

An Overview of Unrelated Donor HPC(A) Usage Under the NMDP-held IND

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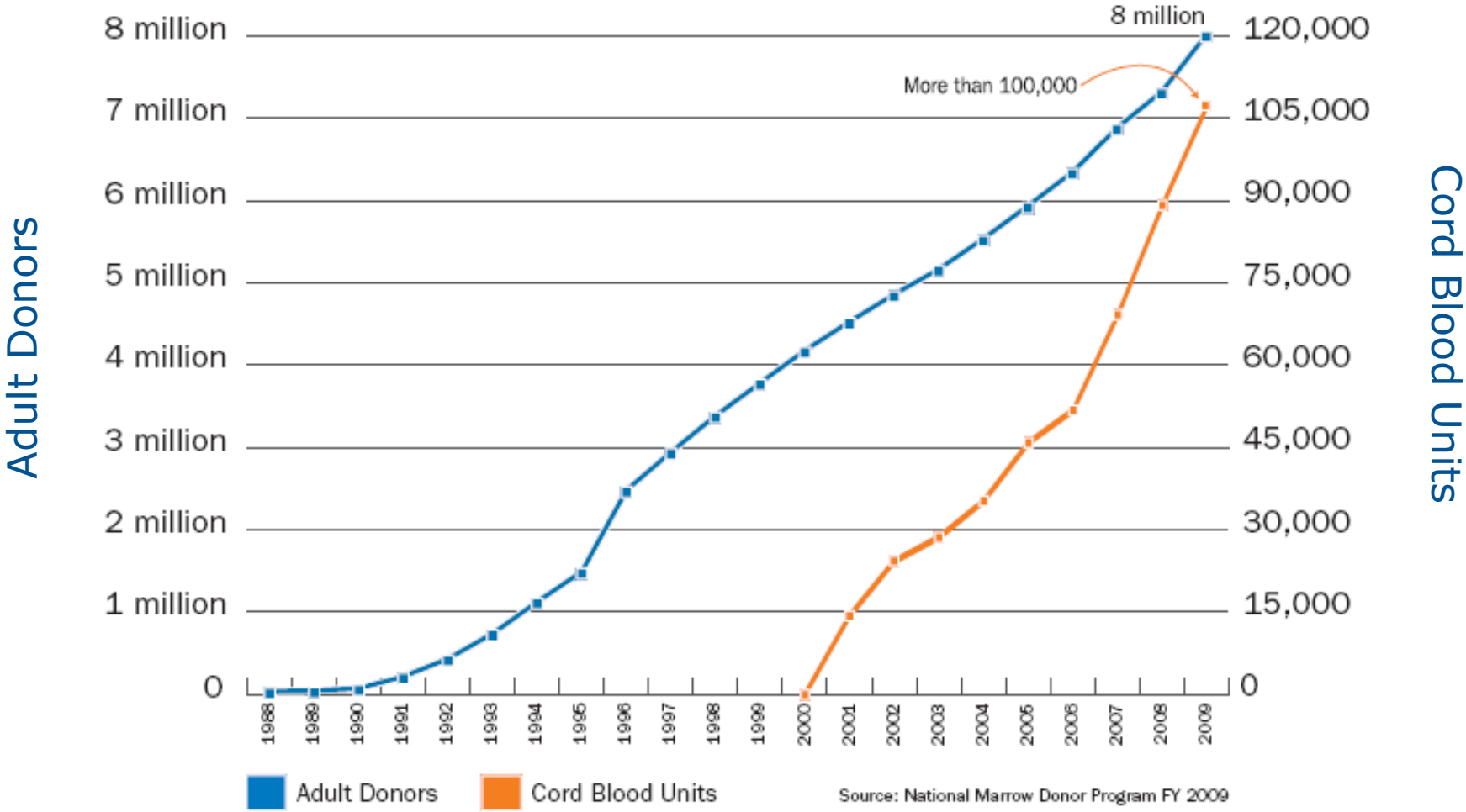
The National Marrow Donor Program

- Nonprofit 501(c)(3) corporation
 - Founded in 1986
- Headquartered in Minneapolis, MN
- Three contracts from Health Resources and Services Administration for the CW Bill Young Cell Transplantation Program
- Research conducted with the Center for International Blood and Marrow Transplant Research (CIBMTR)
 - HRSA contract for the Stem Cell Therapeutic Outcomes Database

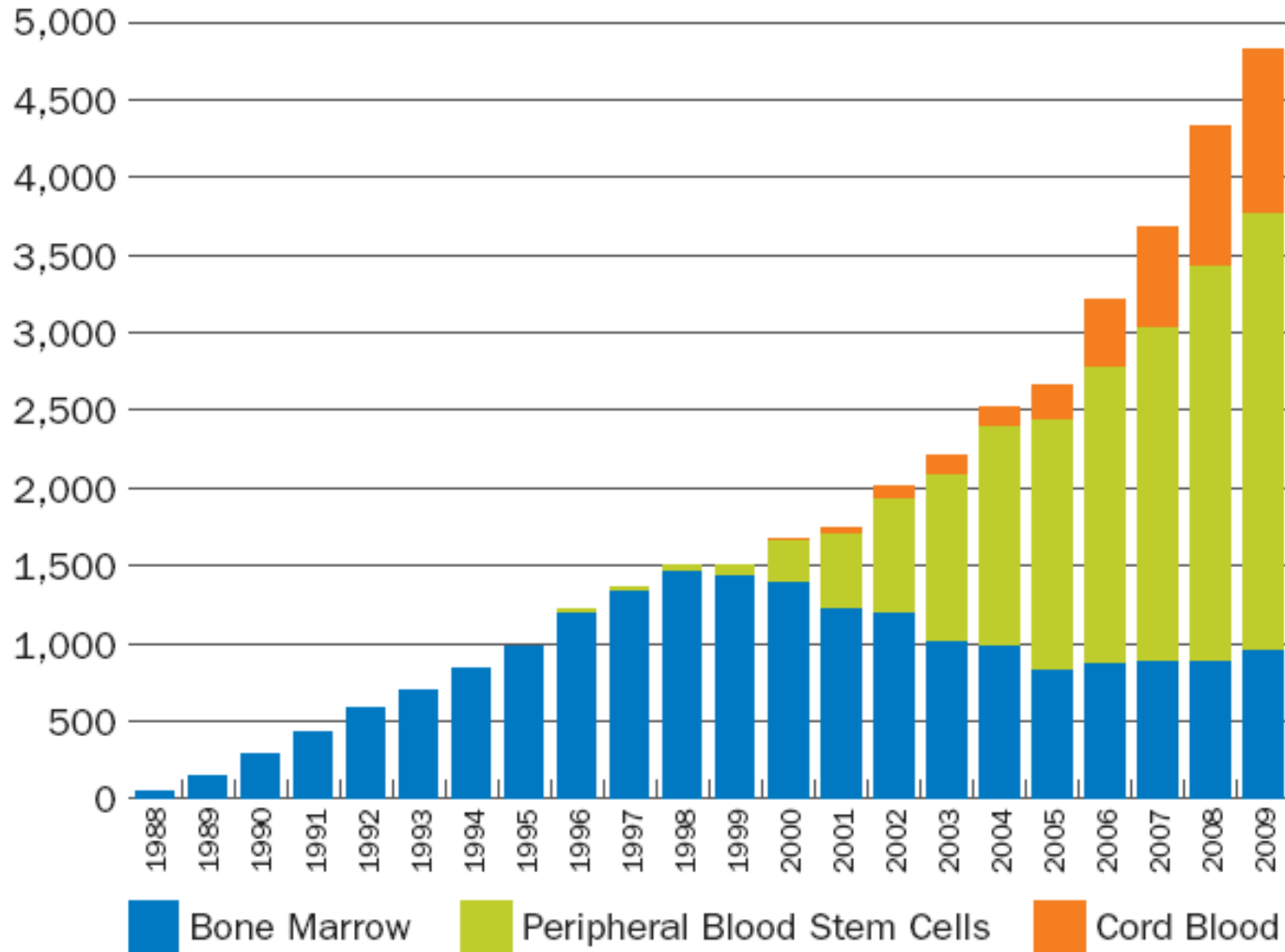
The National Marrow Donor Program

- Operating the Be The Match[®] Registry, the world's largest file of unrelated adult donors and cord blood units
- Member of the World Marrow Donor Association
 - 69 Registries and >120 cord blood banks worldwide
 - www.worldmarrow.org
- Member of Bone Marrow Donors Worldwide
 - Consolidated listing of donors and CBUs
 - Search engine functionality
 - www.bmdw.org

