Update on FDA Review of Bacterial Detection Devices for a Platelet Release Test Indication and Extension of Platelet Dating

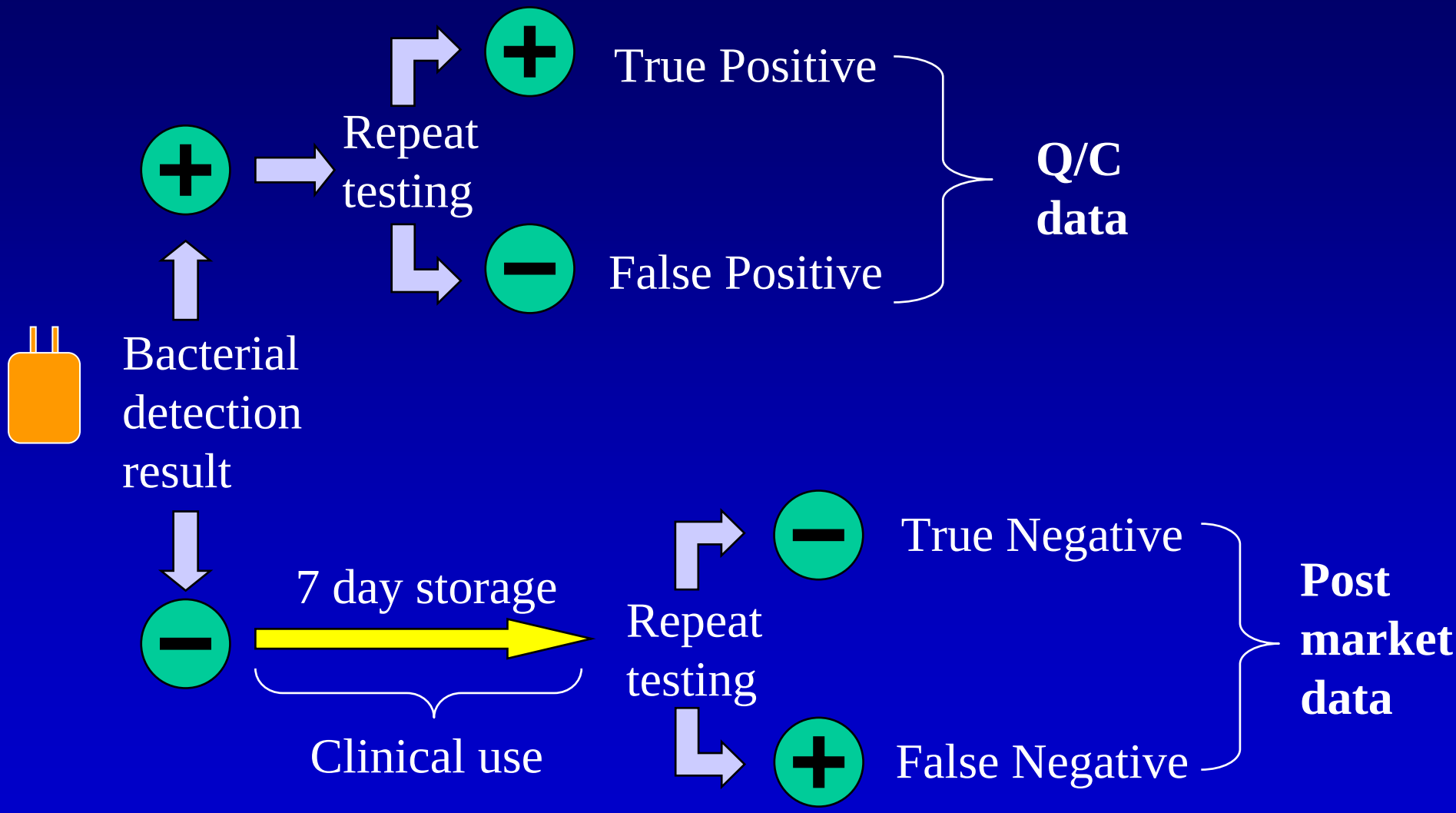
Jaro Vostal, M.D. Ph.D.
Division of Hematology, OBRR, CBER

ACBSA
May 17, 2005

Current approach to validation of a release test indication for bacterial detection devices

- Obtain data on performance of the FDA cleared devices when used to meet the AABB bacterial detection standard 5.1.5.1 since 3/04
- Use data as a basis for approval of 7 day platelets provided there is a commitment to perform a post marketing study
- Post marketing study will consist of additional cultures on outdated products (day 7) to confirm the day 1 negative culture readings
- Goal is to demonstrate a point estimate of risk at day 7 to be 1/10,000 with a 95% upper confidence limit that the risk is <1/5,000
- Study size ~ 50,000 platelet units

Testing Scheme for Bacterial Detection Device Performance Validation (Q/C and Post Market Data)



Current post marketing study design outline

- First sample collected early in storage
  - Aerobic and anaerobic bottles
- Second sample collected at outdate after day 7
  - Aerobic and anaerobic bottles

