Seven Day Platelet Storage Using Platelets Collected with the COBE® Spectra™ Apheresis Systems and the Trima® Automated Blood Component Collection Systems and Release Tested with the BacT/ALERT® Microbial Detection Systems

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Gambro BCT, Inc.

Objectives

1. Provide brief history of 510(k) clearance

2. Highlight issues related to 2-bottle testing
   (a.k.a., Why use an anaerobic bottle?)

3. Present overview of Gambro BCT
   post marketing surveillance study

Background

The “First” clearance – platelet function

BK010037, September 24, 2003

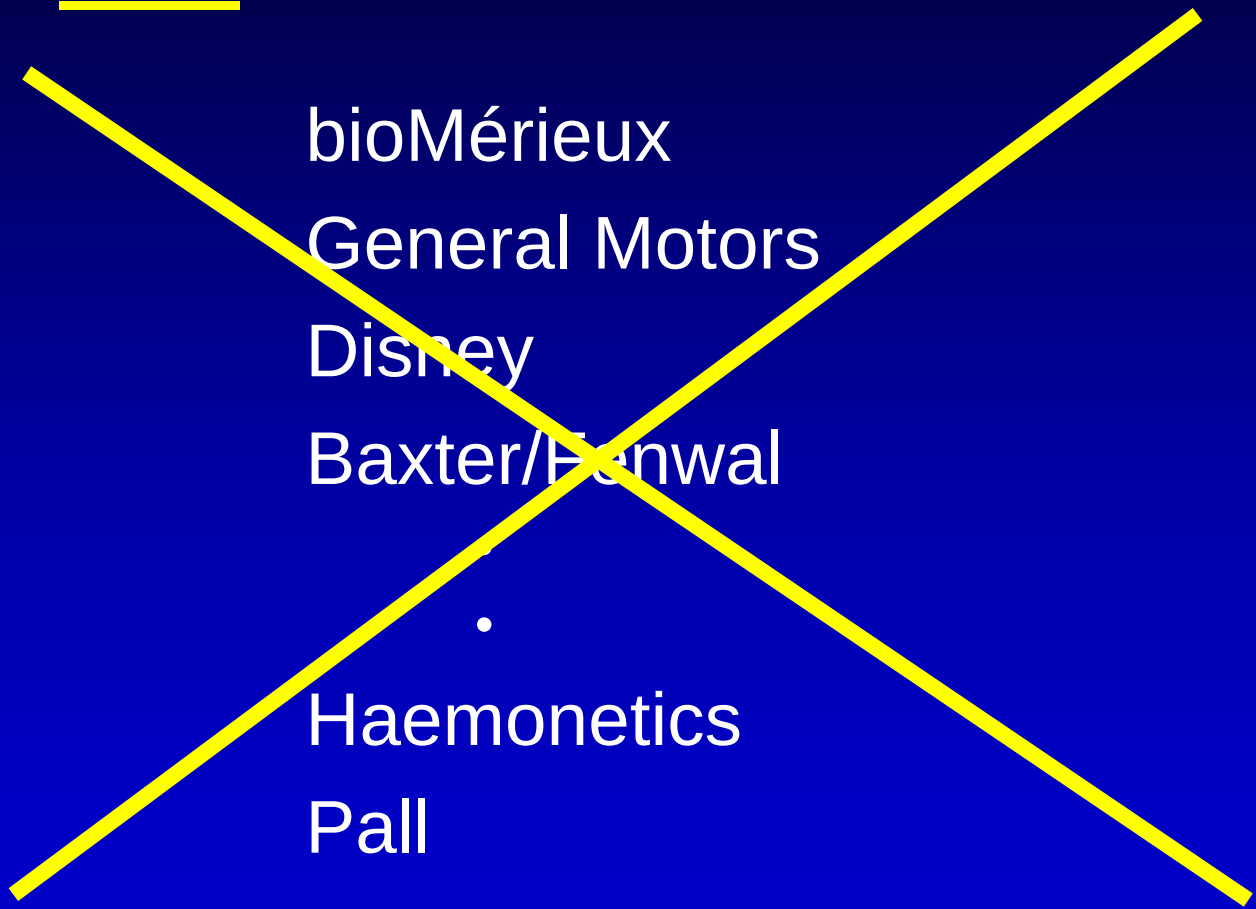
7 day shelf life in the platelet collection ELP bag, when coupled with a 100% screening for bacterial contamination, using a marketed device and recommended method, prior to transfusion

The “Second” clearance – Release Test

BK040086, March 15, 2005

7 day shelf life in the platelet collection ELP bag, when coupled with a 100% testing for bacterial contamination, using the bioMérieux BacT/ALERT and the recommended methods, prior to transfusion.