Total Growth of the Be The Match Registry 2009

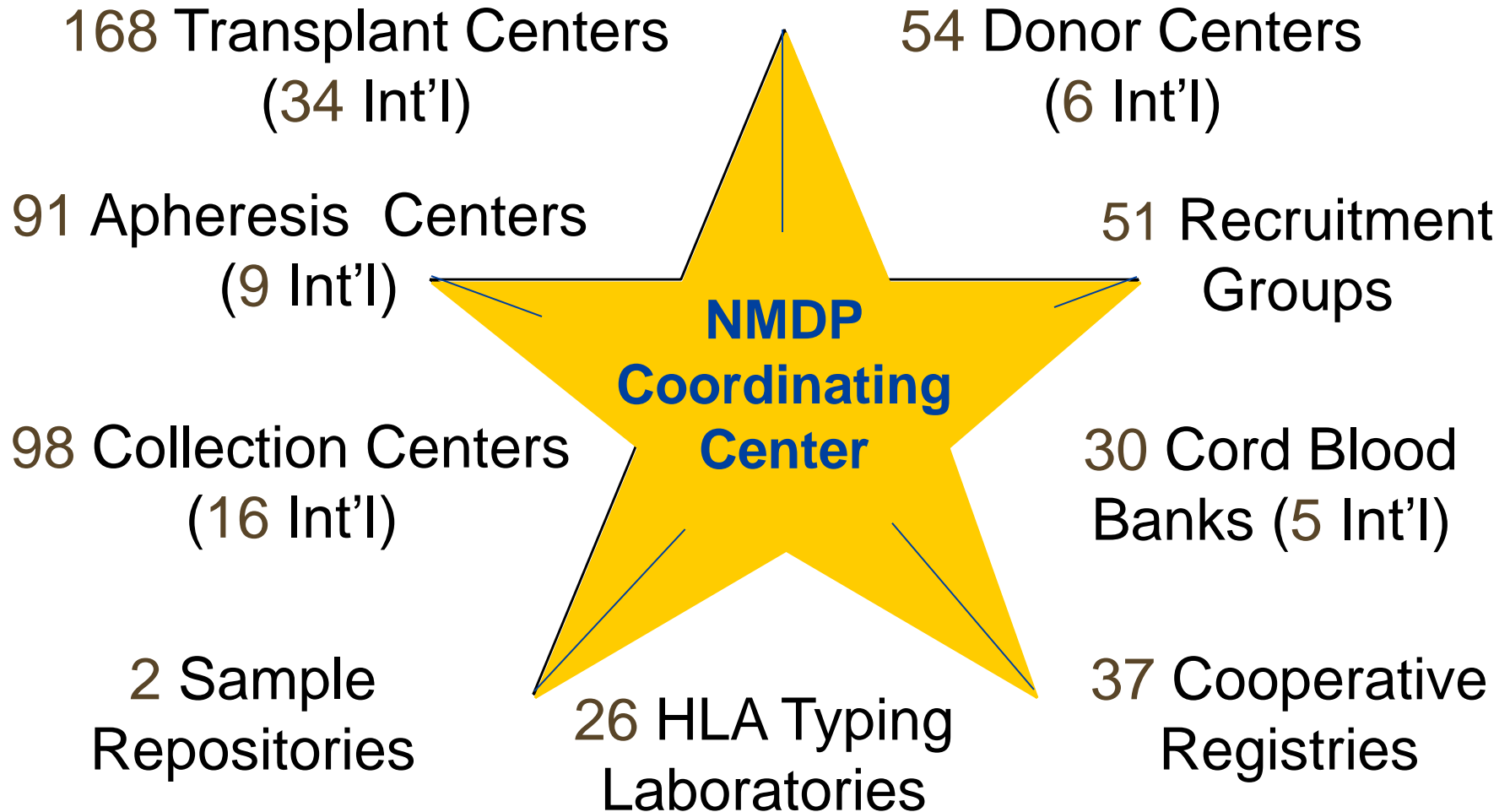


NMDP Transplants by Cell Source and by Fiscal Year



Source: National Marrow Donor Program FY 2009

The NMDP Network



History of the NMDP IND: BB-IND 6821

- To establish and evaluate a system for collection of filgrastim-mobilized peripheral blood stem cells from NMDP donors
- Filed in November 1996
 - Protocol for second donation PBSCs opened in February 1997
 - First donation protocol opened July 1999
 - Single consolidated protocol in June 2005
 - Continues today as version 17.0

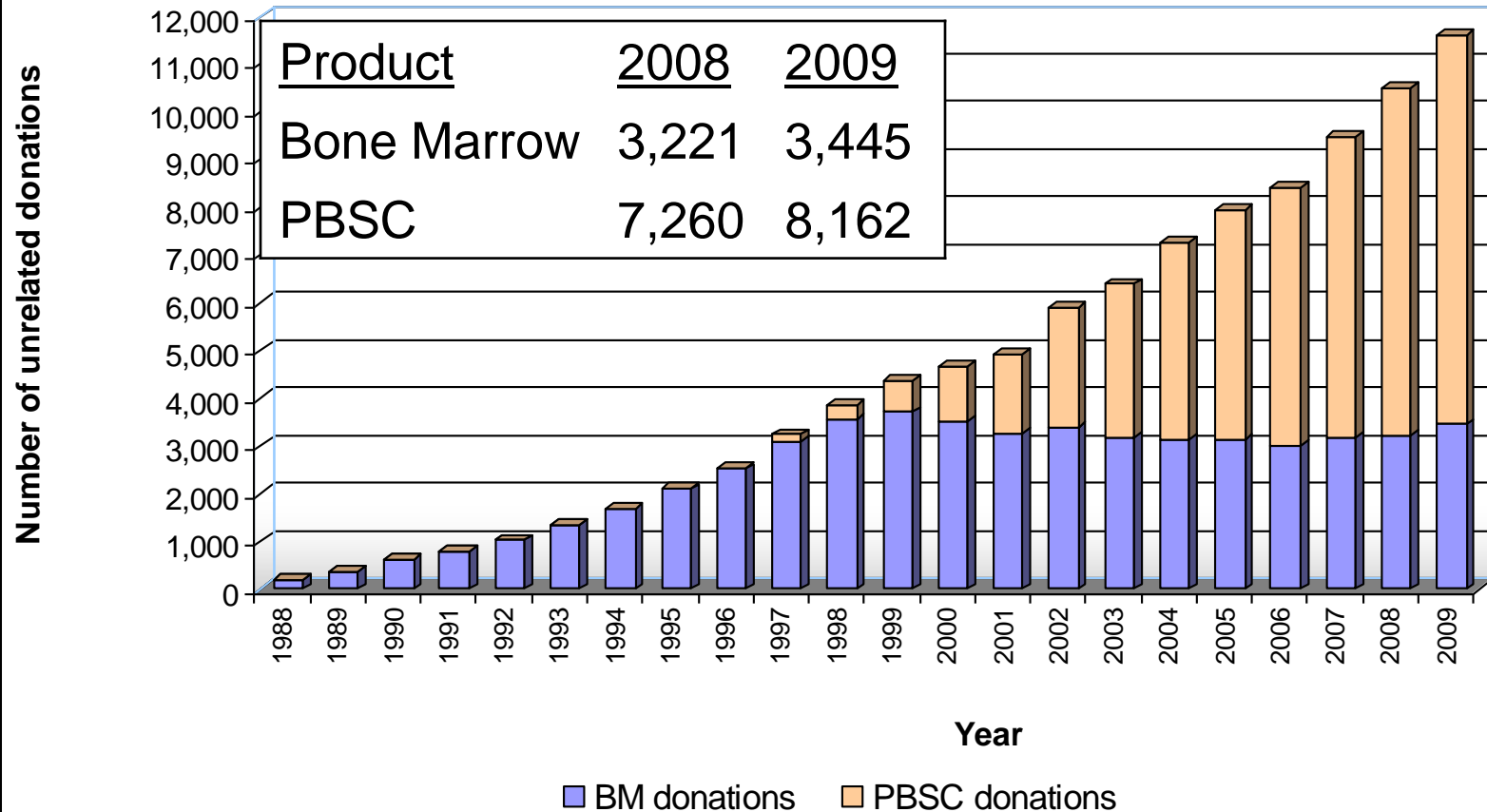
History of the NMDP IND: BB-IND 6821

- The NMDP IND excludes international PBSC
 - Domestic donor centers and apheresis centers are the investigators under the protocol
 - All donors provide IRB-approved consent
 - IND for unrelated donor PBSC is voluntary
- NMDP has facilitated more than 18,500 PBSC transplants
 - ~12,000 PBSC products from donors enrolled on the IND protocols



