FDA's current considerations for 7 day platelets and bacterial detection in single and pooled platelet products

January 25, 2005

Jaroslav G. Vostal, M.D., Ph.D.

Division of Hematology, OBRR

CBER, FDA

Platelet storage to 7 days- where we are

- FDA cleared storage containers:
  - 2 apheresis platelet storage bags for storage to 7 days
  - 1 whole blood derived single unit platelet storage bag for storage to 7 days
- 7 day platelets are not currently approved because platelets stored in the above containers need to be tested with an FDA approved bacterial detection “release” test

Bacterial detection tests

- 3 devices are cleared for quality control monitoring of platelet collection process
- BioMeriuex BacT/Alert, Pall eBDS, Hemosystems Scansystem
- Other non approved and non validated methods are also being used to meet the AABB standard for bacterial detection

FDA concerns with bacterial detection as currently applied

- Test performance characteristics unknown
- Use of non-validated tests (glucose and pH by dipstick, swirling)
- Non-standardized methodology even with culture-based devices
- Potential for excessive false positives or negatives
- Less reliable methods are used on whole blood derived platelets creating a two tiered safety system for apheresis and whole blood derived platelets

Desired improvements to the current state of bacterial detection and storage

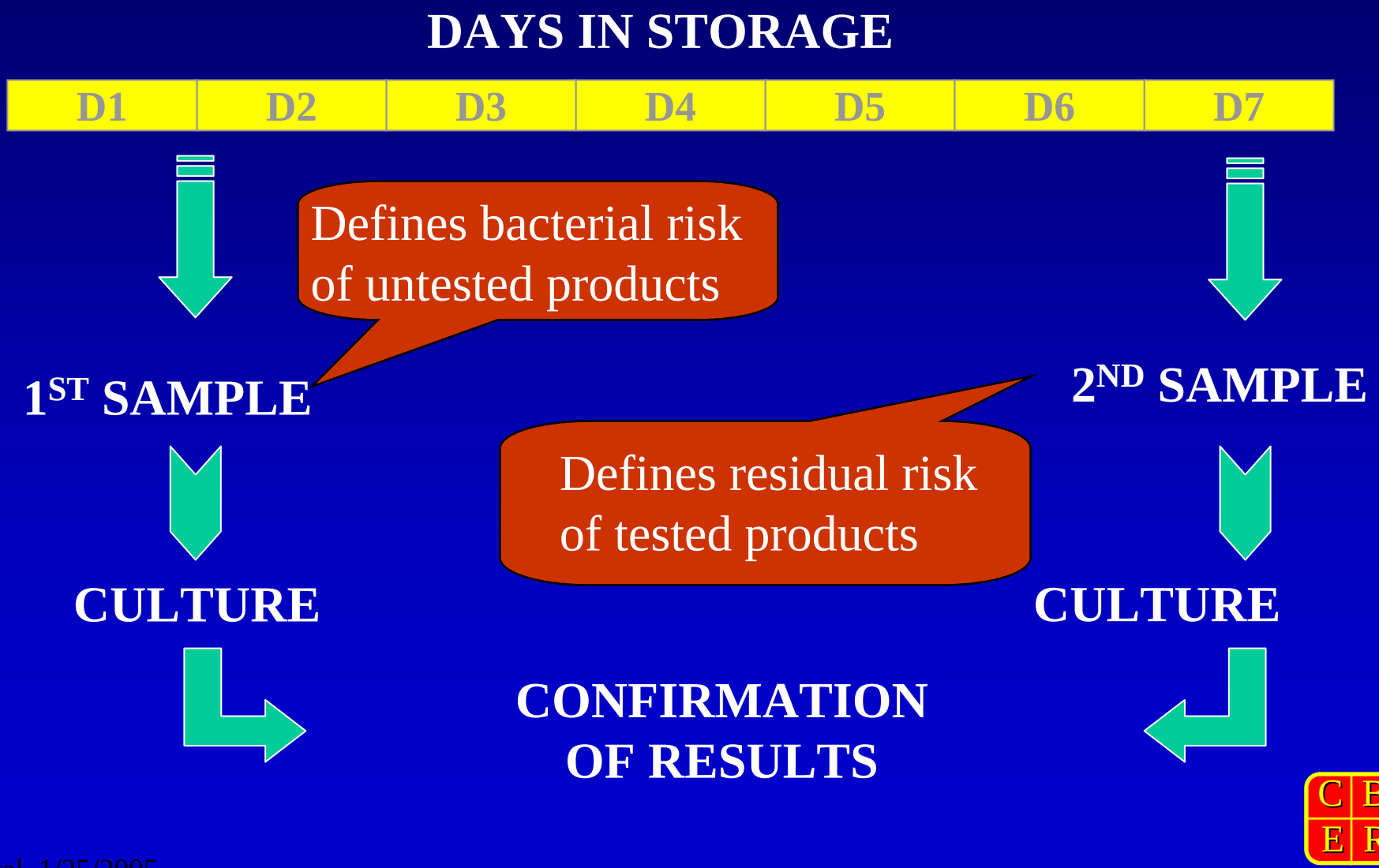
- Standardized methodology for automatic culture systems (timing of sample, volume collected, duration of culture)
- Validation of automatic bacterial culture systems as a platelet release test
- Application of automatic bacterial culture systems to whole blood derived platelets
  - Eliminate use of non-validated methods
  - Testing of pre-storage pools of platelets or testing of pooled samples

