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Regulation of PBSC and DLI from Unrelated Donors: Meeting the Needs of U.S. Transplant Patients

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FDA Liaison Meeting

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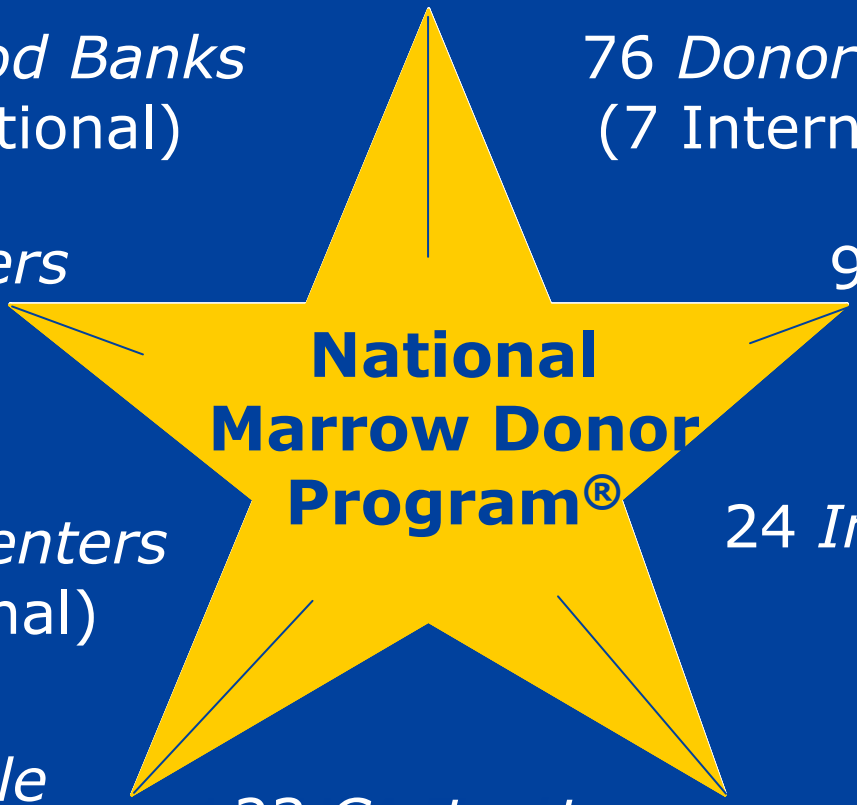
The NMDP Network



165 *Transplant Centers*
(43 International)

18 *Cord Blood Banks*
(2 International)

76 *Donor Centers*
(7 International)

90 *Apheresis Centers*
(8 International)

9 *Recruitment Groups*

100 *Collection Centers*
(17 International)

24 *Intl Registries*

Research Sample Repository

23 *Contract Laboratories*

Donor DNA Repository

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NMDP U.S. Product Collection Sites

88 FDA-registered domestic tissue establishments currently collect PBSC and DLI products

- 63 of 88 (72%) are hospital-based
- Only 3 of 63 are licensed biologics establishments*
- The 60 unlicensed establishments collected 1053/1371 (77%) of the products in 2005

Primary activities of these centers include: related donor PBSC and DLI; platelet apheresis and therapeutic plasma apheresis

Concern is that some of these centers would stop collections if licensure is required

*www.fda.gov/cber/ep/part1.htm, 5/23/06

Issues in Unrelated PBSC Regulations

- The safety and efficacy of unrelated PBSC, related PBSC and bone marrow are similar, yet they are regulated differently (351, 361, HRSA)
- If licensure of unrelated PBSC is required, requirements must reflect current data on safety and efficacy and be feasible to implement in different types of apheresis centers
- Importation of PBSCs is essential to meet the needs of US transplant patients; the regulatory framework needs to allow continued importation of these products without becoming burdensome

Level and Type of Regulation Should be Commensurate with the Risk Posed by the Product Characteristics

Only relevant controllable risk associated with collection of unrelated PBSC & DLI is *transmission of communicable disease*

PBSC & DLI are very different from traditional biological drugs:

- Patient-specific, with a high degree of HLA matching
- Minimally manipulated and infused fresh
- Manufacturing beyond the apheresis collection is minimal
- Quality is uniformly high; variability is dependent on donor factors, not the manufacturing process
- Product will be infused no matter what

Thus, the provisions in 21 CFR 1271 through donor eligibility & GTPs adequately cover the risk of communicable disease transmission

NMDP's Proposal for FDA Consideration

FDA will regulate *unrelated donor* PBSC and DLI products that are…

- Minimally manipulated,
- Homologous use,
- HLA-matched, and
- Used for hematopoietic reconstitution…

in same manner as *related donor* PBSC and DLI.