In 2009, 69 Stem Cell Donor Registries worldwide participated

Number of unrelated stem cell donations (BM/PBSC)



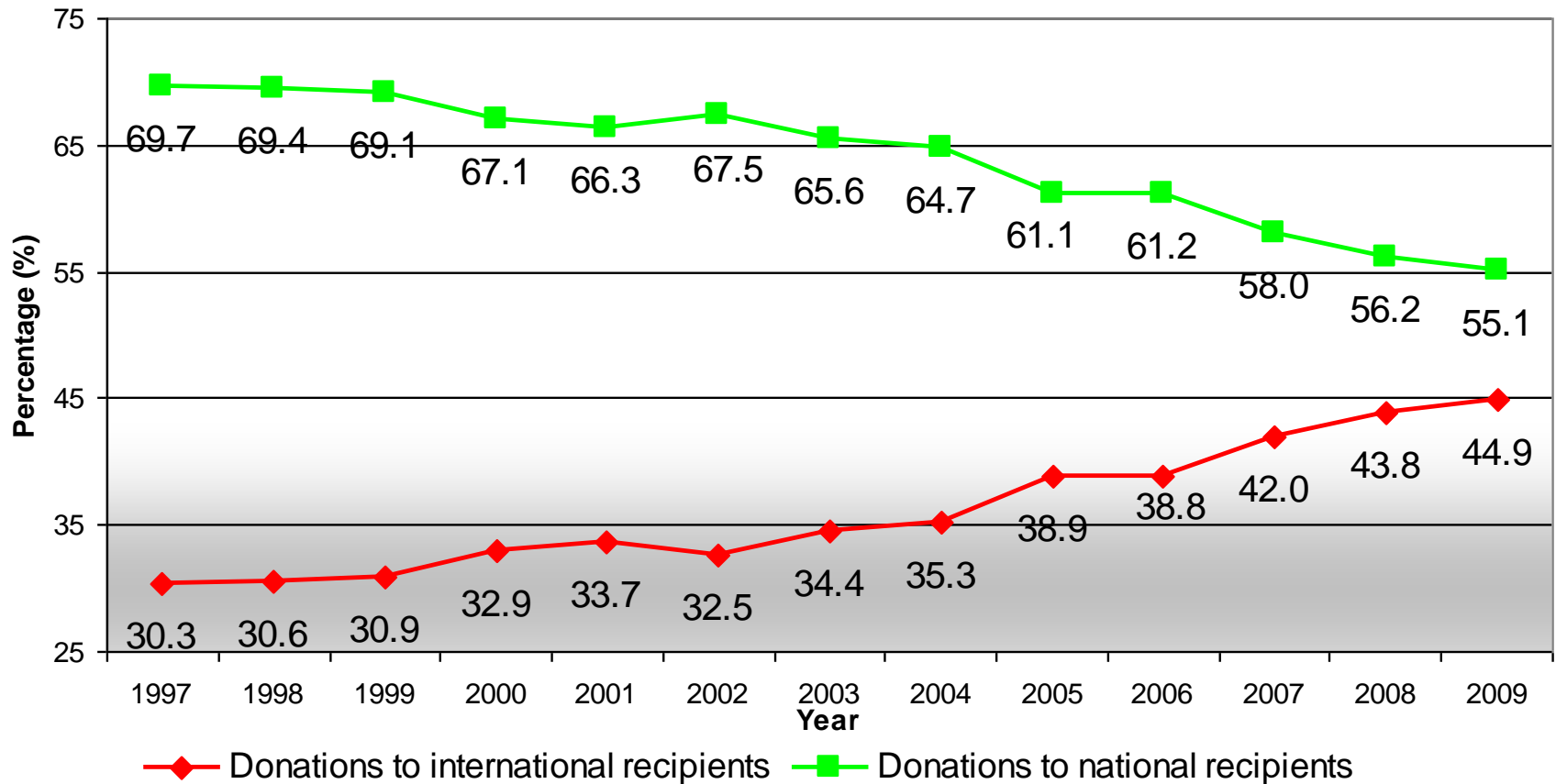


In 2009:

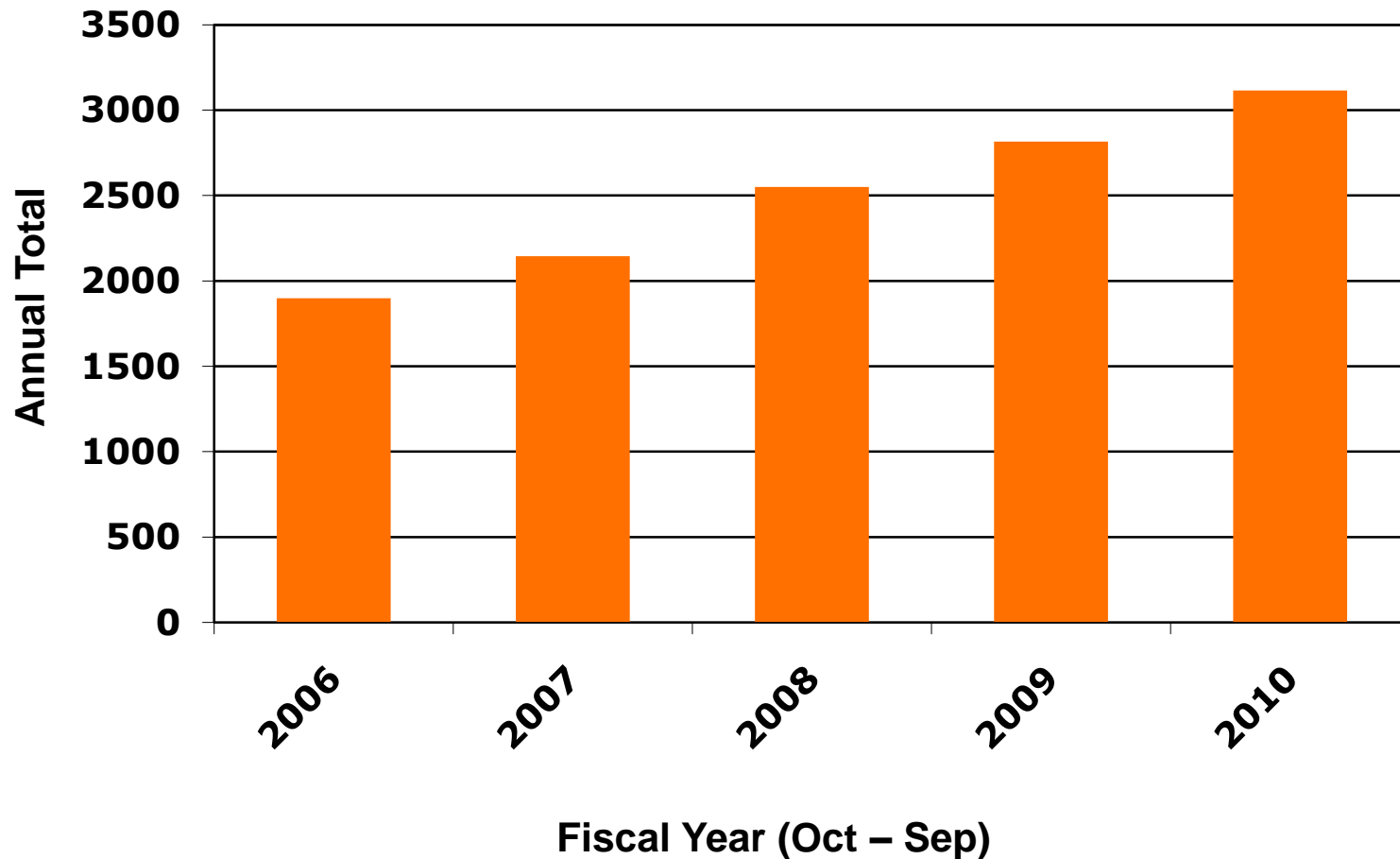
- 6,461 products total crossed a border

- 18 products a day

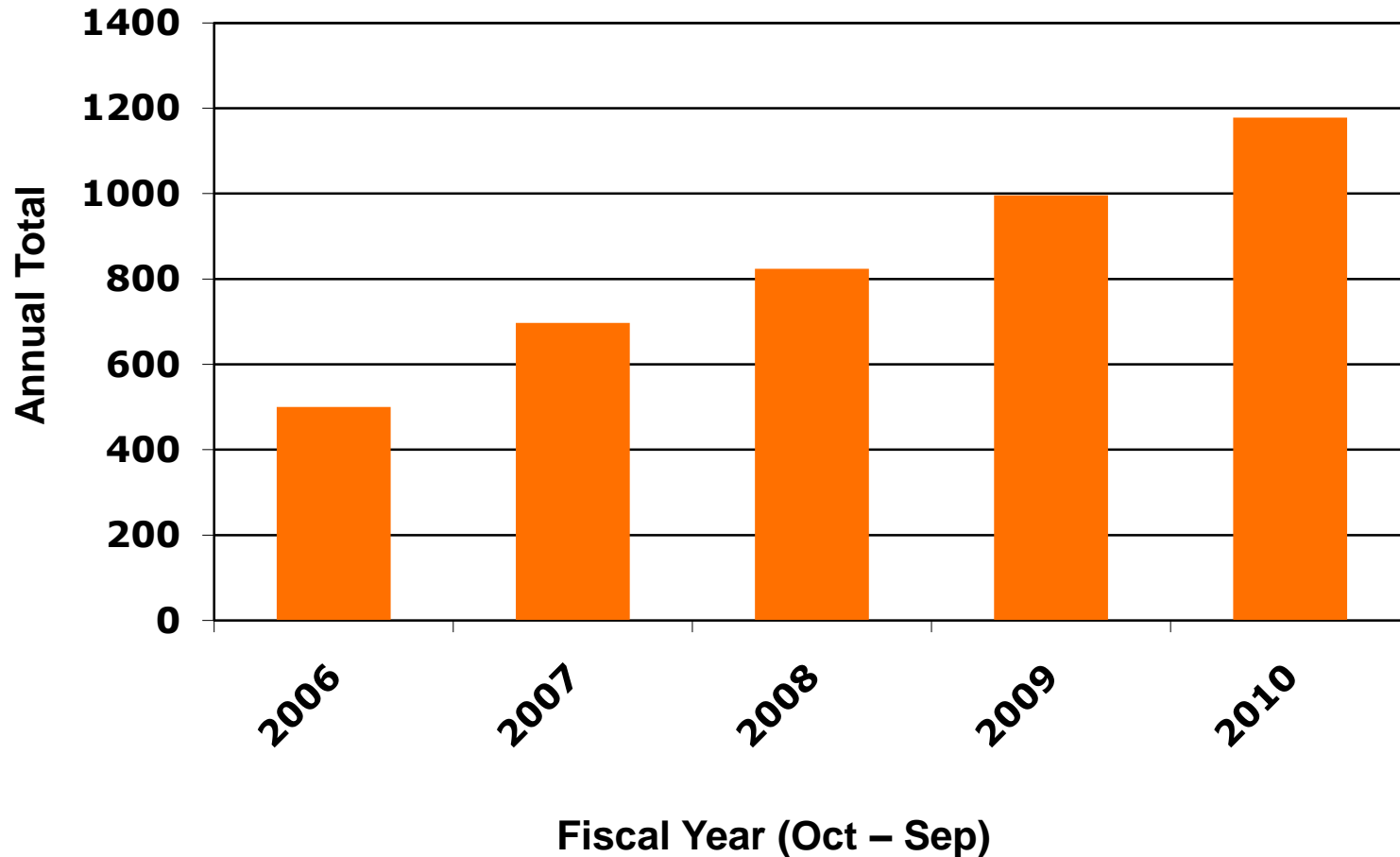
Percentage of bone marrow/PBSC donations provided for national and international patients