Proposed field study to validate bacterial detection prior to approval of a release test

(FDA and AABB bacterial detection task force **August 2004**)

- Sample platelet product early in storage
- Confirm the results with a second culture at day 7
- Estimate residual bacterial risk for a 7 day old platelet unit tested for bacteria on day 1
- Approve 7 day platelet storage if the bacterial risk at day 7 is lower than the current bacterial risk of untested platelet products
- 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

MODIFIED FIELD TRIAL OF AUTOMATIC CULTURE DEVICES FOR 7 DAY STORED PLATELETS - Using "off- line" units



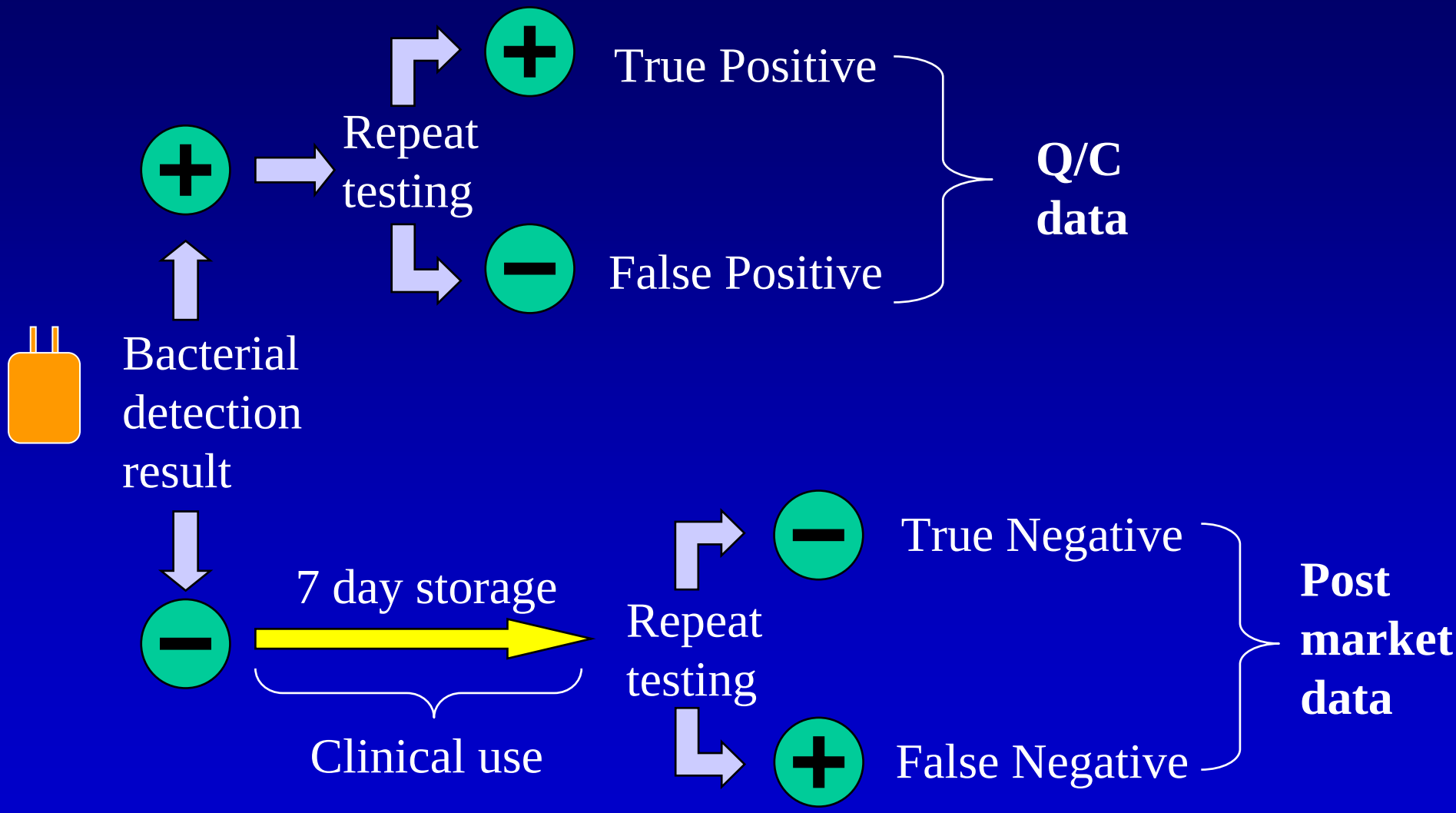
Continuing concerns about the logistics of a field trial