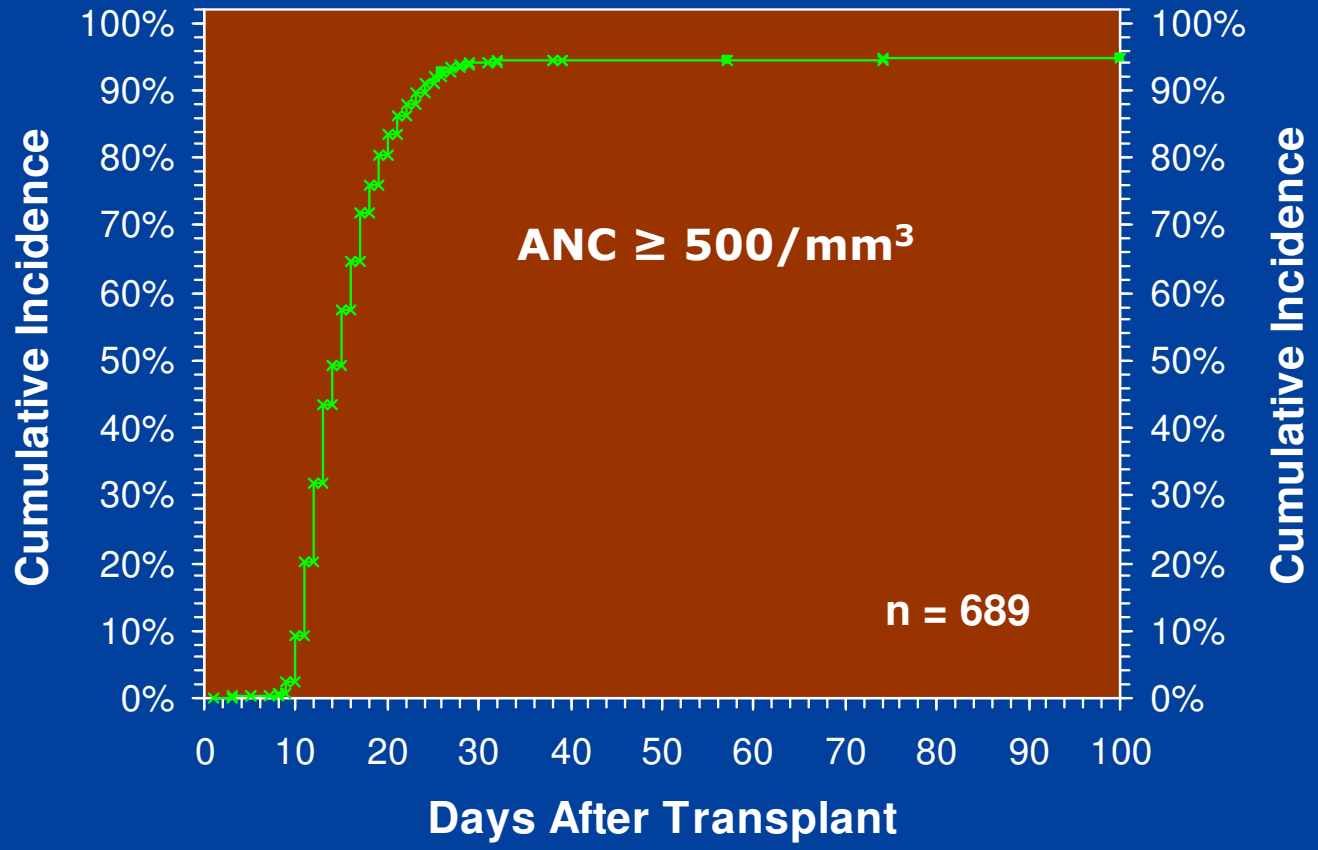
Study Cohorts

- 1178 Primary PBSC transplant recipients between August 1999 and December 2003 with at least 100 days follow-up or who died prior to day 100
- Donors of the products received by these recipients
- Only products that were minimally manipulated, but T-cell depletion excluded

