FDA Current Thinking on:

- sample diversion pouches in whole blood collection kits
- detection of bacteria in platelet products
- alternate platelet storage

Advisory Committee on Blood Safety and Availability, DHHS, April 7-8, 2004

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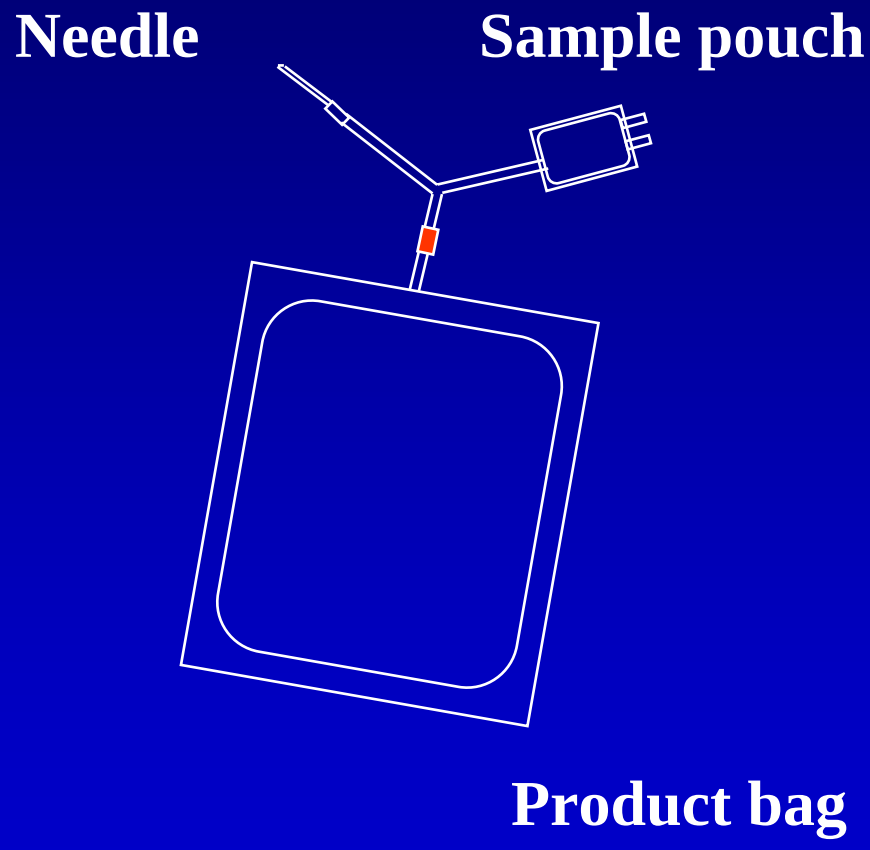
Diversion of Initial Blood to a Sample Pouch

- DESIGN
- closed system
- diverted blood is separated from final blood product by unidirectional flow
- volume of diverted blood is sufficient to provide samples for disease testing and potentially reduce bacterial contamination in the transfusion product



FDA Approved NDA Supplements for Sample Diversion Pouches

- Diversion pouch blood collection kits
  - Baxter (Jan 03)
  - Pall (Dec 02)
  - Terumo (Sept 03)

Approval Criteria for Sample Diversion Pouches

- Conformance with FDA design proposed at BPAC Dec 2002
- No clinical data requirements if without claims for decreasing bacterial contamination
- Initial approved designs continue to be improved based on clinical experience

Bacterial Detection Devices Cleared by the FDA

- Automatic culture devices for Quality Control (Q/C) of platelet collection process
  - BacT / Alert (BioMerieux Inc) (Feb 02)
  - BDS (Pall Corp) (Oct 02)

FDA Current Thinking for Clearance of Bacterial Detection Devices Based on Intended Use of Device

- **Quality control (Q/C) indication:** sampling of small number of collected products to assure collection process is in control (as few as 4/month)
  - Transfuse product without waiting for results

- **Product release indication:** screening of all products prior to release for transfusion
  - Decision to transfuse depends on results

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Bacterial Detection by Automated Bacterial Culture Devices-points to consider

- Contamination at collection is very low, need to allow bacterial proliferation in product to reach detectable levels (24-48 hrs)
- To preserve shelf life of product need to sample product soon after collection (can lead to sampling error)
- Larger sample volume improves sensitivity but depletes product
- Detection requires proliferation of bacteria in the device (additional 24-48 hrs)
- Detection is based on metabolically active bacteria in the device; may not detect dead bacteria or endotoxin

