Impact of FDA Licensure on Cord Blood Banking and Transplantation

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Carolinas Cord Blood Bank

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Duke Translational Medicine Institute

The Journey and inherent challenges:

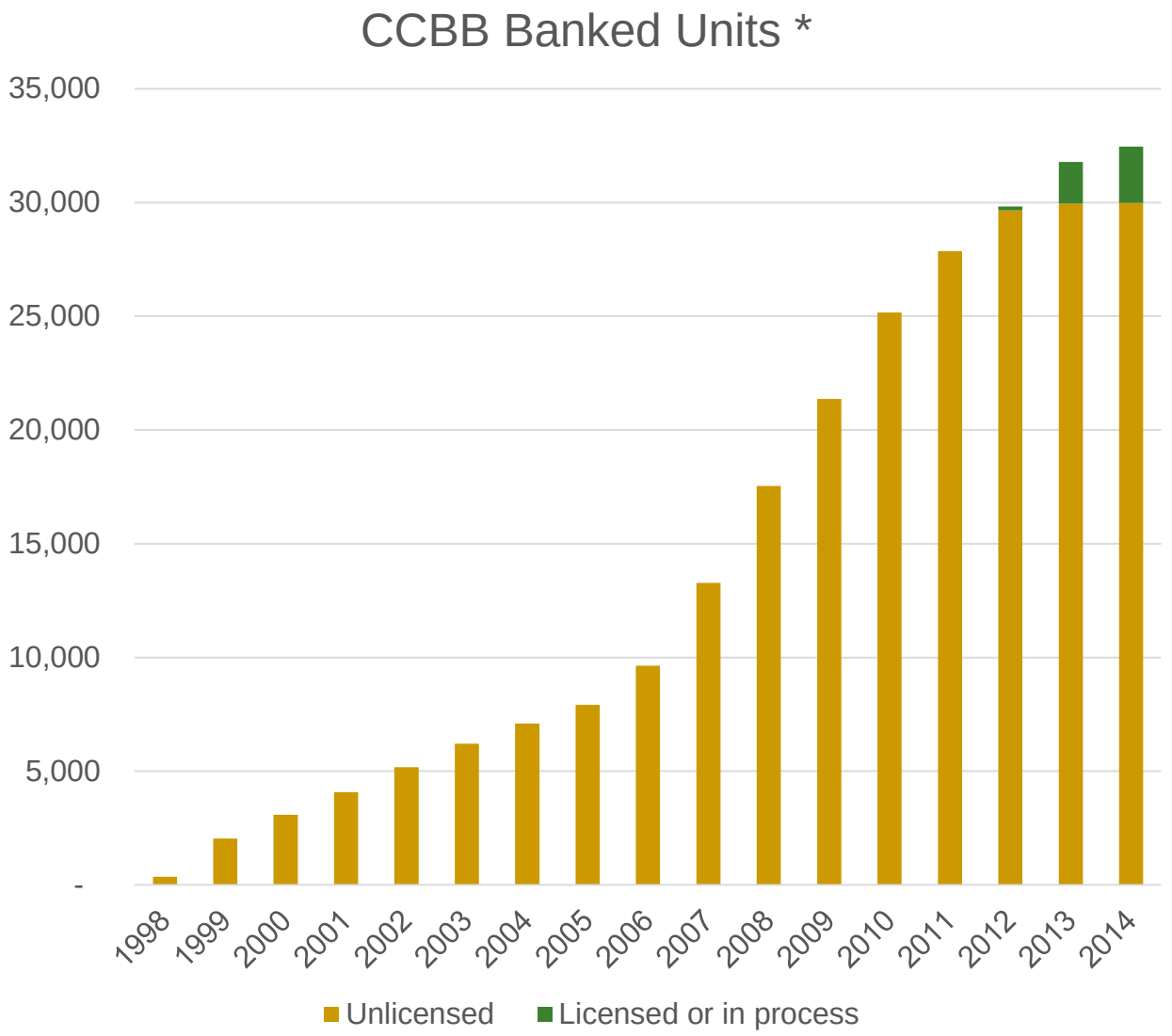
- **New culture**
- **New vocabulary**
- **New way of thinking**
- **Academic medical center**
  - Never held a BLA
  - Didn’t understand facilities requirements
  - Resistance to enhanced needs for cleaning, increased monitoring, increased documentation
  - Not oriented towards QSUs

