogous testing) by a validated method will provide a reliable indication of the rate of contamination for all the labile products. However, the number of samples tested must be very large. (For example, based on Poisson statistics, it would require 0 failures out of 750 samples to be 95% confident that the contamination rate did not exceed 0.4%.) For very large blood collection centers, sampling on this order of magnitude may be possible by culturing platelets only at outdate. Conversely, small centers should consider testing of all units older than 24-48 hours by a process of sterile sampling at the time of issue or outdate. Daily (or, if frozen, weekly) samples can be pooled to reduce the number of cultures. Individual samples contributing to positive pools should be retested singly to determine the identity of the contaminated units, thereby permitting a prompt investigation of potential correctable causes. Correlations with common causal factors such as operator errors, shift, reagent batch, or procedure should be considered. Retained duplicate samples should be used to confirm or reevaluate the initial bacteriological findings.

The following will be presented by FDA for consideration as a minimal quality control program for all platelet products collected at blood centers.

- a) As a quality control for aseptic collection and processing of labile components, blood collection centers should determine the rate of bacterial contamination in platelets at least yearly by culturing 1,500 or more units (about 30 units per week or 5% of units released after 24 hours of storage, whichever is larger.) Standard statistical methods should be used to identify significant deviations from a baseline contamination rate not to exceed 0.2%. The chosen method should be based on a predetermined level of confidence to exclude a maximum tolerated rate of contamination, and an action limit should be established.
- b) All instances of a positive culture should be investigated promptly to facilitate identification of a correctable cause.
- c) Whenever the observed rate of bacterial contamination exceeds the defined action limit, a comprehensive investigation into potential causes of contamination should be undertaken and all collection and processing procedures should be revalidated.

Example:

A blood center wishes to establish surveillance to detect bacterial contamination rates significantly in excess of 0.2%. The following chart is derived from binomial statistics:

<i>Candidate Action Limit @ #(+)/# sampled</i>	<i>Confidence in Positive Result</i>	<i>Power to detect actual contamination rate</i>			
	<i>0.4%</i>	<i>0.6%</i>	<i>0.8%</i>	<i>1.0%</i>	
<i>≥3 per 400</i>	<i>95.3%</i>	<i>22%</i>	<i>43%</i>	<i>62%</i>	<i>76%</i>
<i>≥5 per 800</i>	<i>97.6%</i>	<i>22%</i>	<i>52%</i>	<i>77%</i>	<i>90%</i>
<i>≥7 per 1600</i>	<i>95.5%</i>	<i>46%</i>	<i>84%</i>	<i>97%</i>	<i>99.6%</i>

The blood center collects 12 units of platelets per day, five days per week. Cultures of units released after 48 hours, plus outdated units, number 30 units per week that are processed as 6 weekly cultures of five unit pools. An action limit is set to revalidate the collection procedures if the observed contamination rate exceeds 0.42% for yearly samples of 1,560 units. The action limit was established based on an expected contamination rate of 0.2%, a sample size of 1,560, and a cut-off determined as baseline plus 2-sigma variation. For this scheme, the likelihood of rejecting a conforming process is 4.5% (once every 22 years). The confidence levels (i.e. power) to exclude actual contamination rates of 1%, 0.8% and 0.6% are 99.6%, 97% and 84% respectively.

Over a one-year period, 7 positive platelet pools are identified, traceable to 7 individual units. The individual cases were investigated, but no attributable cause was identified. The observed contamination rate of 7/1,560=0.45% exceeds the action level. Confidence

that the actual contamination rate exceeds 0.2% is greater than 95%. An intensive review is conducted, and all collection and processing procedures are revalidated.

Questions for the BPAC:

Do available data on the sterility of the sterile connecting device procedure support the use of this procedure to collect samples for bacterial detection from in-date platelet products?

Does the Committee concur with FDA's proposed statistical approach to providing quality control for platelet contamination?

References:

1. FDA Guidance for Industry (Use of Sterile Connecting Devices in Blood Bank Practice, November, 2000)
2. AuBuchon JP, Pickard C, Herschel L. Sterility of plastic tubing welds in components stored at room temperature *Transfusion* 1995 35:303-307.
3. AuBuchon et al. Experience with universal bacterial culturing to detect contamination of apheresis platelet units in a hospital transfusion service. *Transfusion* 2002; 42, 855-861.
4. Mertens G, Muylle L, Goossens H. Possible implication of sterile connecting device in contamination of pooled platelet concentrates. *Trans Sci* 1997, 18(3),387-392
5. Wagner SJ, Moroff G, Katz AJ, Friedman LI, Comparison of bacteria growth in single and pooled platelet concentrates after deliberate inoculation and storage. *Transfusion* 1995; 35; 298-302.