Bacterial Growth in Transfusion Products

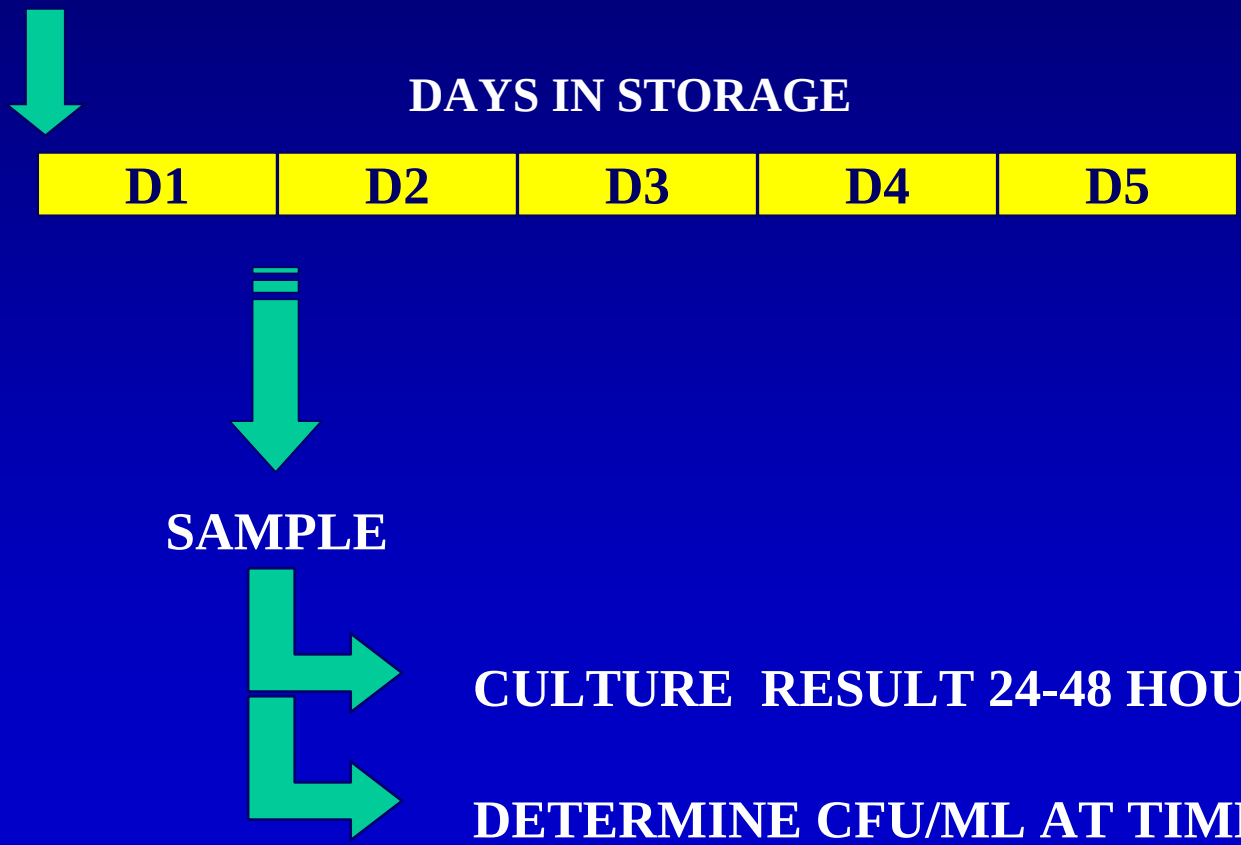
- Wide variety of bacterial species has been identified as contaminants of transfusion products (Gram negative and Gram positive)
- The level of initial inoculum is very low (1-5 CFU/ml or less)
- Bacteria proliferates in product (can reach $10^{5\text{-}6}$ CFU/ml)
- Rate of bacterial proliferation in the product is dependent on bacterial species, storage temperature, donor characteristics (antibodies, complement)

FDA Current Thinking on Clearance of Bacterial Detection Devices Used for Q/C of Platelet Products

- In vitro testing
  - Device is tested on platelet products intentionally contaminated with variable levels of bacteria (spiking study)
- Testing identifies
  - Device sensitivity for particular bacterial species
  - Optimal sampling time and sample volume
- Devices with low sensitivity need to allow time for bacterial proliferation in the platelet product and thus sampling is done later in storage of product

LABORATORY TESTING OF BACTERIAL CULTURE DEVICES

“SPIKE” IN BACTERIA, 1-10 CFU/ML



Bacterial Species Relevant to Validating Automated Bacterial Culture Devices

- Suggested minimal list of bacteria
  - Brecher, M. E. et al. Evaluation of automated culture system for detecting bacterial contamination of platelets: an analysis with 15 contaminating organisms. Transfusion 41:477-482, 2001
- Labeling of cleared device will reflect the specific bacteria tested