CCBB Timeline

- **9/2010: Pre-BLA meeting with FDA**
- **9/2011: Initial Submission**
- **3/2012: PAI**
  - Requests for many repeat validations
- **6/2012: Amendment (Large)**
- **10/4/2012: Approval**
- **12/2013: Post 1 year inspection**
  - Upgrade OOS processes
  - Enhance deviation reporting and investigations

~2,800 units distributed for transplantation

* Includes CORD:USE units; Data up to Apr 2014



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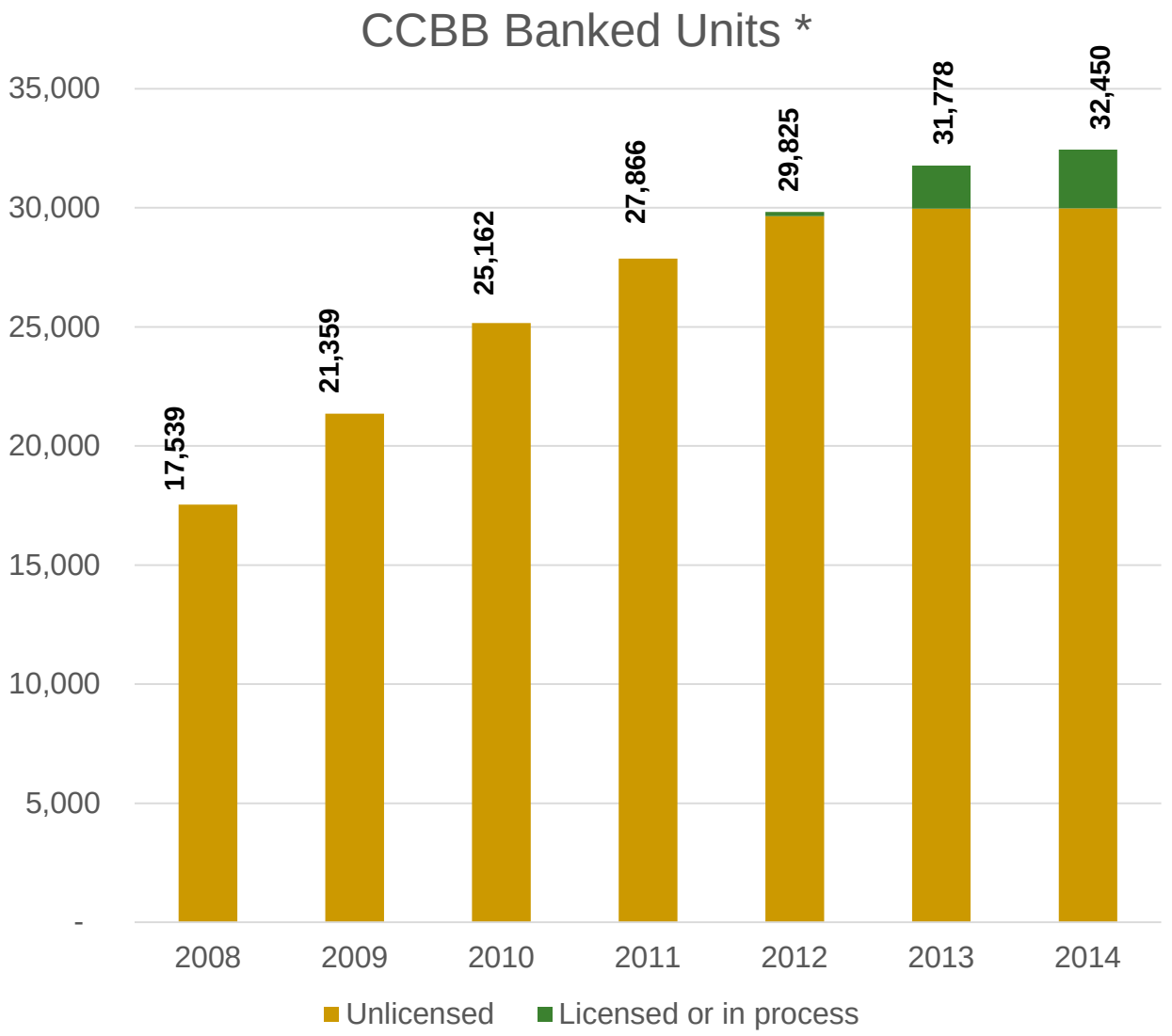