- High cost due to size of study
- No manufacturer support so far
- Public funding through NIH requires time for protocol review and competition against other research initiatives
- Data collection will take a significant amount of time

Exploring alternative approaches to validation of a release test indication for bacterial detection devices **(September 2004)**

- Obtain data on performance of the FDA cleared devices when used to meet the AABB bacterial detection standard 5.1.5.1 for last 6 months
- Use data as a basis for approval of 7 day platelets provided there is a commitment to perform post market study
- Post market study will consist of an additional culture on outdated products (day 7) to confirm the day 1 negative culture reading
- Size of post market study will be determined by the contamination rate identified by the Q/C testing data

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



Obtaining device evaluation from existing data and a post market study

- **Q/C testing** –confirms early culture positives with a repeat culture
  - identifies true positives and false positives
  - Can derive **expected rate** of positive tests
  - Can derive **positive predictive value** of the device
- **Post market field trial**-confirms early culture negatives with a 7 day culture
  - Identifies true negatives and false negatives
  - Can derive **sensitivity** of the device
  - Can derive **negative predictive value** of device
  - Can derive **residual risk** of contamination

Alternative plan for approval of 7 day platelet storage.

- Sponsor compiles existing Q/C data on performance of the bacterial detection device
- Develop uniform standard operating procedure (SOP) for screening platelet products by the device
- FDA will approve storage of platelets out to 7 days if
  - platelets are stored in bags approved for 7 days
  - bacterial detection SOP is followed
  - sponsor commits to a post market study to further track bacterial detection device performance

Pre-storage pooling for whole blood-derived platelets

Pre-storage pooling

- **FDA's current thinking is that pre-storage pooling systems can be cleared if Q/C by culture monitoring is performed by tests with analytical sensitivity similar to that cleared for single units**.
- Bacterial detection devices applied to pools will need to be validated by analytical testing to demonstrate sufficient sensitivity to account for the dilution of the bacterial inoculum by the pooling process
  - Testing of pre-storage pools
  - Testing of pooled samples

Additional requirement for approval of pre-storage pooling

- Approval of pre-storage pooling will require validation of platelet storage containers to preserve platelet efficacy in a pool for 5 days or longer
- Validation approach discussed in March 2003 BPAC
  - Testing of platelet “efficacy” by following corrected count increments in thrombocytopenic patients
  - Compare pre-storage pooled platelets to post-storage pooled platelets
  - Approximately 50 patients per arm
- Pre-storage pooling creates a new product
  - Quality standards should be established

Summary of current FDA thinking for …

- extension of platelet storage for 7 days
  - Compile existing Q/C data on bacterial detection device performance
  - Develop uniform SOP for testing of platelet products with device
  - Commit to a post market study
- pre-storage pooling
  - Validate analytical sensitivity of bacterial detection devices on pools where one unit is contaminated
  - Validate storage bags for pools to preserve efficacy in a pool for 5 and 7 days
  - Quality standards should be established