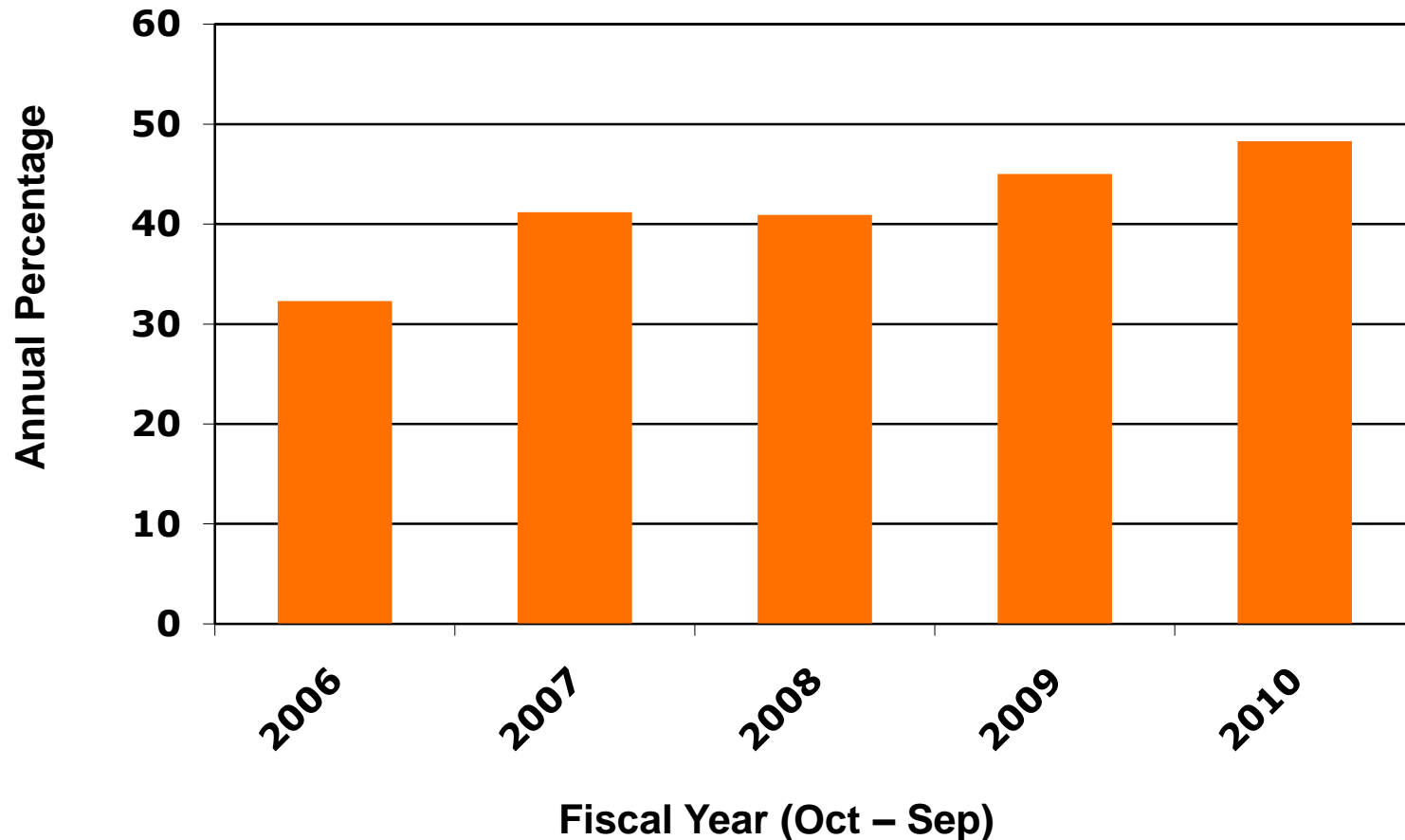
Total Annual NMDP PBSC Transplants



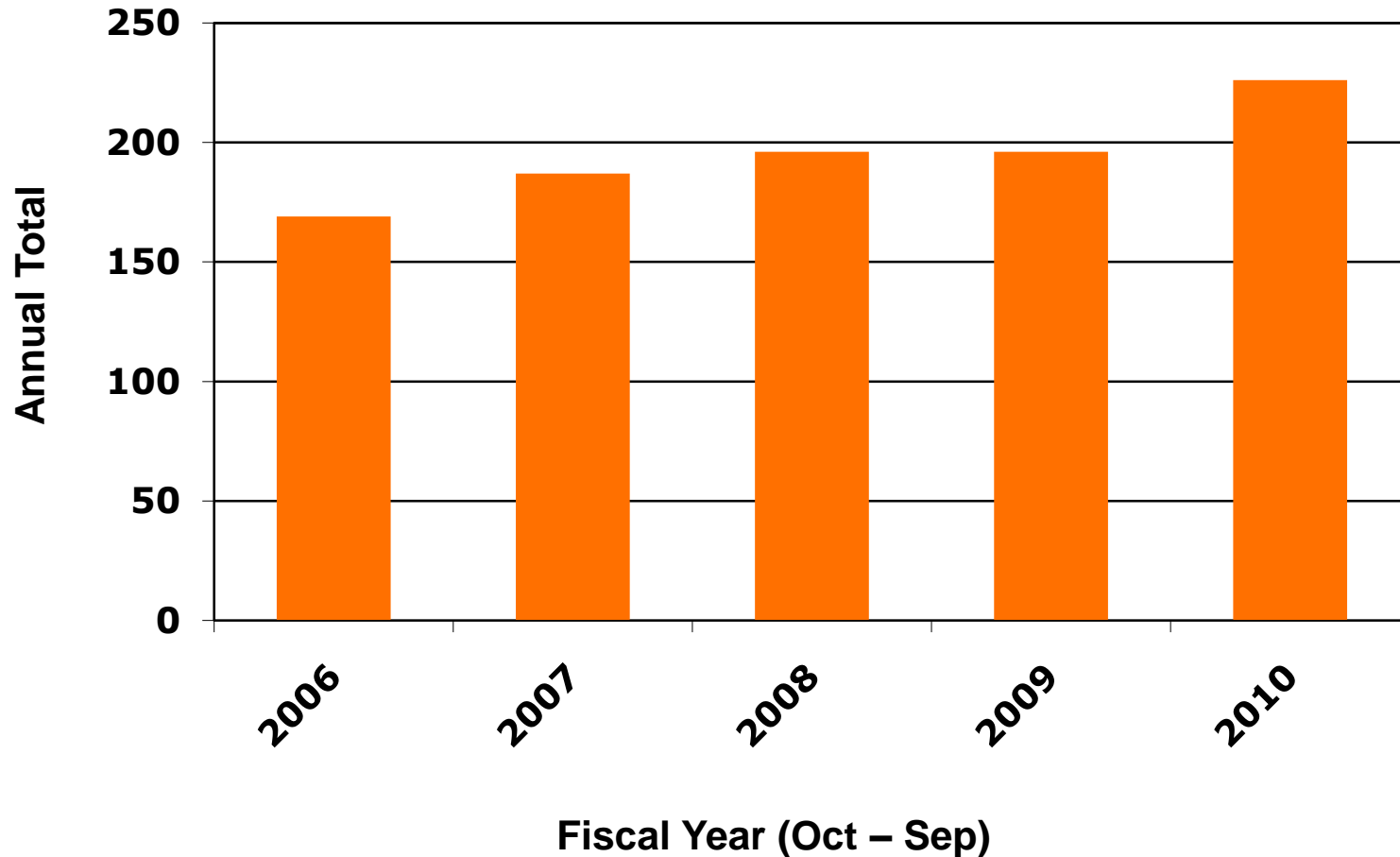
Annual Imports of PBSC Products



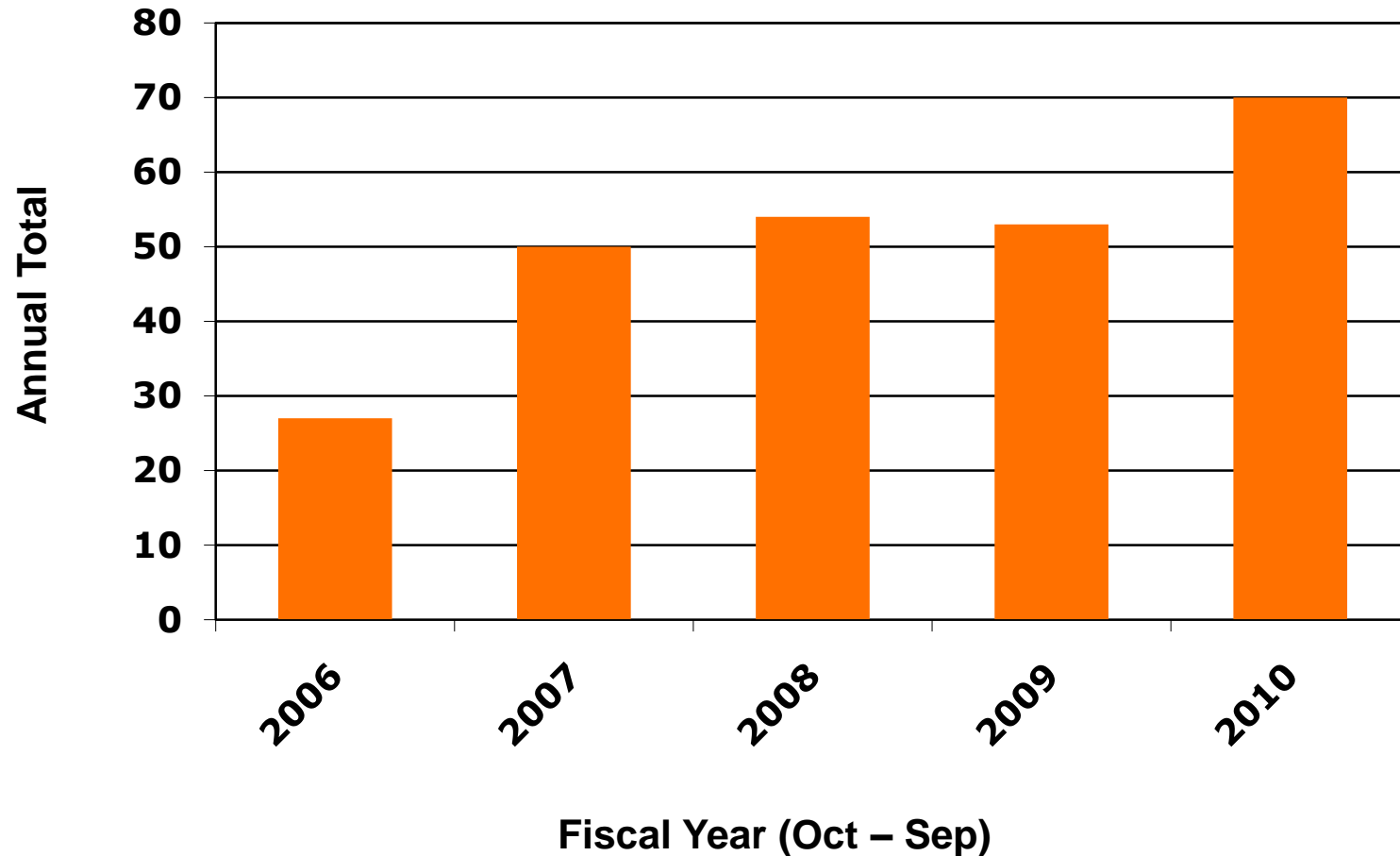
Percentage of US PBSC Recipients Receiving Imported Products