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PAI issues

- **QSU**
- **Stability**
- **Signoffs**
- **Bact-T alert validation**
- **CD34 validation**
- **Increased environmental monitoring**
- **Requalification of FDA approved supplies/reagents:**
  - Hespan (hetastarch); collection bags
  - DMSO

Post 1 year inspection issues

- **OOS Deviations**
  - Biologic versus process deviations
    - Small collections
    - Positive cultures
- **Hespan**
- **EM: transport of control media**
- **Qualification of in house vendors**
- **Comprehensiveness of investigations**

LICENSURE HAS INCREASED COSTS!

- **One time costs: ~$5M**
  - **Major facility renovation: $3.2M**
  - **New electronic document management system**
  - **Expansion of QSU**
  - **Process engineering**
- **Ongoing yearly increases: $1.5M**
  - **QSU**
  - **New employees: CRAs, Lab Technologists, QSU**
  - **Cleaning, EM, engineering and operations**
  - **Increased documentation**

Other important issues

- **Cord blood sales are not increasing, may be decreasing. Utilization may be equilibrating.**
- **‘Manufacturing” costs have increased 10-20%.**
- **The transplant centers are pushing for reduction of charges for CBUs, particularly in the double cord setting.**
- **How do we reconcile this situation?**

NMDP Data

To project numbers of potential discards if we use various TNCC cutoffs

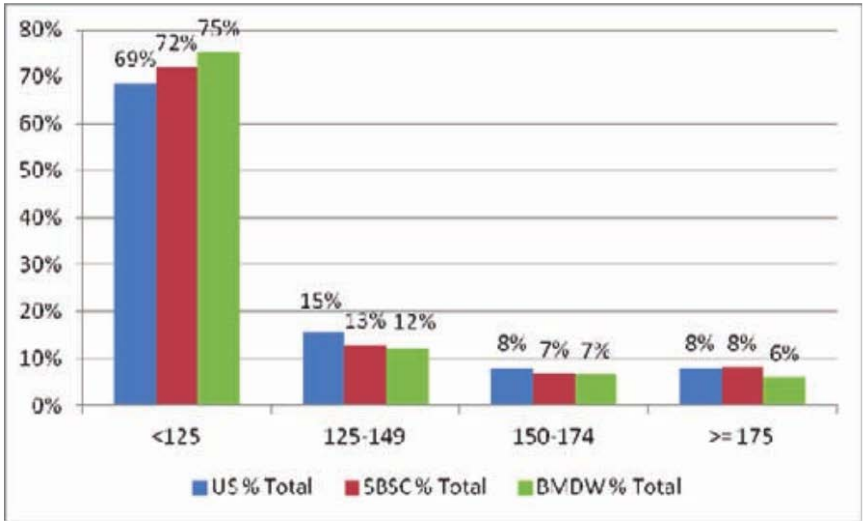


Fig. 2. Inventory distribution by TNC count (US/NMDP, Swiss/SBSC and international/BMDW data 2010).