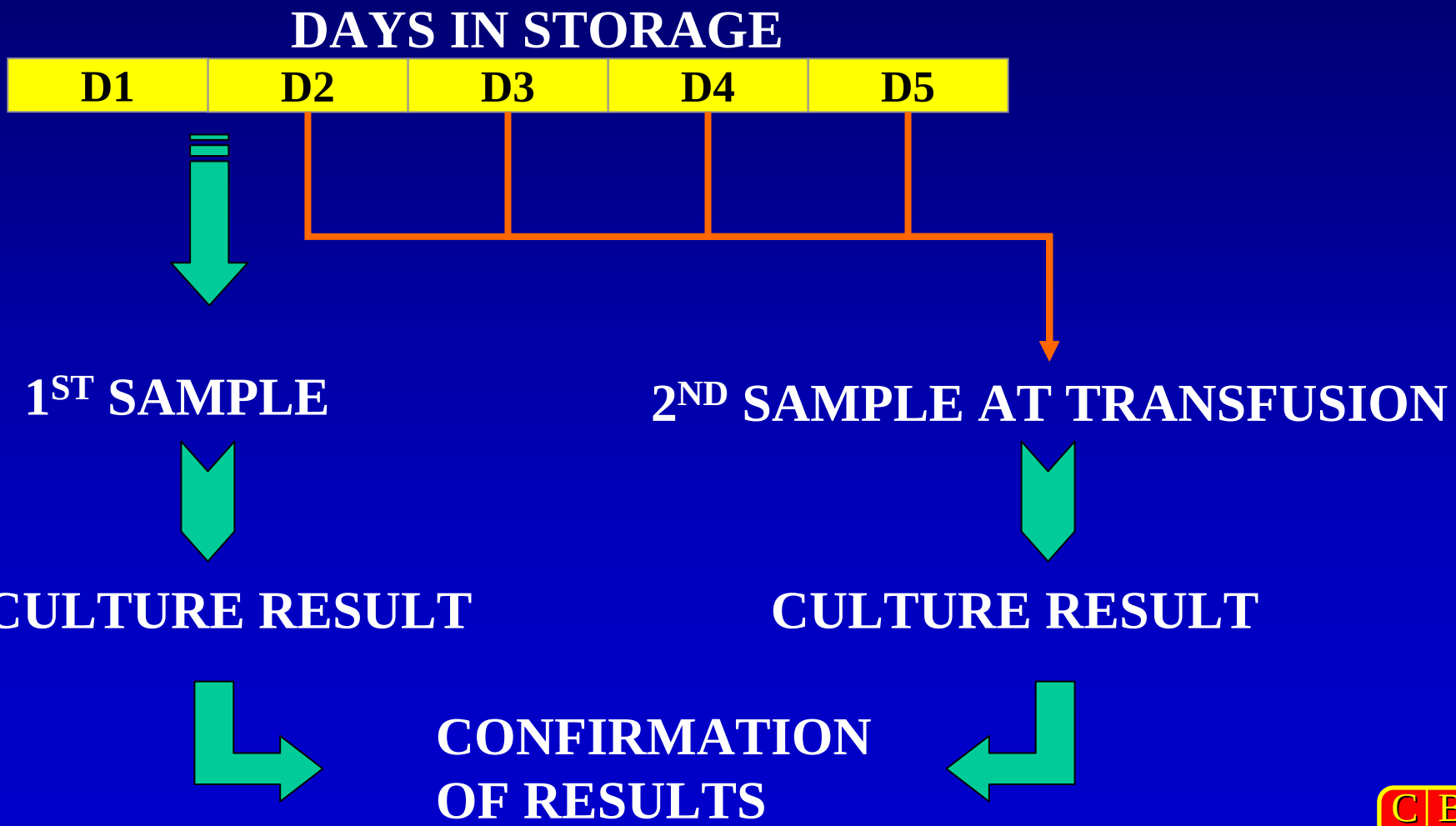
FDA Current Thinking on Evaluation of Bacterial Detection Devices for Release of Platelet Products for Transfusion

- More stringent criteria because device assures that products are not contaminated with greater than a certain level of bacteria (based on labeling of the device)
- For culture based detection devices need to establish the predictive value of an early culture sample
- Need to establish the false negative rate and the false positive rate for the device under actual use conditions

FDA Current Thinking on Evaluation of Bacterial Detection Devices for Release of Platelet Products

- In vitro testing same as for Q/C indication
- “Field trial” to demonstrate performance of device under actual use conditions
- Sampling of transfusion products from routine collections
- For culture-based devices:
  - Demonstrate that culture results of a sample taken early in storage period are predictive of results of a sample taken at end of storage or at time of release of product

DESIGN OF A FIELD TRIAL FOR BACTERIAL CULTURE DEVICES (BPAC Dec 2002)