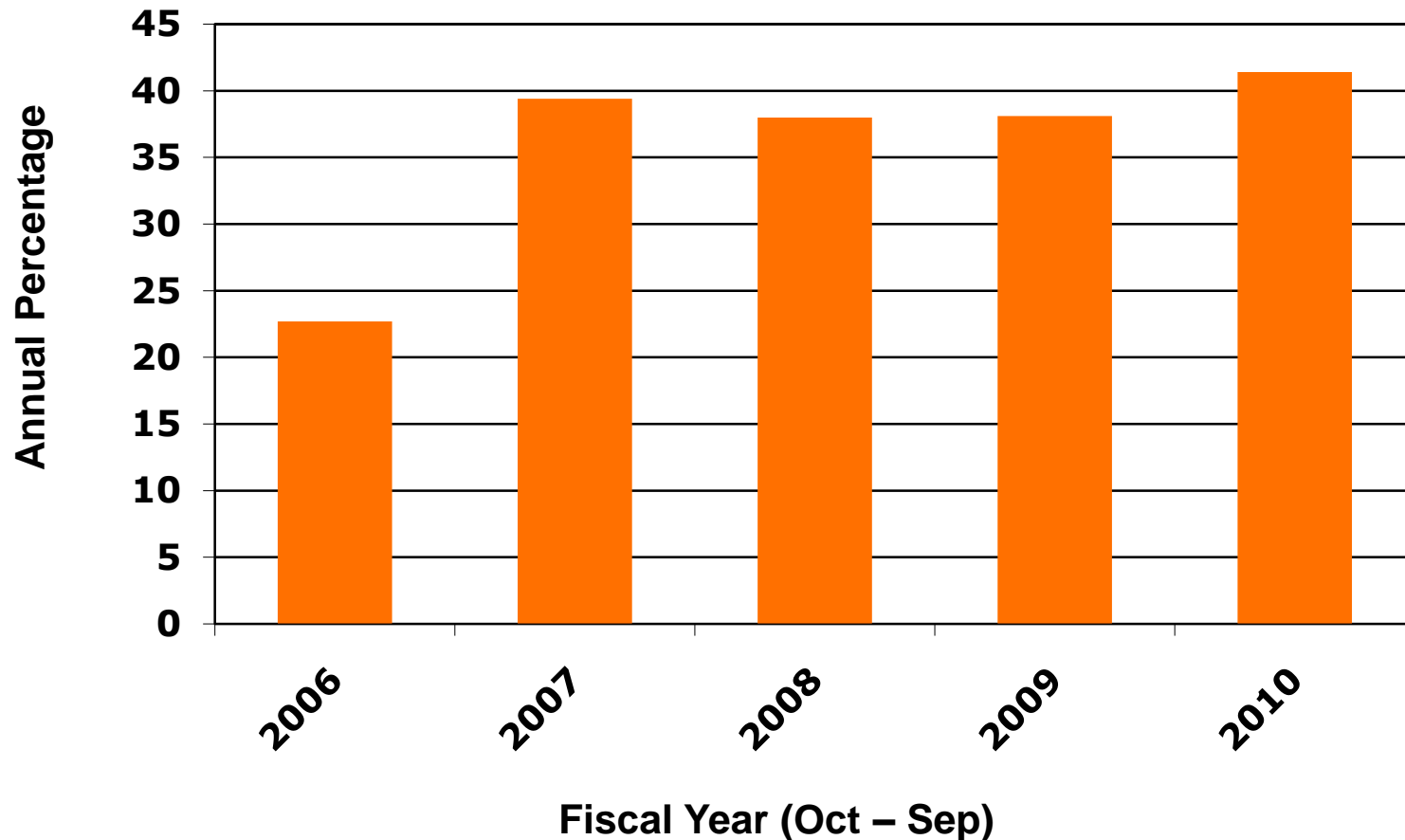
Total Annual NMDP DLI Treatments



Annual Imports of DLI Products



Percentage of US DLI Recipients Receiving Imported Products



Why is Importation of These Products so Prevalent?

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

Donor HLA is the Single Most Important Survival Factor

- Donor HLA is more important than -
 - Donor age
 - Donor CMV status
 - Donor sex
 - Donor race
 - Donor size
 - Donor ABO type
 - Donor anything

Findings from the NMDP IND

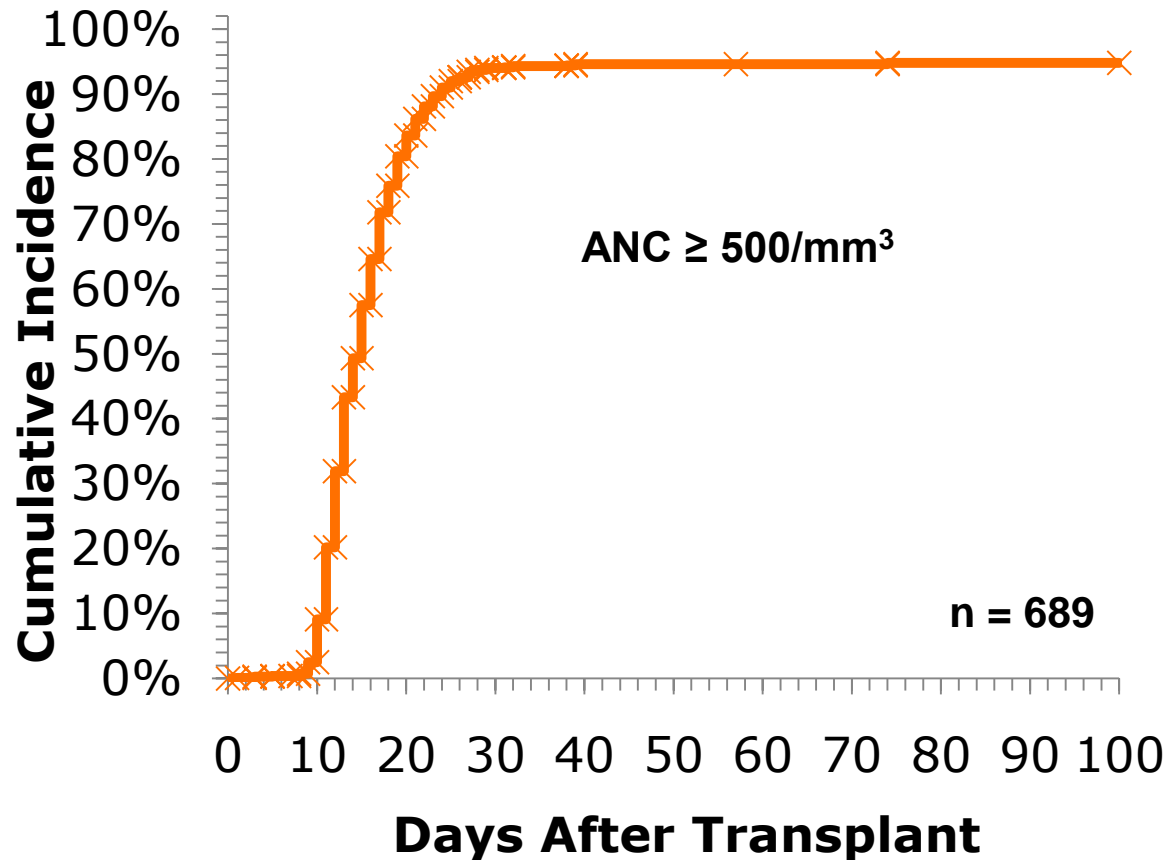
Study Cohorts

- 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



Engraftment at Day 25

Univariate Analysis

Apheresis Procedure/Handling

Factor	<i>p</i> -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	<i>p</i> -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	<i>p</i> -value
% neutrophils	0.72
Total neutrophils	0.20
% mononuclear cells	0.68
Total mononuclear cells	0.045

Engraftment at Day 25

Univariate Analysis

Product Hematology at Transplant Center

Factor	<i>p</i> -value
PBSC volume infused	0.08
WBC concentration	0.54
Total WBC	0.037
Platelets	0.73
Hematocrit	0.22

Engraftment at Day 25

Univariate Analysis

Product Hematology at Transplant Center, Cont.

