US Regulations for Import and Export of Cell Therapy Products

Kurt Gunter, MD

2007 Annual Meeting

International Society for Cellular Therapy
ISCT

U Minnesota UCB Transplants (2001-2007)*

Total units:	790
Number US banks:	19
Number non-US banks:	12
% units from non-US banks:	17 (138/790)

*Dave McKenna, MD, U of Minnesota

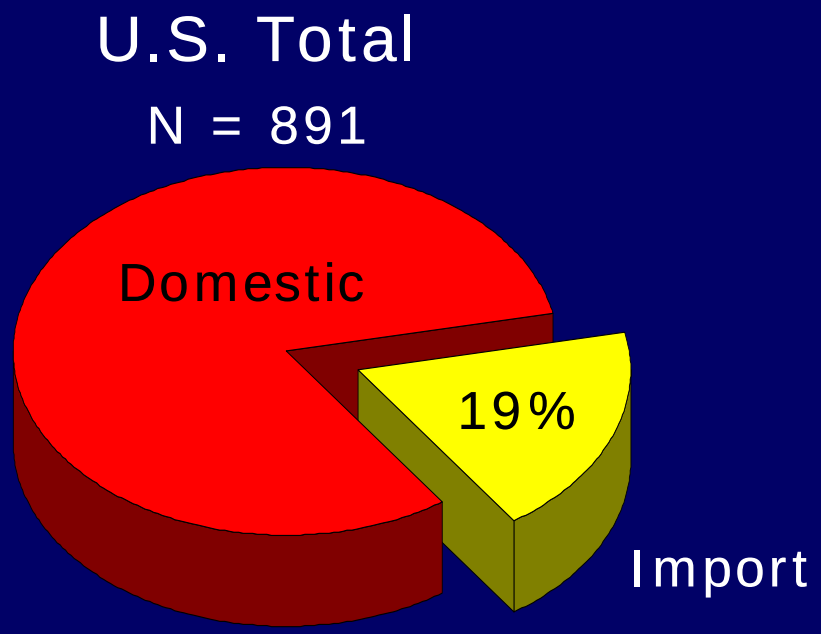
U Minnesota UCB Transplants (2001-2007)*

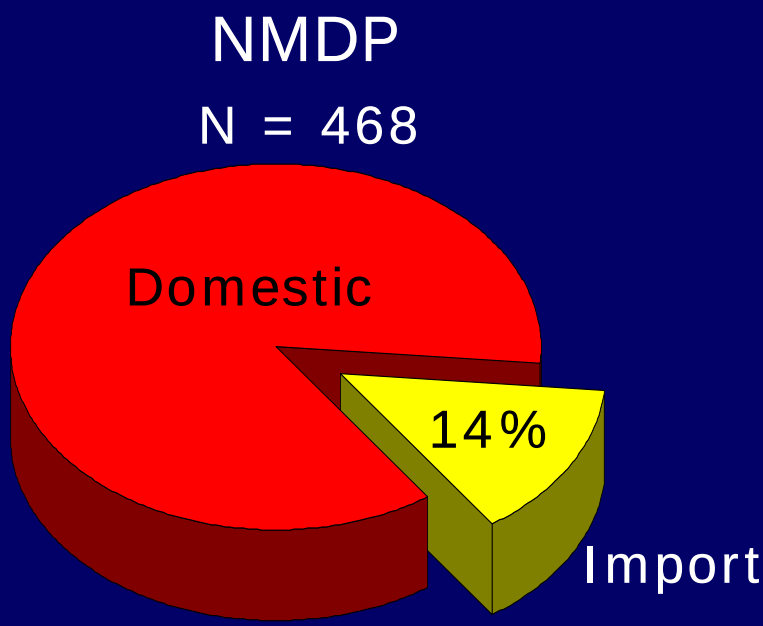
% from non-US banks by year:

2001 – 0% (0/18)
2002 – 2% (2/84)
2003 – 8% (10/118)
2004 – 19% (23/118)
2005 – 16% (34/207)
2006 – 26% (45/172)
2007 – 33% (24/73)