Field Trial of Bacterial Detection Devices for Screening of Platelet Products

- Primary endpoint: concordance of 1st and 2nd cultures with 95% confidence
- Establish sensitivity, specificity and predictive value of the first culture
- May require a large study due to low level of contamination (30-50,000 units screened)
- This approach was supported by Blood Products Advisory Committee (BPAC)

  Dec 2002

Using Bacterial Screening to Approve Future Platelet Products

- Applying culture-based bacterial detection for a product release limits shelf life by 24-48 hrs
- Shelf life of platelets is limited by concerns over bacterial contamination (1986 BPAC)
- Application of bacterial screening and shelf life extension could be combined in field trials to reduce cost and eventually in clinical practice

Bacterial Contamination of Platelet Products-Relative Risk of Various Products

Lower Risk	Current Risk	Higher Risk
5 day platelets screened with validated bacterial detection method	5 day platelets	7 day platelets[1] Pre-storage pooled platelets[2]

1- higher risk based on 1986 BPAC decision to reduce platelet shelf life to 7 days

2- higher risk based on Wagner et al. Comparison of bacterial growth in single and pooled concentrates after deliberate inoculation and storage
Transfusion 55:298-302, 1985

Approval of Future Platelet Products Based on Relative Risk

- The bacterial risk of future products should not be greater than the risk of a 5 day platelet screened for bacterial contamination with FDA-approved method or device
- Relative bacterial risk of a novel platelet product should be demonstrated in a field trial