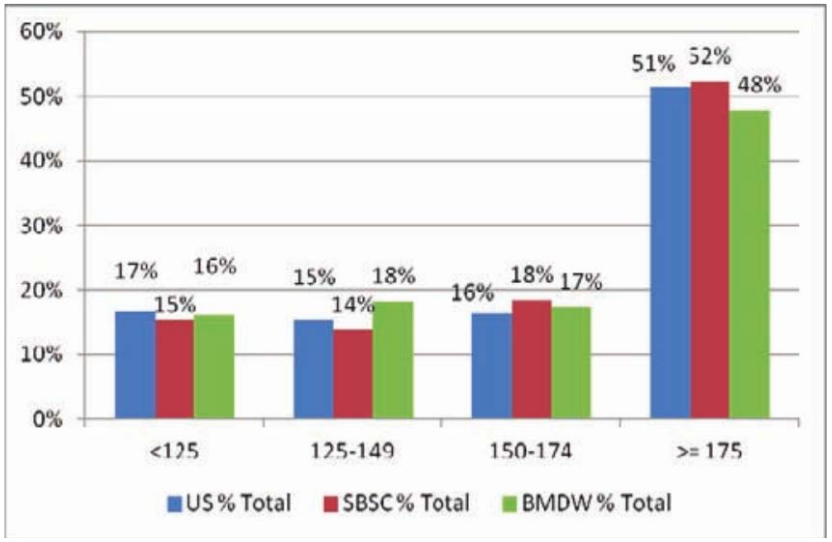


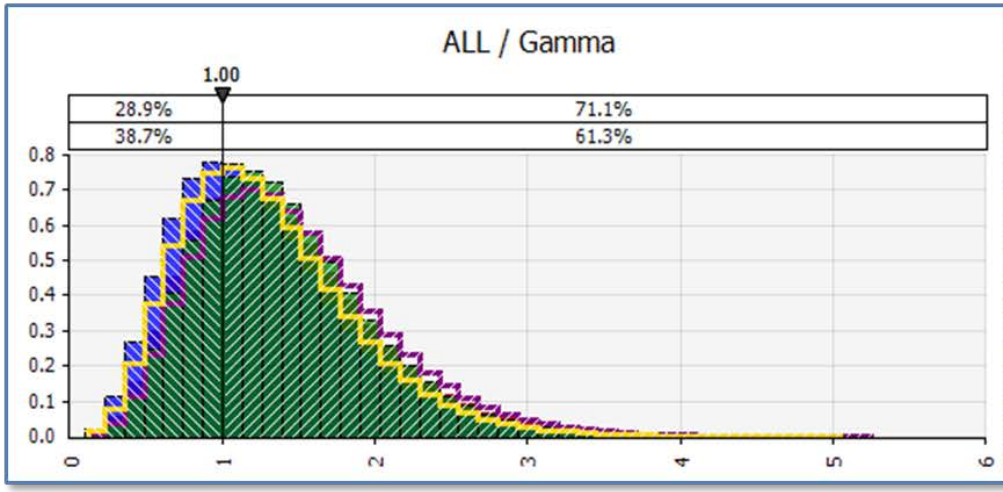
Fig. 3. Selection distribution by TNC count (2010 BMDW data).

Bart et al, Transfusion Medicine and Hemotherapy, 2013; 40: 14-20

CBU Pre-Processing TNCC Modeling

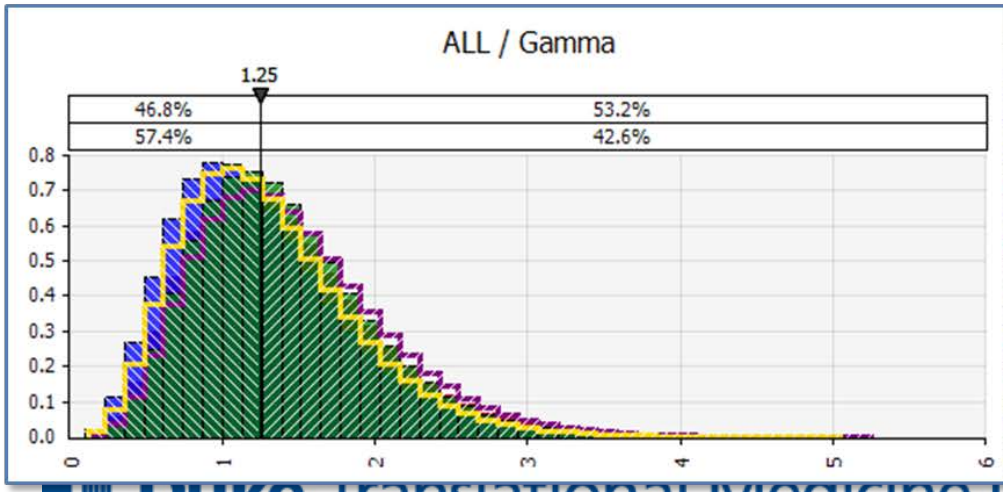
Summary Statistics by Race (TNCC10^9)					
Race	Lvl	N	Mean	Std Dev	median
AFA	1	10,254	1.231	0.612	1.119
OTHER	2	7,666	1.396	0.611	1.278
CAU	3	32,231	1.453	0.649	1.326
HIS	4	9,577	1.292	0.615	1.171
ALL	0	59,728	1.381	0.639	1.260
Note: Includes all CBU's with TNCC and Race (Excluded 416 - No Race)					