*Dave McKenna, MD, U of Minnesota

Importation of CBUs: CY 2006*





*John Miller, MD, PhD
NATIONAL MARROW DONOR PROGRAM®

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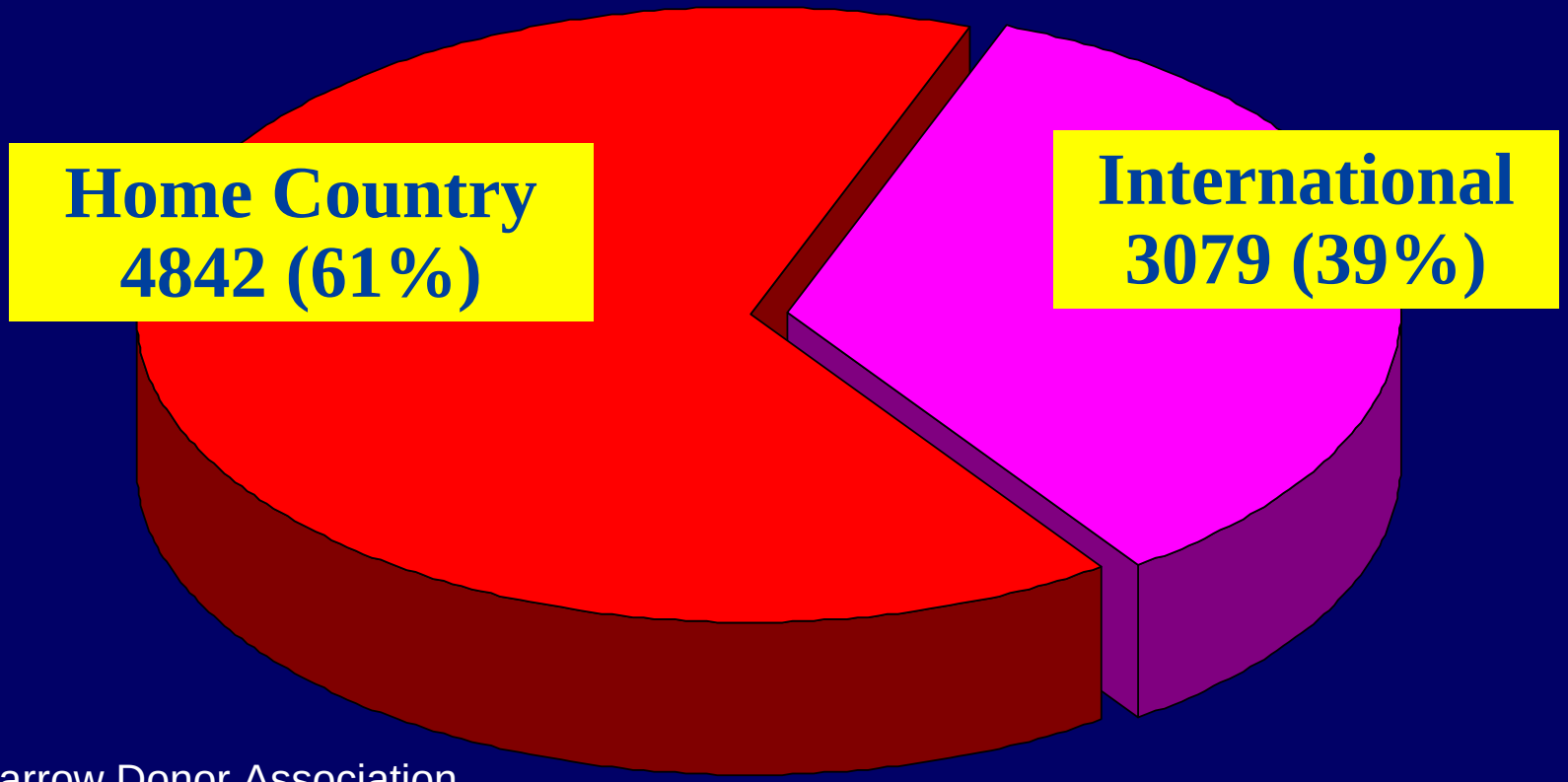
2005 Global Unrelated Donor PBSC and Bone Marrow Collections*

n = 7921



*World Marrow Donor Association

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FDA Risk Based Approach to Regulation of Cell Therapy

- Higher risk products
  - Public Health Service (PHS) Act Section 351 applies
    - Biological licensure required for interstate commerce
    - Safety and efficacy must be established (generally through clinical trials)
    - INDs required for clinical trials
    - Good Manufacturing Practice (GMP) and Good Tissue Practice (GTP) regulations apply
- Lower risk products
  - PHS Act Section 361 applies
    - Focused on prevention of communicable (infectious) disease
    - No licensure requirement
    - No clinical trial requirement
    - GTP regulations apply (21 CRF 1271)
- Higher tier HCT/Ps must comply with both Section 351 and 361 requirements
- Lower tier HCT/Ps must comply with only Section 361 requirements

What are HCT/Ps?