Gambro Did NOT Collaborate With:



- bioMérieux
- General Motors
- Disney
- Baxter/Fenwal
- Haemonetics
- Pall

The Release Test

1. Sampling 24 - 36 h post apheresis collection
2. 4mL aliquots of SDP in both
   one aerobic and one anaerobic culture bottles
3. Release if no growth indicated after 24 h on test
4. Culture bottles remain on test until positive or SDP expiry
5. Standard practices indicated for microbiology and clinical follow-up for any positive cultures.

Basis of Approval

FDA web site – Summary of Safety and Effectiveness

US blood centers:

One bottle test - (n=405,089 SDP)

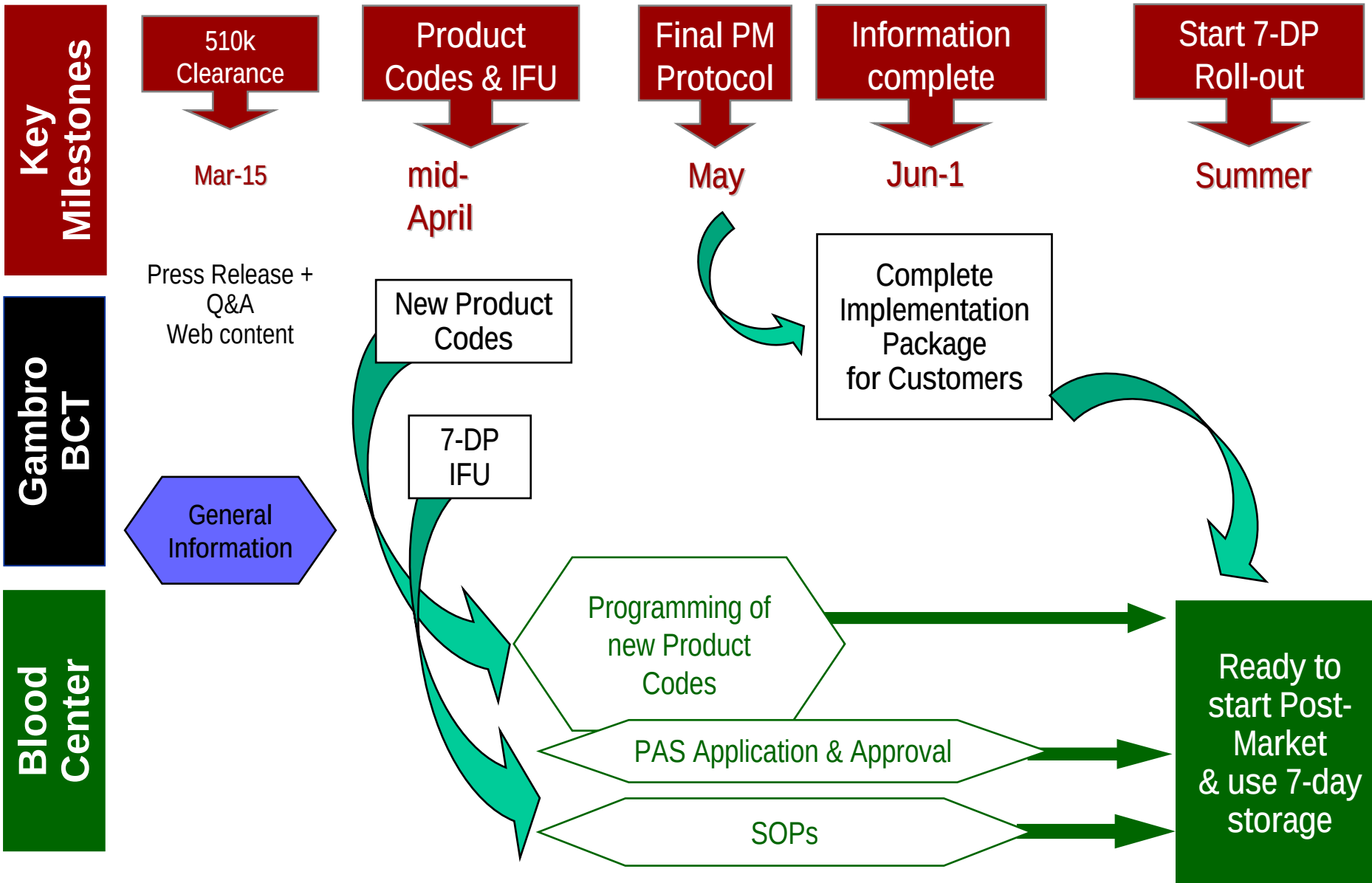
True, confirmed positive 178/M (95%CI 139/M to 224/M)

Include indeterminate 291/M (95%CI 241/M to 349/M)

Two bottle test – (n=6600 SDP)

True, confirmed positive 606/M (95%CI 165 – 1551)

Tentative Roll-out Plan



Two Bottle Test System

Original submission was with a one bottle (aerobic only) test system.