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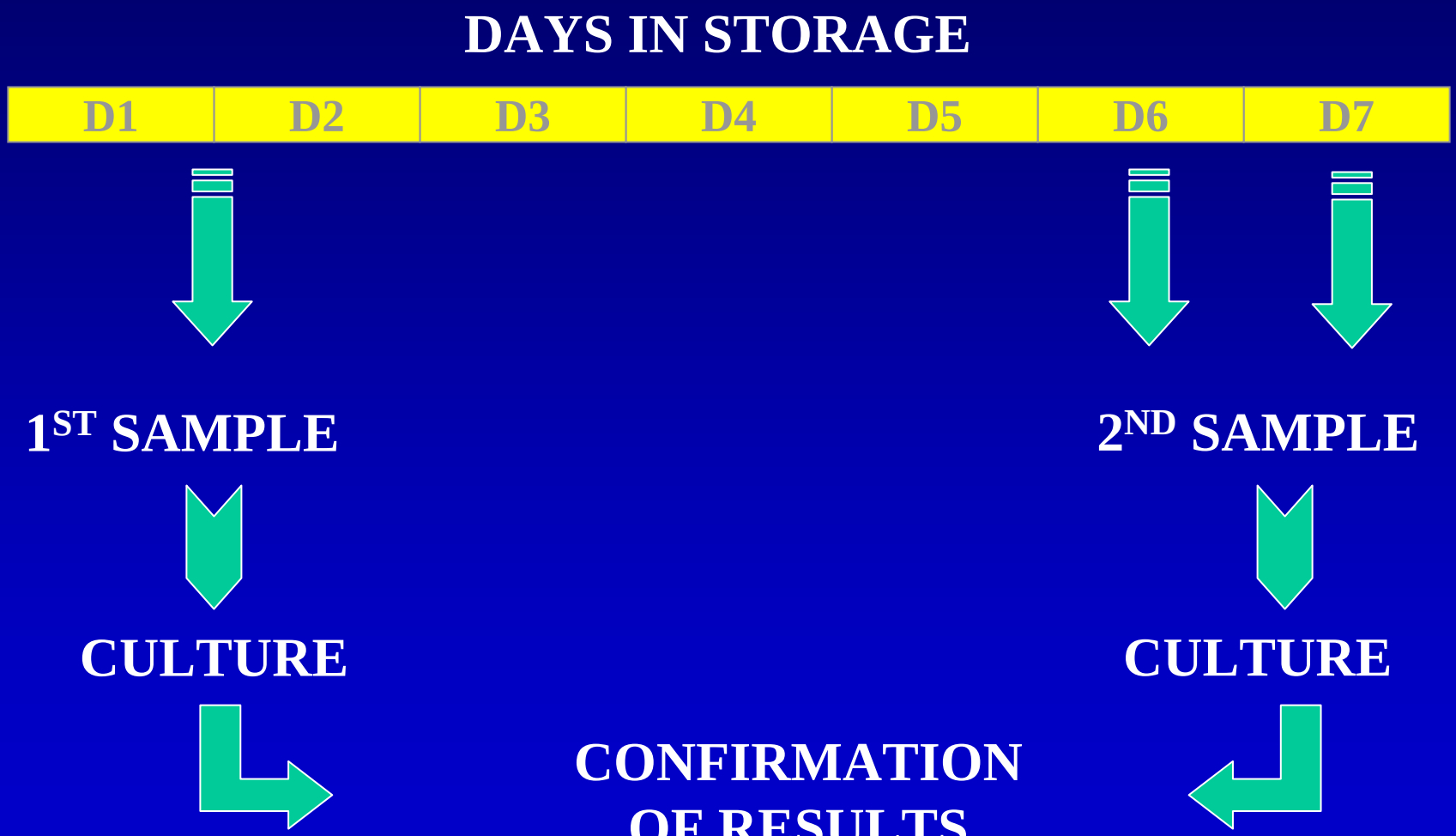
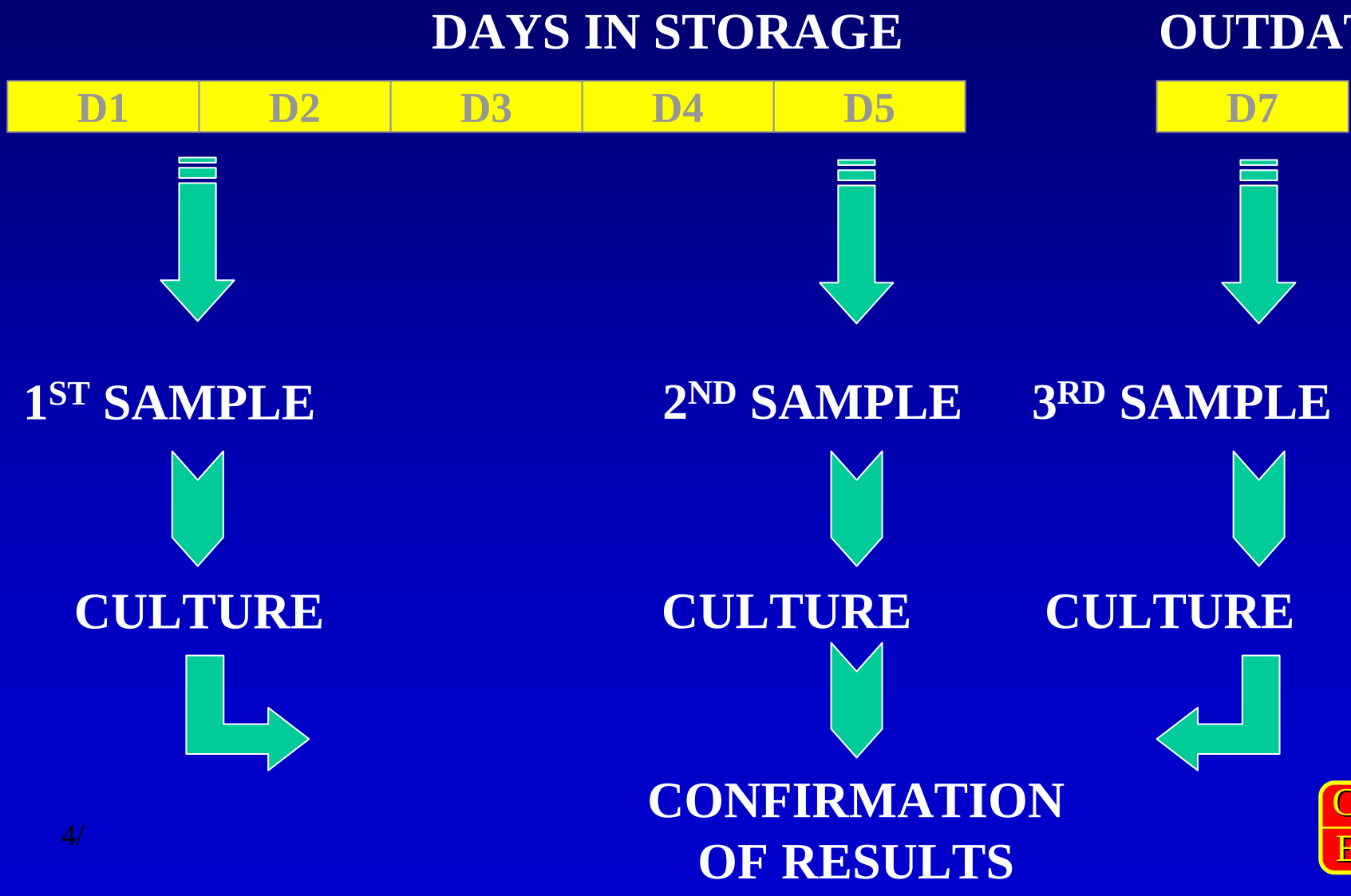