Factors Impacting Engraftment and other Outcomes

- Recipient-related factors
- Transplant-related factors
- Donor-related factors
- Product-related factors

Neutrophil Engraftment
Cumulative Incidence, n = 689



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Engraftment at Day 25
Univariate Analysis

Apheresis Procedure/Handling

Factor	*p*-value
Cell separator manufacturer	0.75
Duration of procedure	0.40
Vol. of blood processed	**0.001**
Vol. of blood processed per hour	0.50
Time from collection to infusion	0.34

Engraftment at Day 25
Univariate Analysis

Product Hematology at Apheresis Center

Factor	*p*-value
PBSC volume collected	0.48
WBC concentration	0.12
Total WBC	**0.028**
Platelets	0.65
Hematocrit	0.81

Engraftment at Day 25
Univariate Analysis

Product Hematology at Apheresis Center, Cont.

Factor	*p*-value
% neutrophils	0.72
Total neutrophils	0.20
% mononuclear cells	0.68
Total mononuclear cells	**0.045**

Engraftment at Day 25
Univariate Analysis

Product Additives after Collection

Factor	*p*-value
Whether any additives were used	0.17
Whether heparin was added	0.25
Heparin units, if used	0.24
Whether citrate was added	**0.008**
Citrate volume, if used	0.20

Engraftment at Day 25

Logistic Regression

Factor	*p*-value	Favorable Characteristic
RECIPIENT/TRANSPLANT RELATED FACTOR		
Karnofsky/Lansky Score	< 0.001	90 - 100
PRODUCT RELATED FACTOR		
Volume of whole blood processed	0.002	≥ 23.5 L

Overall Survival at Day 100

Logistic Regression

Factor	*p*-value	Favorable Characteristic
RECIPIENT/TRANSPLANT RELATED FACTORS		
Recipient age	**0.003**	Younger than 45
Karnofsky/Lansky score	**< 0.001**	90 - 100
Disease risk	**0.007**	Early and Intermediate
HLA matching	**0.004**	6/6 Matched
Conditioning Regimen	**< 0.001**	Non-myeloablative/RIC

Summary

Product related factors that significantly impact day 25 neutrophil engraftment (at .01 level)

Univariate Analysis:

- Volume of blood processed
- Whether citrate was added

Multivariate Analysis:

- Volume of blood processed

Summary

Product related factors that significantly impact day 60 platelet engraftment (at .01 level)

- Total CD34+ cells in the infused product

Summary

Product related factors that significantly impact day 100 overall survival (at .01 level)

- None

Inherent Low Risk: PBSC Recipient Serious and Unexpected AEs

PBSC transplants (2/97- 4/2006): 5,607

Reported recipient unexpected SAEs: 12 (0.21%)

- Recipient-related, n = 4

  [pulmonary embolism (6 mo. Post), VOD, Cyclosporine toxicity, aerodigestive mucositis]
- Product-related, n= 5