Analysis of post marketing data

- Determine residual risk of bacterial contamination for 7 day platelets tested early in storage by a bacterial detection device
- Acceptable risk for aerobic and anaerobic bacteria
  - point estimate of risk at day 7 to be 1/10,000 with a 95% upper confidence limit that the risk is <1/5,000
- Comparison of detection rates for aerobic and anaerobic bacteria in the aerobic and anaerobic bottles
- If aerobic detection method is capable of reducing the residual risk of anaerobic bacteria as defined above, then anaerobic method will not be required for release of platelets

Alternative post market studies for a release test indication of a bacterial detection device

- Sponsor may choose not to test the early storage sample by an anaerobic method (aerobic testing only) if test sensitivity is enhanced in other ways
- Due to the undefined risk of anaerobic bacteria this type of a study design will need to be performed under an IND if platelets are transfused after day 5 storage

Alternative post market studies for a release test indication of a bacterial detection device

- The final sample at storage out-date will need to be tested with both an aerobic and anaerobic method
- A finding of clinically significant anaerobes at outdate would require a change in the study protocol to culture for anaerobes early in storage
- Data from the study can be used to seek clearance of the device as a release test

Current estimate of risk from anaerobic bacteria contaminating platelet products

- True risk has not been defined
- Published studies and reporting to the FDA indicate that the risk exists although it is small
- Three mortalities from transfusion transmitted anaerobic bacteria reported to the FDA
- 2000- Clostridium p. red cells
- 2001- Clostridium p. platelets
- 2005- Eubacterium limosum platelets

Literature reports of anaerobic bacteria in blood products

Year	Product	Organism	Outcome
1998*	Platelets	Clostridium p.	fatal
2001**	RBCs	Clostridium p.	sepsis

* McDonald et al. Transfusion Medicine 8:19-22

** Blajchman, M.A. et al. Transfusion 41: 427

te Boekhorst, P.A.W et al. Clinical significance of bacteriologic screening in platelet concentrates. Transfusion 45: 514-519, 2005

- Sanquin Blood Bank Southwest Region, Rotterdam, the Netherlands
- 28,104 pooled platelet concentrates
- Aerobic and Anaerobic BacT/ALERT (5-10 ml/bottle)
- 184 (~1/153) confirmed positive for bacteria
- 9 (~1/3000) anaerobic Gram positive cocci
- 9(~1/3000) Propionibacterium acnes

European experience with extended storage of platelet pools. Ruby N.I Pieters et al. FDA Blood products Advisory Committee, March 2003

- Sanquin Blood Bank Northwest Region, Amsterdam, The Netherlands
- 8,778 pooled platelet concentrates
- BacT/ Alert, Aerobic and Anaerobic bottles (5-10 ml/bottle)
- 76 confirmed positive (~1/120)
- 37 Propionibacterium spp (~1/237)
- 3 Peptostreptococcus spp (~1/3000)

Munksgaard, L. et al. Detection of bacterial contamination of platelet components: six year experience with the BacT/ALERT system. Transfusion 2004; 44:1166-1173

- Odense University Hospital, Odense, Denmark
- 22, 057 platelet concentrates (buffy coat)
- Aerobic bottle only, 10 mL/bottle
- 70 confirmed positives (~1/300)
- 20 Propionibacterium acnes (~1/2000)
- 1 Clostridium perfringens (~1/20,000)

Is Propionibacterium acnes contaminated blood a risk to transfusion recipients?

Jakab, E. et al. Severe infections caused by proprionibacterium acnes: an underestimated pathogen in late postoperative infections Yale J. Biol. Med 1996, 69:477-82

- **Frequent contaminant of blood**
- **Has been associated with clinical syndromes of endocarditis, post craniotomy infections, arthritis, spondylodiscitis, endophthalmitis, pansinusitis**
- **Predominant predisposing conditions were surgery preceding infection 2wks – 4 years and implantation of foreign bodies**
- **Can be a pathogen in certain patients**
- **May cause disease in some patients receiving contaminated blood**

Clinical consequences of transfusing P.acnes contaminated platelet products

Perez, P et al. Determinants of transfusion associated bacterial contamination: results of the French BACTHEM Case-control study. Transfusion 2001, 41:862-872

- Clinical presentation of 16 cases of bacterial contamination associated with PC transfusions (nonfatal)
- 3/16 were positive for Propionibacterium acnes

Patient	clinical presentation	shock or sepsis
Male 41	fever, urticaria	none
Male 62	fever, fatigue, consciousness disorders	severe sepsis
Male 71	fever, chills, anxiety, tachypnea, erythematous rash	none

Summary of submission process for bacterial detection devices to release platelet products and extend platelet shelf life to 7 days.

- Define analytical sensitivity (spiking studies)
- Device cleared for Q/C use
  - Collect Q/C data to determine true and false positive rate in clinical setting
- Use Q/C data to support submission of a release test indication
- Clearance of release test with commitment to do a post marketing study
- Current study design: aerobic and anaerobic detection from early sampling confirmed with aerobic and anaerobic detection at outdate
- Alternate designs of post marketing studies will be considered but may need to be done under an IND