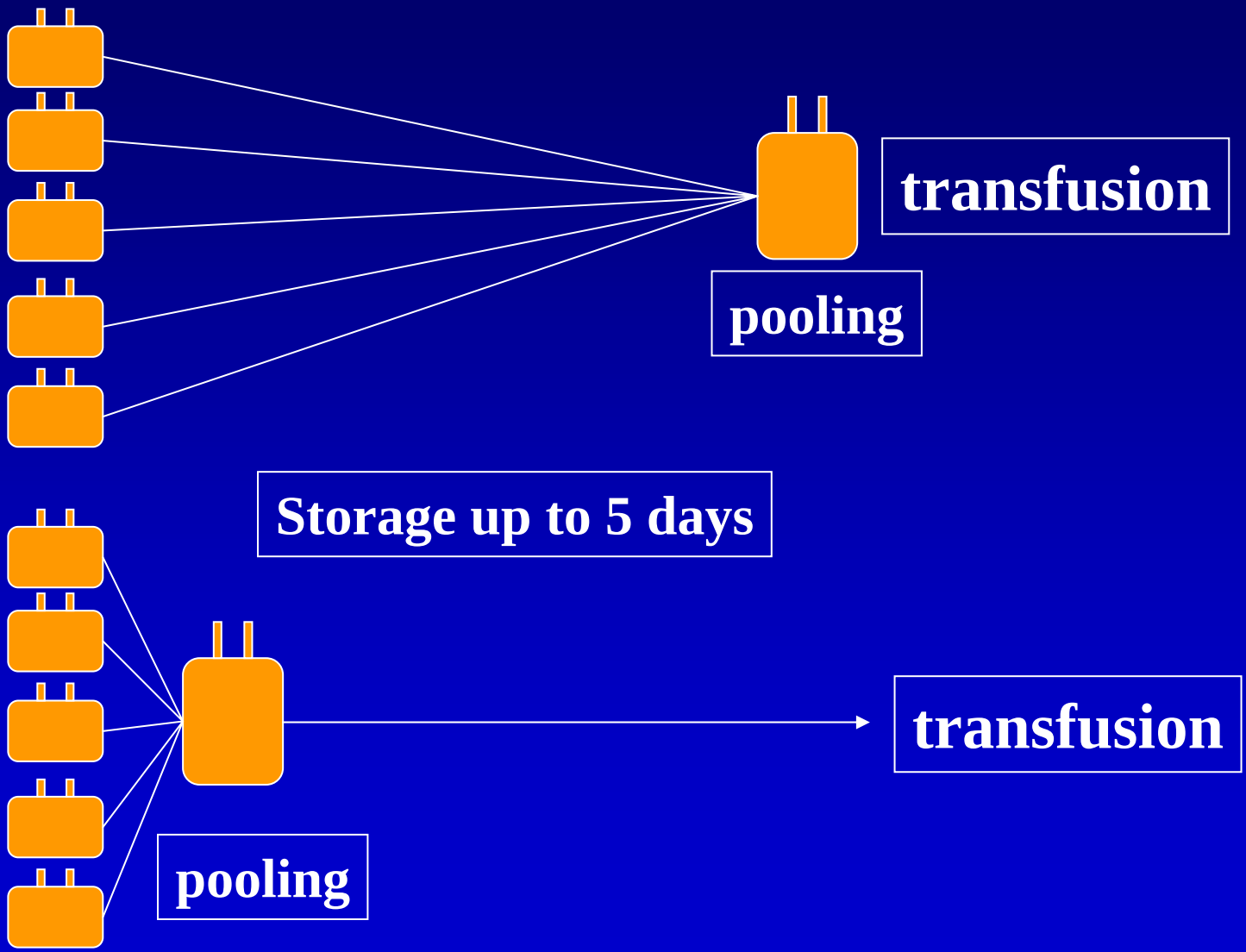
BACTERIAL DETECTION IN 7 DAY-STORED PLATELETS-units transfused under IND