CBU Pre-TNCC Discard Modeling



Statistics

	ALL / Gamma	AFA / Gamma	OTHER / Gam..	CAU / Gamma	HIS / Gamma
Minimum	0.1249	0.0951	0.0971	0.1212	0.1191
Maximum	5.1782	4.8008	4.7991	5.2567	5.0522
Mean	1.3811	1.2306	1.3956	1.4527	1.2921
Mode	1.1893	0.9847	1.1776	1.1587	1.0439
Median	1.2953	1.1470	1.3189	1.3671	1.2097
Std Dev	0.5995	0.5589	0.5697	0.6139	0.5684
Skewness	0.8687	0.9090	0.8158	0.8463	0.8829
Kurtosis	4.1338	4.2400	3.9928	4.0780	4.1871
Values	10000	10000	10000	10000	10000
Errors	0	0	0	0	0
Filtered	0	0	0	0	0
Left X	1.00	1.00	1.00	1.00	1.00
Left P	28.9%	38.7%	26.3%	24.6%	34.1%



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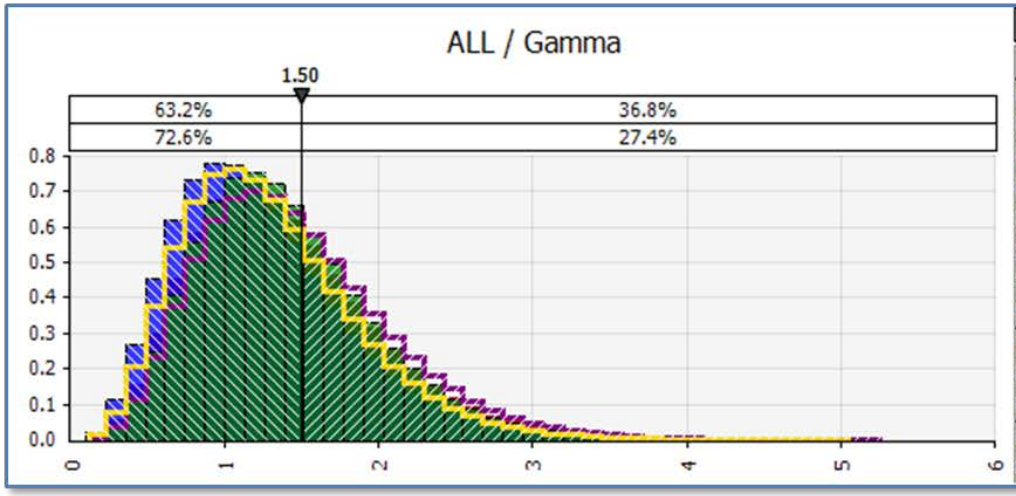
Values	10000	10000	10000	10000	10000
Errors	0	0	0	0	0
Filtered	0	0	0	0	0
Left X	1.25	1.25	1.25	1.25	1.25
Left P	46.8%	57.4%	44.9%	41.9%	52.9%

CBU Pre-TNCC Discard Modeling



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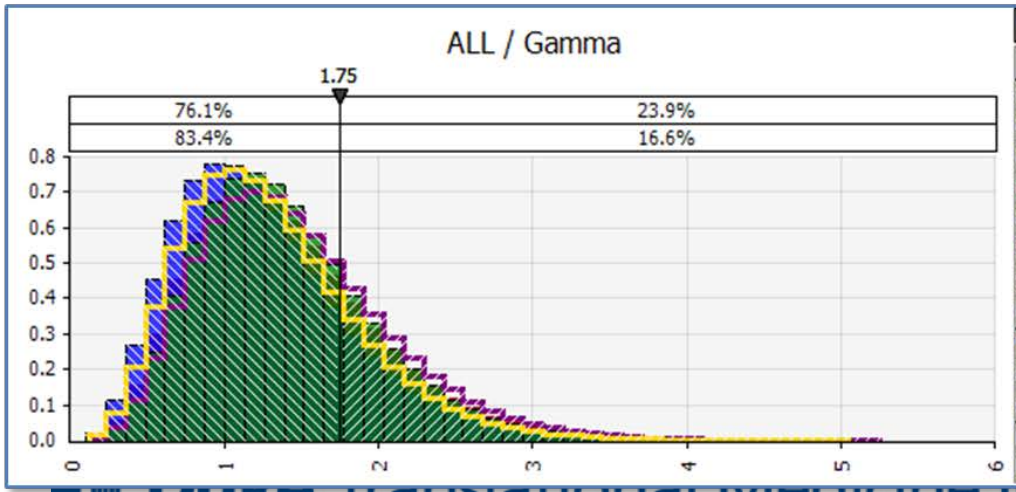
Values	10000	10000	10000	10000	10000
Errors	0	0	0	0	0
Filtered	0	0	0	0	0
Left X	1.50	1.50	1.50	1.50	1.50
Left P	63.2%	72.6%	62.4%	58.6%	68.9%