After review of the data, FDA concluded the evidence did not support exclusion of the anaerobic bottle.

There are data to suggest the two bottle system is superior.

Surveillance Results 2004 – Two Bottle Test (n=6600)

	Aerobic	Anaerobic	
Enterobacter aerogenes	2.1 h	2.1 h	True positive
Staphylococcus aureus	10.5 h	12.5 h	True positive
Coagulase-negative Staphylococcus	negative	2.5 d	True positive
Coagulase-negative Staphylococcus	negative	25.6 h	True positive
Staphylococcus aureus	Pos	Pos	False positive
P. acnes		Pos	False positive
P. acnes		n=8 ; > 3 d	No clinical sequelae

One or Two Bottle Test?

Aerobic

1. ⇓ Platelet volume
2. ⇓ Supply cost
3. Only aerobic organisms are important in platelets
4. Clinical cases do not support need to detect obligate anaerobes
5. Reduce action needed to respond to non-clinically important organisms
6. TTD too long to make detection useful

Anaerobic

1. ⇑ Volume = ⇑ Sensitivity
2. Obligate anaerobes are clinically important in platelets
3. Anaerobic bottle more than just no oxygen:
   - Richer source of peptones, amino acids, vitamins, carbon sources
4. Facultative anaerobes grow faster in anaerobic bottle

Facultative Anaerobes

1. *Corynebacterium* spp.
2. *E. coli*
3. *Klebsiella* spp.
4. *Listeria monocytogenes*
5. *Salmonella* spp.
6. *Serratia marcescens*
7. *Staphylococcus aureus*
8. *Streptococcus spp.*

Rationale for the Anaerobic Bottle

Operational / biological principle	Likely Observations
Obligate anaerobes will only be detected with this bottle	•Discordance between aerobic and anaerobic results (pos/neg) in favor of anaerobic for Release Test •Bacteria will be identified as an obligate anaerobic organism

Clostridium perfringens

McDonald CP, Hartley S, Orchard K, et al. Fatal *Clostridium perfringens* sepsis from a pooled platelet transfusion. Transfus Med 1998;8:19-22.

Blajchman MA, Sarwal S, Loeb M. A second example of a transfusion-associated septic reaction associated with *Clostridium perfringens.* Transfusion 2001;41:427.

Rationale for the Anaerobic Bottle

Operational / biological principle	**Likely Observations**
Obligate anaerobes will only be detected with this bottle	•Discordance between aerobic and anaerobic results (pos/neg) in favor of anaerobic for Release Test •Bacteria will be identified as an obligate anaerobic organism
Facultative anaerobic organisms grow better (i.e., more rapidly) in anaerobic bottles	**•Discordance between aerobic and anaerobic results (pos/neg or TTD) in favor of anaerobic for Release Test**

Dutch Experience, 2001 (N=71053)

Sanquin Research at CLB, Amsterdam, The Netherlands

Dirk de Korte, Ph.D.

	Aerobic Only	Anaerobic Only	Both	Total
CN Staphylococcus	**78**	**60**	**10**	**148**
Bacillius Species	**12**	**6**	**5**	**23**
Cornebacterium species	**10**	**8**	**0**	**18**
All Positive	**146**	**303**	**25**	**474**

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Facultative anaerobic organisms grow better (i.e. more rapidly) in anaerobic bottles	•Discordance between aerobic and anaerobic results (pos/neg or TTD) in favor of anaerobic for Release Test
Increasing SDP test volume meaningfully increases the Release Test sensitivity **(bacterial concentration is right at critical level for selection with a 4 mL aliquot)**	**•Discordance between aerobic and anaerobic results (pos/neg), but not favoring one bottle over the other.**

bioMérieux FDA 510(k) Study Pooled Platelets

	Klebs. Pneumoniae 3 CFU/mL		*Serratia marcescens* <2 CFU/mL		*Strep. Viridans* <2 CFU/mL	
Set	**BPA**	**BPN**	**BPA**	**BN**	**BPA**	**BPN**
1	R		R	R	R	R
2	R			R	R	R
3	R	R	R		R	R
4	R	R	R		R	R
5	R	R		R	R	R
6	R	R		R	R	R
7	R	R	R		R	R
8	R	R			R	
9	R	R				R
10	R	R			R	R

Two Bottle Test System

Does the two bottle test system provide a clinically important as well as a practical improvement in the safety of platelet products?