  [TRALI, allergic reaction, fever x 3]
- ABO mismatch*, n = 3

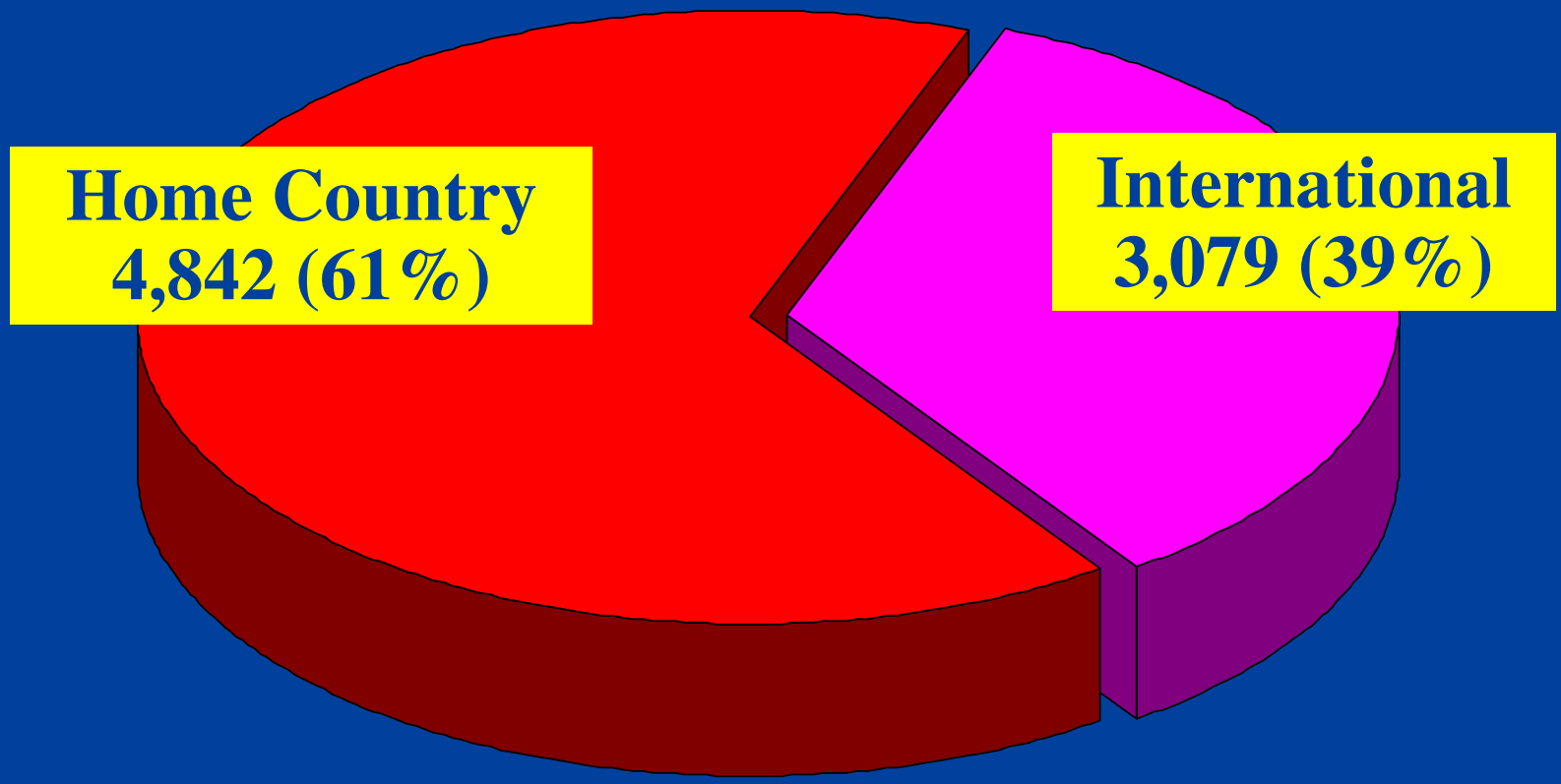
SAEs would not have been avoided through additional manufacturing controls or licensure