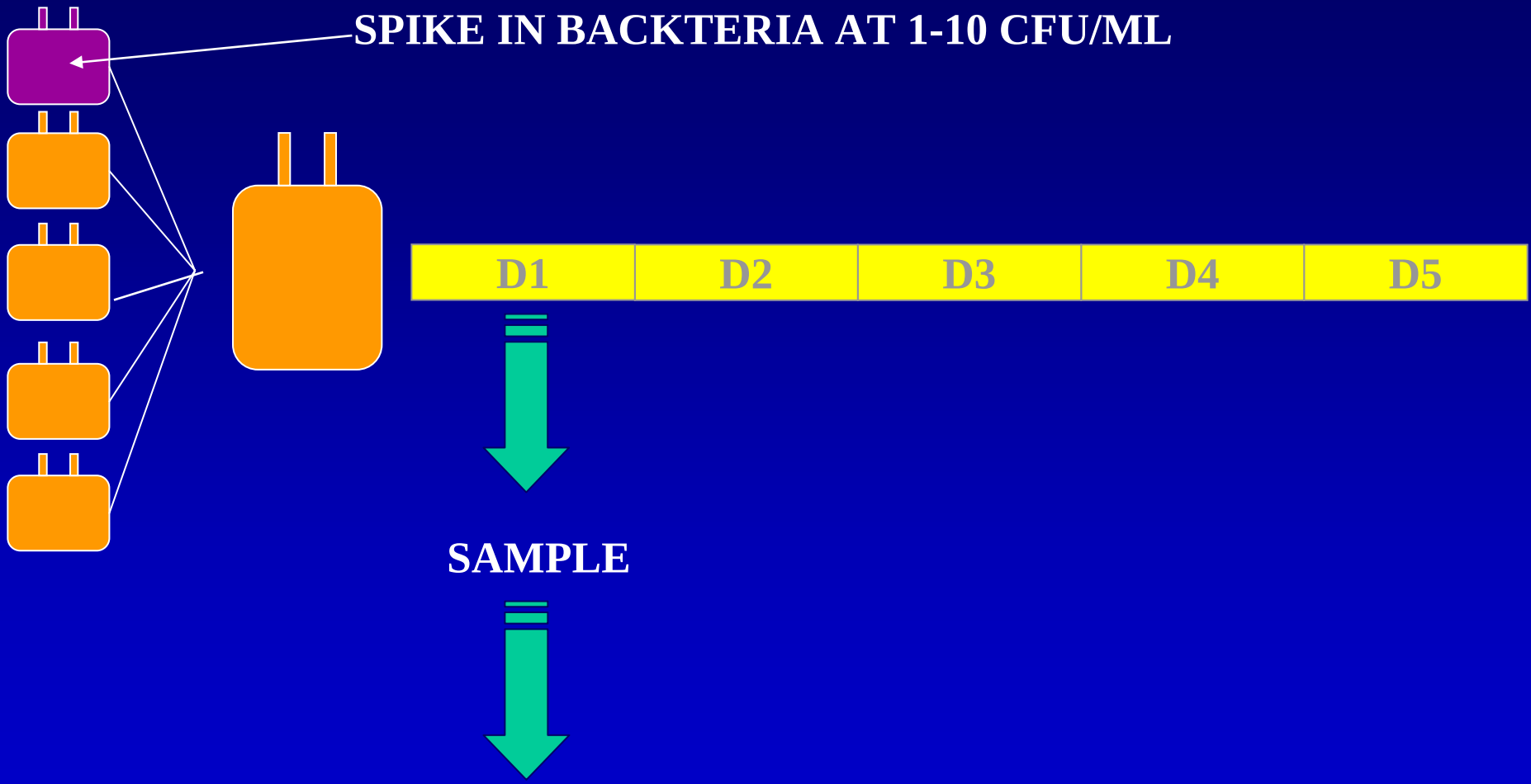
FIELD TRIAL OF AUTOMATIC CULTURE DEVICES FOR 7 DAY STORED PLATELETS- Using outdated units