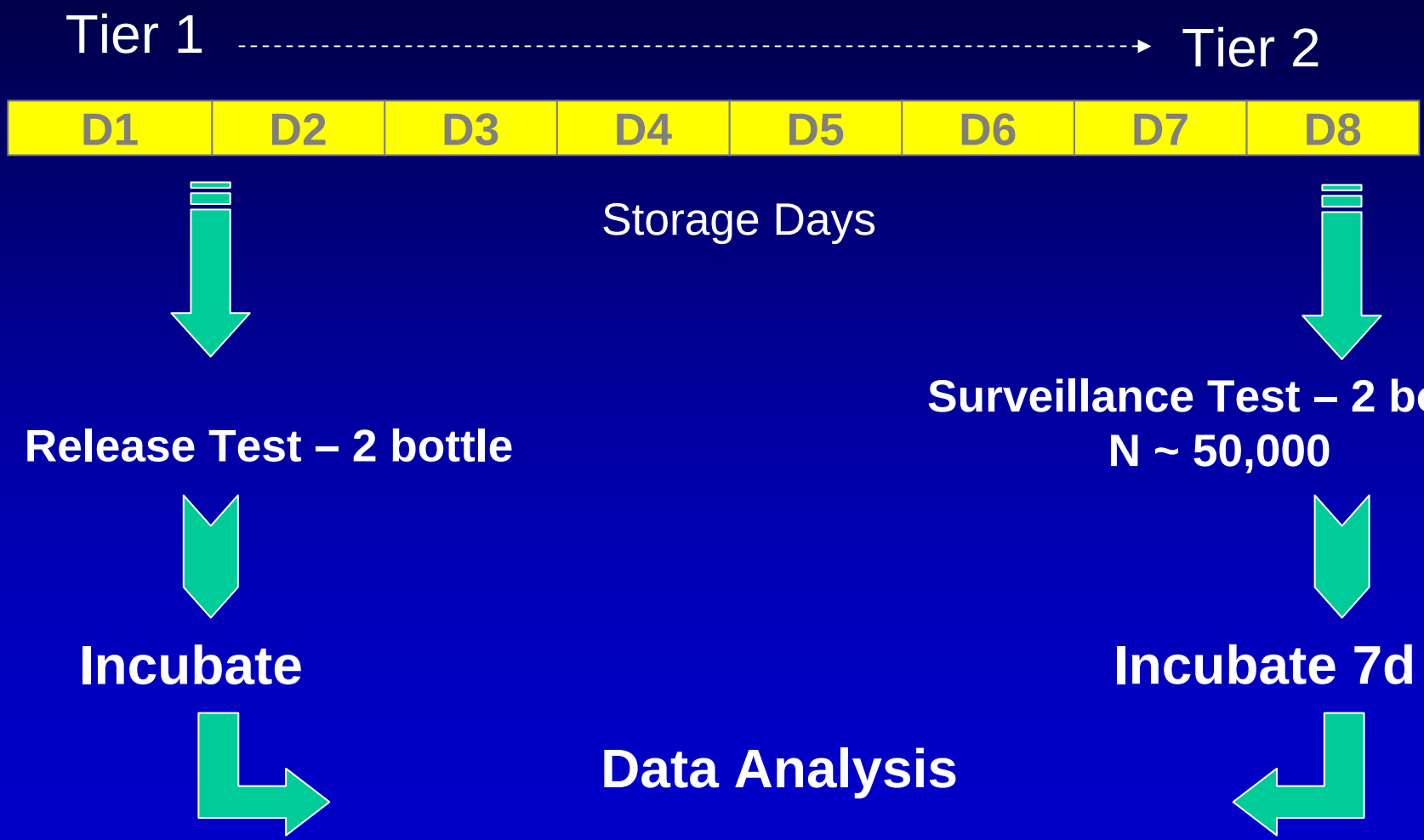
➔ **EQUIPOISE** ➔

DATA ?

Gambro BCT Post Marketing Surveillance Study

NB: FDA conducting final review of protocol

Gambro BCT Post Marketing Surveillance



PRIMARY HYPOTHESIS

7 Day SDP when tested using the BTA Device and Methods as described (i.e., at 24-36 hours post collection, aerobic and anaerobic bottles) will not present a greater risk of a detectable bacterially contaminated platelet unit than 5 Day SDP untested for bacterial contamination.

"New endpoint [for a modified study design]: 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." FDA's Current Thinking on Bacterial Detection in Platelets. ACBSA. August 27, 2004

SECONDARY HYPOTHESES

7 Day SDP when tested using the BTA Device and Methods as described, but using the aerobic bottle only, will not present a greater risk of a detectable bacterially contaminated platelet unit than 5 Day SDP untested for bacterial contamination.

Use of an anaerobic culture in addition to an aerobic culture does not contribute meaningful and/or timely information to improve the risk profile of 7-day SDP compared to 5-day SDP untested.

SPECIFIC AIMS

Determine the Specificity, Sensitivity, Negative Predictive Value, and Positive Predictive Value of the 2 bottle Release Test.

Determine prevalence of bacterial contamination for untested and for 2 bottle BTA tested SDP.

Determine performance contribution of the anaerobic bottle to the BTA and assess the need for anaerobic culturing in this application.