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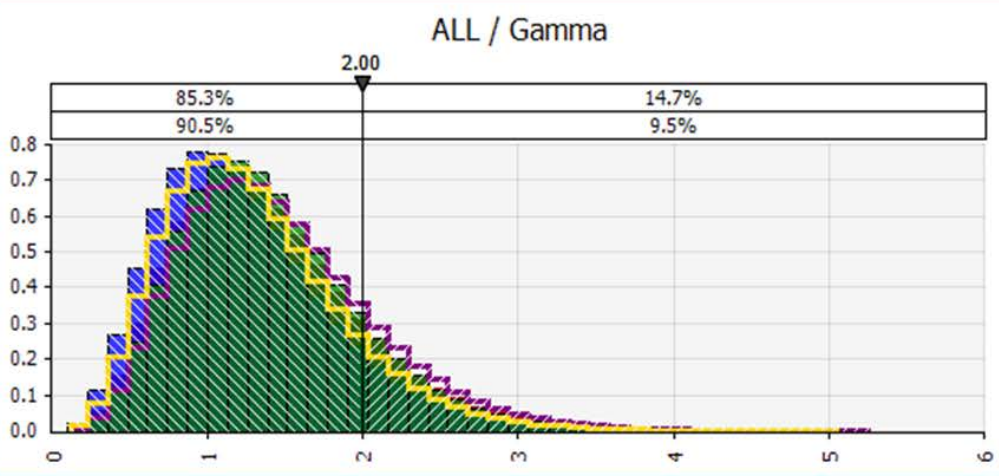
Kurtosis	4.1338	4.2400	3.9928	4.0780	4.1871
Values	10000	10000	10000	10000	10000
Errors	0	0	0	0	0
Filtered	0	0	0	0	0
Left X	1.75	1.75	1.75	1.75	1.75
Left P	76.1%	83.4%	76.1%	72.4%	80.8%

CBU Pre-TNCC Discard Modeling



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Kurtosis	4.1338	4.2400	3.9928	4.0780	4.1871
Values	10000	10000	10000	10000	10000
Errors	0	0	0	0	0
Filtered	0	0	0	0	0
Left X	2.00	2.00	2.00	2.00	2.00
Left P	85.3%	90.5%	85.8%	82.6%	88.7%

Pre-TNCC Discard Modeling

% of CBUs Discarded Based on Minimum Pre-TNCC Requirement			
Pre-Processing TNCC ($x10^9$ cells)	% CBUs Discarded		
	All	African American	Caucasian
1	28.9	38.7	24.6
1.25	46.8	57.4	41.9
1.5	63.2	72.6	58.6
1.75	76.1	83.4	72.4
2	85.3	90.5	82.6

Post-TNCC Discard Modeling

- **Similar trend seen as with pre-TNCC modeling**
  - **16% of CBUs with measured post-TNCC are AA**
  - **59% of CBUs with measured post-TNCC are Caucasian**

- **At the current qualifying post-TNCC cutoff of 0.9 x 10^9 cells, we would need more than 4x the number of AA CBUs with measured post-TNCC to have an equivalent rate of discard to the Caucasian CBUs**

Other issues

- **Rigid specs results in exclusion of units that are likely to have equivalent quality**
- **Do we increase the TNCC thresholds for banking?**
- **Implementation of new supplies, procedures, reagents, is very difficult and slow**
  - Validations and qualifications
  - Long times for reviews and approvals
    - Despite FDA approvals of products
  - Example: new sepax cryobags

Recommendations

- Increase HRSA reimbursement or find alternative sources of funding
- Do not require requalification of FDA approved for human use reagents and supplies
- Increase the ‘nimbleness’ of the system to allow for minor changes in processes/reagents/supplies
- Lower sales, increased costs
- Potency, stability
- Outcomes data - increasing efficiencies

THANKS!!!!!!!!!!!!!!!!

ANY QUESTIONS????????