Post-Storage vs Pre-Storage Pooling of Whole Blood-Derived Platelets



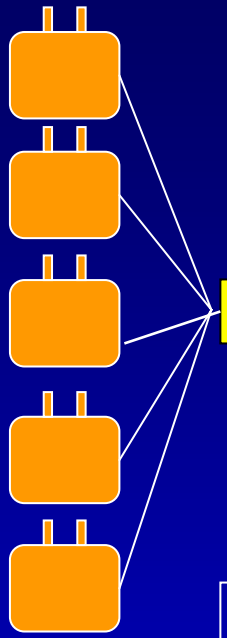
In vitro spiking protocol for pooled platelets



CULTURE RESULT 24-48 HOURS LATER

DETERMINE CFU/ML AT TIME OF SAMPLING

Field Trial of Pre-Storage Pooled Platelets



DAYS IN STORAGE

D1	D2	D3	D4	D5

1ST SAMPLE

2ND SAMPLE

CULTURE RESULT

CULTURE RESULT

CONFIRMATION OF RESULTS

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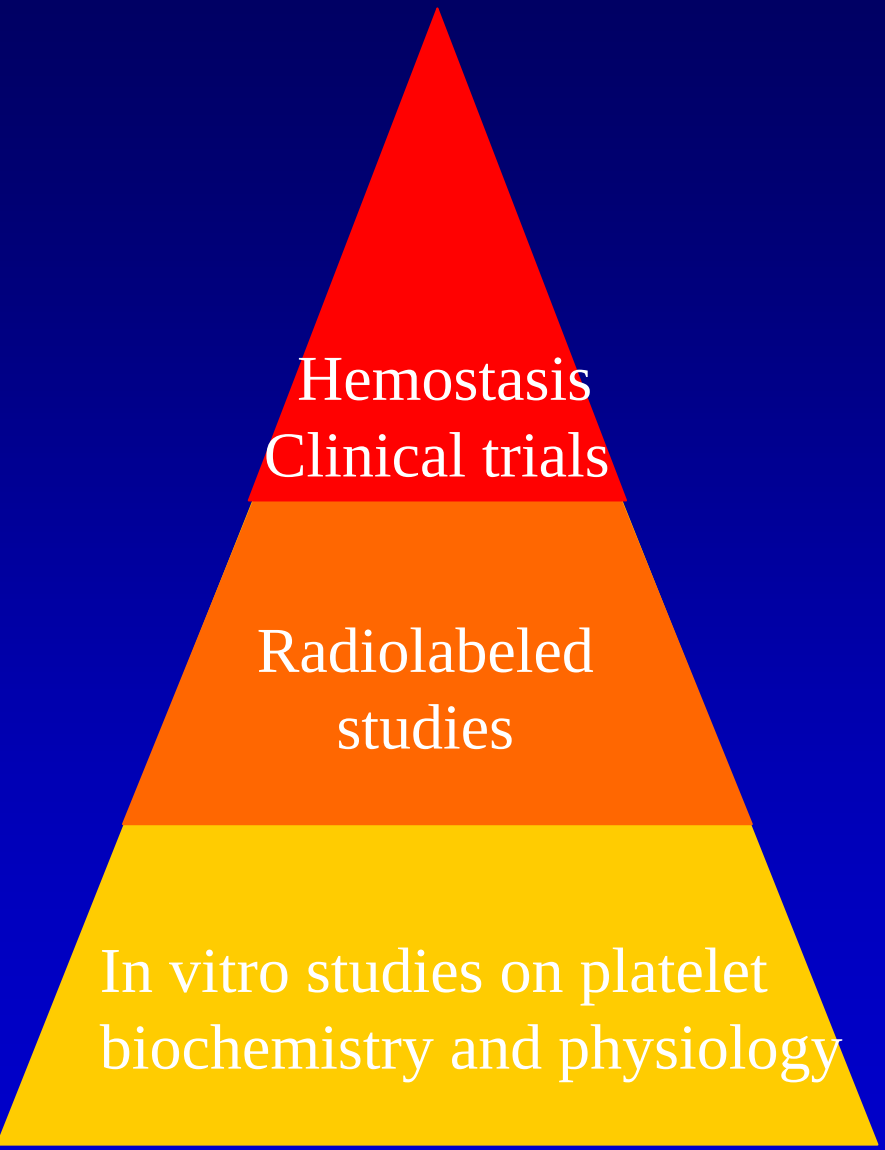
Detection of bacteria in a novel platelet product is only half the story…..

Demonstration of Adequate Platelet Efficacy After Storage

- Platelets with extended shelf life or pre-storage pooled platelets need to function as well as the current platelet product when transfused
- Storage containers need to be validated for extended storage or pre-storage pooling

MAJOR CONCERNS ABOUT PLATELET EFFICACY



Platelet substitutes
Chemically modified platelets

Storage extension beyond 7 days
New storage media

New 5-7 day storage container
New apheresis collection device

Minor modifications to
current storage conditions

Current storage condition validation

MINIMAL CONCERNS ABOUT PLATELET EFFICACY

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Radiolabeling Studies to Validate Platelet Storage Containers

- Appropriate for validation of single donor products (autologous)
- Ethical issues prevent use of this approach with pooled products and healthy volunteers (alloimmunization)
- FDA suggested a new approach using transfusion responses in thrombocytopenic patients receiving platelet products as therapy
- (BPAC March 2003)

Monitoring Transfusion Responses in Thrombocytopenic Patients

- Transfuse with pooled products (4 hour pool vs extended storage pool product)
- Measure Corrected Count Increments and transfusion frequencies
- Study size will depend on expected variability to platelet transfusions in a given patient population (in the range of 50 pts per arm)

Summary of Gaps in Current Regulatory Landscape

- Bacterial Detection Devices
  - Are not cleared for release of platelet products (5 or 7 day)
  - Are not cleared for testing (release or Q/C) pooled whole blood derived platelets
  - Are not cleared for platelet release based on point of care sampling
- Storage devices (bags) are not cleared for pre-storage pooling of whole blood platelets (5 or 7 day)

Studies Needed

- Field trial of culture-based devices for screening platelets to determine predictive value of test (5 day, 7 day, pooled product)
- In vitro tests for bacterial detection of pooled random donor platelets
- In vitro and field trials for point of care bacterial detection devices
- Platelet efficacy:
  - validation of bags for storing pre-storage pooled platelets