*Expected SAEs

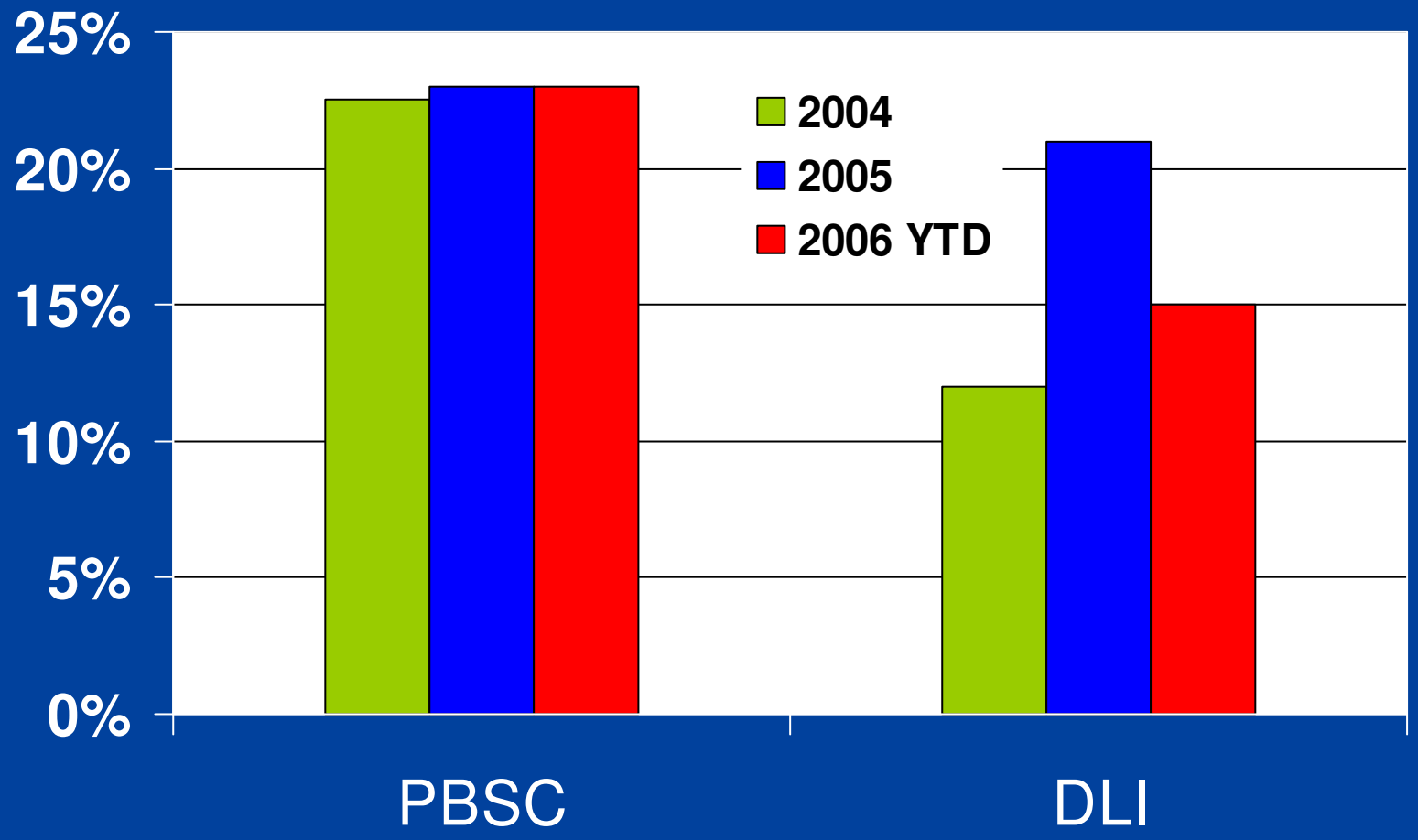
Why is Importation of unrelated PBSC Products so Prevalent and Essential?

HLA and the Need for HLA-Matching Drives the International Exchange of Hematopoietic Stem Cells

2005 Global Unrelated Donor PBSC and Bone Marrow Collections, n = 7,921



Percentage of PBSC & DLI Products Imported



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Exercise Regulatory Oversight only to the Degree Appropriate to Protect the Public Health

- The greatest predictor of transplant success is not product-related; rather it is the patient's disease, clinical condition and treatment regimen
- BLA licensure under 351 for unrelated PBSC & DLI provides little or no added value in protecting the public health and poses a resource drain on both domestic and international establishments
- GMP manufacturing controls will not decrease transplant-related mortality or morbidity
- The controls in place for the manufacture of 361 products are sufficient for unrelated PBSC & DLI

NMDP's Proposal for FDA Consideration

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Summary

- Related and unrelated PBSCs have similar safety profiles
- Recipient SAEs are infrequent and would not be avoided by additional manufacturing controls
- NMDP data indicates tranplant outcome best prediced by patient related factors
- No product-related factors significantly correlate with patient overall survival at day 100
- Continued importation of PBSC products is essential to meet the needs of US transplant patients for the best HLA match

Conclusions

- We recommend that unrelated PBSCs be regulated under 361 based on the safety and efficacy data; risk is communicable disease
- Alternatively, licensure requirements should reflect current understanding of PBSC safety and efficacy and not be so burdensome as to risk loss of PBSC collections by some apheresis centers
- Any proposed regulatory framework needs to accommodate importation of products essential to meeting patients' need for HLA-matched products