Factor	<i>p</i> -value
% neutrophils	0.92
Total neutrophils	0.33
% mononuclear cells	0.79
Total mononuclear cells	0.048
% CD34+ cells	0.74
Total CD34+ cells	0.040

Engraftment at Day 25

Univariate Analysis

Product Additives after Collection

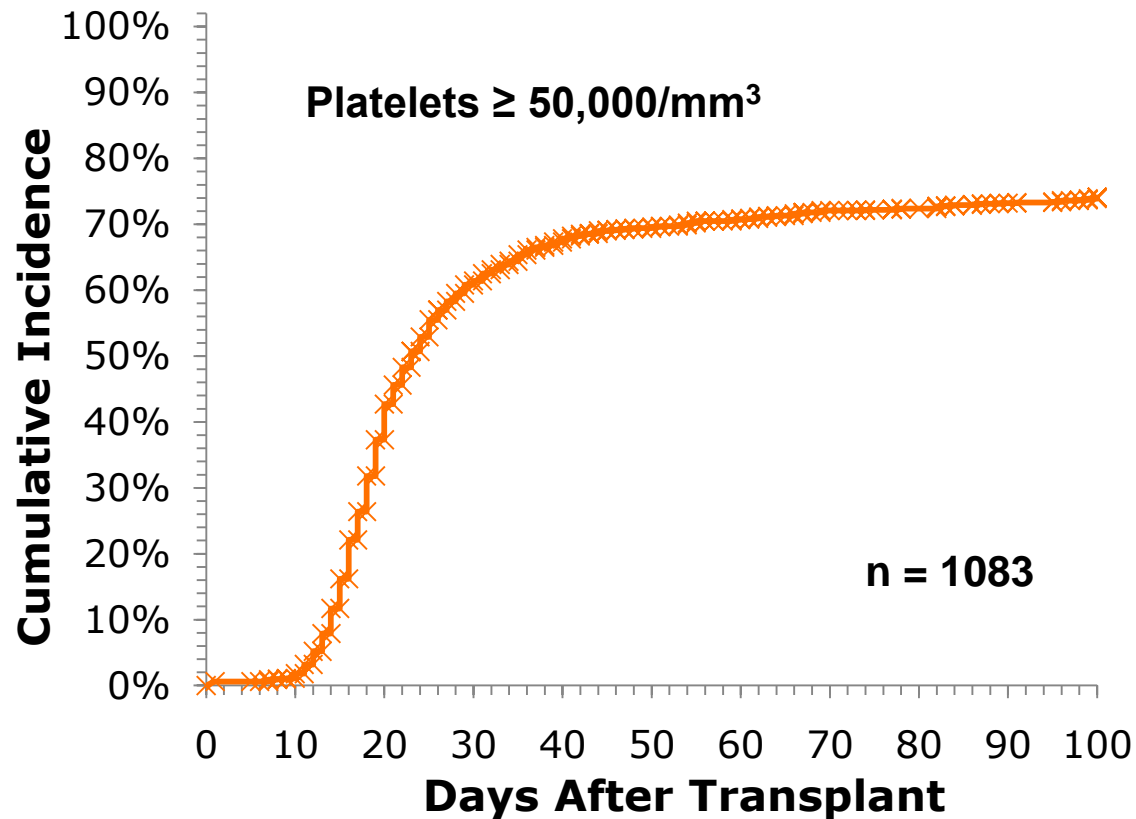
Factor	<i>p</i> -value
Whether any additives were used	0.17
Whether heparin was added	0.25
Heparin units, if used	0.24
Whether citrate was added	0.008
Citrate volume, if used	0.20

Engraftment at Day 25

Logistic Regression

Factor	<i>p</i>-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

Platelet Engraftment Cumulative Incidence

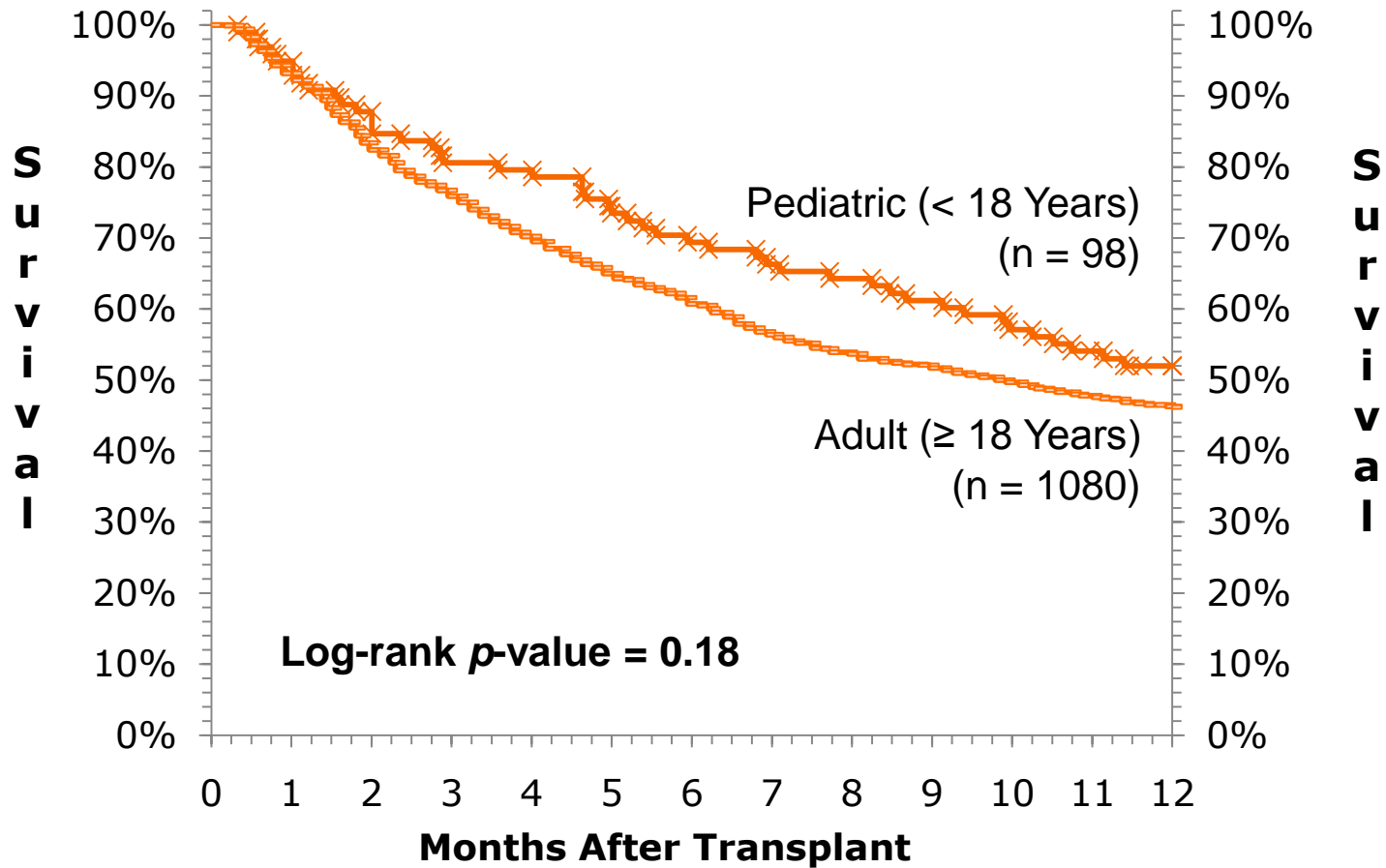


Platelet Engraftment at Day 60 ($\geq 50,000 /\text{mm}^3$)

Logistic Regression

Factor	<i>p</i> -value	Favorable Characteristic
RECIPIENT/TRANSPLANT RELATED FACTORS		
Karnofsky/Lansky score	0.010	90 - 100
Recipient CMV Status	0.004	Negative
PRODUCT RELATED FACTOR		
Total CD34+ cells in infused product	< 0.001	Higher

Overall Survival



Overall Survival at Day 100

Logistic Regression

Factor	<i>p</i> -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:

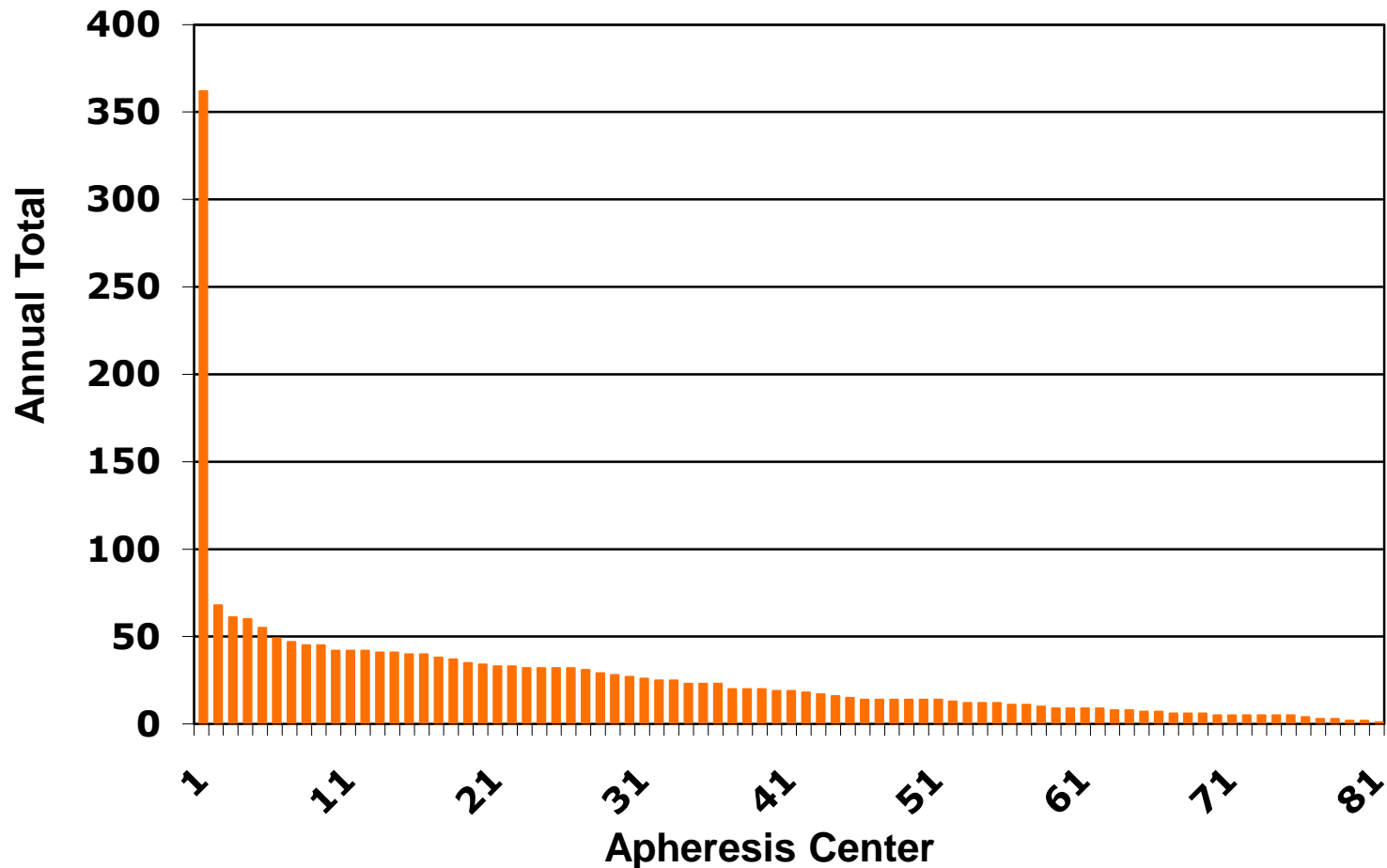
Product-Related Factors that Significantly Impact
Day 100 Overall Survival (at .01 level)

- None

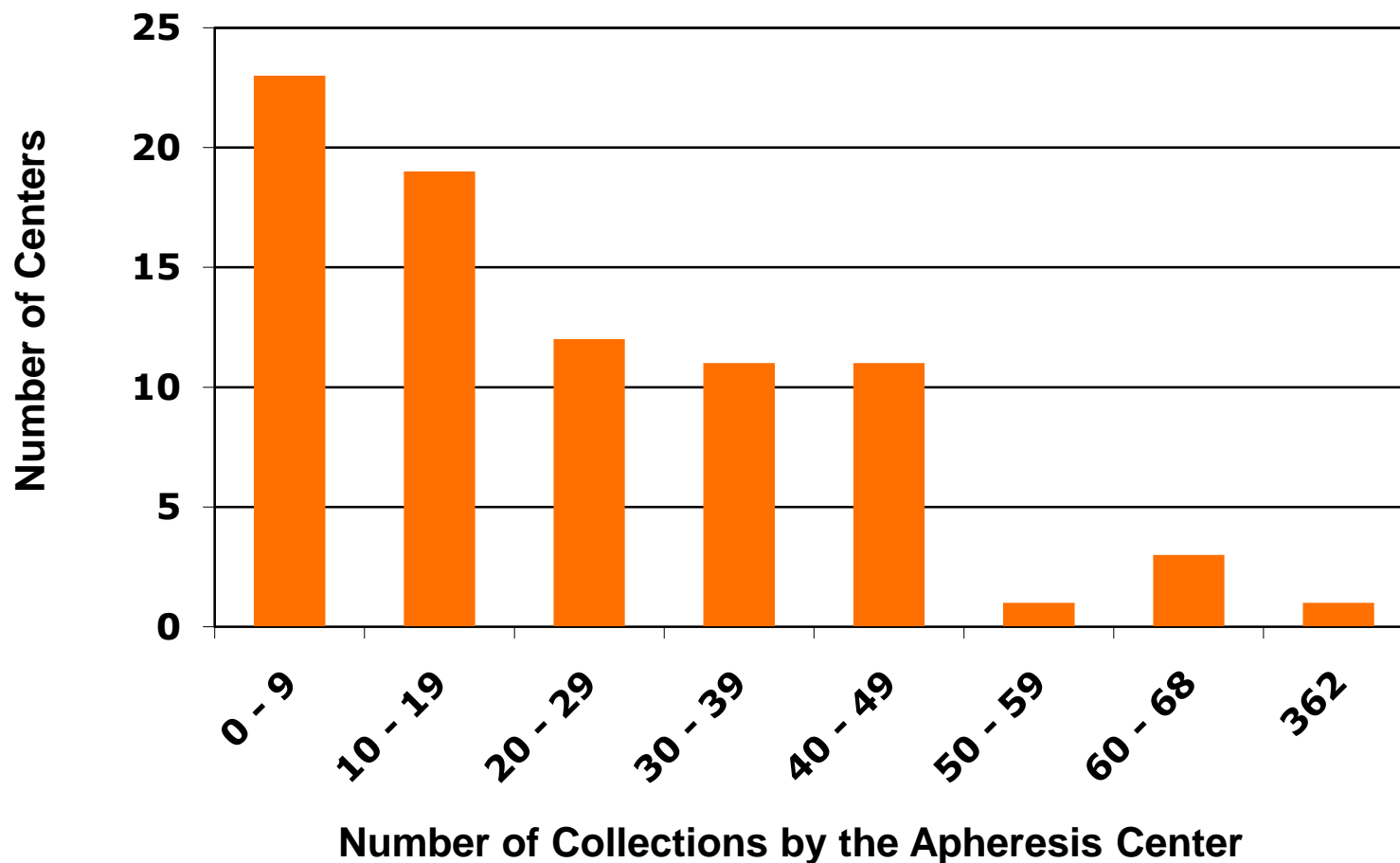
FDA Registered PBSC Facilities (Apheresis Centers and others)

United States		International
235	Distribute	172
294	Label	175
224	Package	175
225	Process	151
254	Recover	165
237	Screen	166
239	Store	159
146	Test	137

PBSC Collections by US Apheresis Centers – CY 2009



Distribution of US Apheresis Centers by 2009 Collection Volumes



Questions to be Addressed

- Who should hold a license?
 - NMDP?
 - Individual apheresis centers?
- How should international centers be managed?
 - Licensure?
 - IND?
- How will licensure impact donors and patients?

Issues for NMDP

- NMDP does not own the manufacturing facilities (apheresis centers)
- The network is large and diverse
- Nearly half of PBSC and DLI products are imported from international sites
- Access to international apheresis centers is usually indirect, i.e., through the parent registry
- Concern about increased costs
- Increased regulatory risk

Issues for Apheresis Centers (AC)

- Unrelated donor HCT/P are unique in the AC business, i.e., different regs than related and autologous products, platelet apheresis, etc.
- URD HCT/P are often a small part of their business and not very profitable
- Administration leadership, particularly in hospital-based centers, may be ambivalent
- Enhanced 351 manufacturing requirements
- Additional paperwork
- Increased regulatory risk

Thank you...