- Human cells, tissues, or cellular or tissue-based products (HCT/ Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.
- Examples of HCT/Ps include, but are not limited to
  - Bone
  - Ligament
  - Skin
  - Dura mater
  - Heart valve
  - Cornea
  - Hematopoietic stem/progenitor cells derived from peripheral and cord blood
  - Manipulated autologous chondrocytes
  - Epithelial cells on a synthetic matrix
  - Semen or other reproductive tissue

HCT/Ps Regulated Solely Under the Lower Tier (Section 361) If They Meet All of the Following Criteria

- Minimally manipulated
- Intended for a homologous use ("the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor")
- Not combined with another article, (except for water, crystalloids, or a sterilizing, preserving, or storage agent…); **AND**
- Either:
  - Do not have a systemic effect and are not dependent upon the metabolic activity of living cells for the primary function; **OR**
  - Have a systemic effect or are dependent upon the metabolic activity of the other cells for the primary function, **AND**:
    a) Are for autologous use;
    b) Are for allogeneic use in a first or second-degree relative; **OR**
    c) Are for reproductive use.

What is Not Covered in the Lower Tier (Section 361)?

- **Vascularized human organs** for transplantation [regulated by Health Resources and Services Administration (HRSA)]
- **Minimally manipulated bone marrow** (regulated by HRSA)
- **Whole blood or blood components or blood derivative products** (regulated under section 351 of the PHS Act, the FD&C Act, and blood regulations)
- **Secreted or extracted human products** such as milk, collagen, and cell factors (except that semen is considered an HCT/P)
- **Ancillary products** used in the manufacture of HCT/Ps
- **Cells, tissues, and organs derived from animals other than humans**
- **In vitro diagnostic products** (regulated as medical devices)

FDA Import Export Controls Vary with Risk Level and Stage of Product Development

- Lower Tier Risk Products (Section 361)
- Higher Tier Risk Products (Sections 351 and 361)
  - Pre commercial stage (IND)
  - Commercial marketing

Import of Lower Tier (Section 361) HCT/Ps

- Compliance with 21 CFR 1271 (registration and listing, donor eligibility and GTPs)
- Importer must notify the director of the district FDA having jurisdiction over the port of entry and must provide sufficient information for FDA to make an admissibility decision.
- An HCT/P offered for import must be held intact by the importer or consignee, until an admissibility decision is made by FDA. The HCT/P may be transported under quarantine to the consignee, while the FDA district reviews the documentation accompanying the HCT/P.
- Does not apply to
  - Reproductive HCT/Ps regulated solely under section 361 of the PHS Act and donated by a sexually intimate partner of the recipient for reproductive use.
  - Peripheral blood stem/progenitor cells regulated solely under section 361 of the PHS Act

Export of Lower Tier (Section 361) HCT/Ps

- HCT/P manufacturer must comply with 21 CFR 1271 (registration and listing, donor eligibility and GTPs)
- Marketing authorization required in destination country
- Requirements will vary by country and region

Import of Higher Tier (Section 351) HCT/Ps for Clinical Trials

- HCT/P manufacturer must comply with 21 CFR 1271 (registration and listing, donor eligibility and GTPs)
- IND in effect
  - The consignee in the United States is the sponsor of the IND; or
  - The consignee is a qualified investigator named in the IND; or
  - The consignee is the domestic agent of a foreign IND sponsor

Export of Higher Tier (Section 351) HCT/Ps for Clinical Trials

- Compliance with 21 CFR 1271 (registration and listing, donor eligibility and GTPs)
- Must comply with one of the following
  - An IND is in effect for the drug, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator
  - The drug has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the EU or EEA, and complies with the laws of the country to which it is being exported
  - The drug is being exported to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or to any country in EU or EEA, and complies with the laws of the country to which it is being exported
  - Written certification to FDA that
    - The drug is intended for investigational use in a foreign country;
    - Compliant with the importing country's laws
    - GMP compliant

Import of Higher Tier (Section 351) HCT/Ps for Commercial Use

- Compliance with 21 CFR 1271 (registration and listing, donor eligibility and GTPs)
- Biological license approval required
  - Safety and efficacy demonstrated in clinical trials
- GMP compliance
  - FDA facility inspection

Export of Higher Tier (Section 351) HCT/Ps for Commercial Use

- Compliance with 21 CFR 1271 (registration and listing, donor eligibility and GTPs)
- GMP compliance
- Marketing authorization required in destination country
- US BLA approval or
- No BLA approval
  - Export to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or any EU or EEA state (no FDA review required)
  - Export to “non-listed” countries
    - FDA review of country’s regulatory system or
    - Special petition

Summary of Records (21 CFR 1271.55)

- The following must accompany the HCT/P at all times
  - Distinct identification code… that relates the HCT/P to the donor and to all records pertaining to the HCT/P …
  - Statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible
  - Summary of the records used to make the donor-eligibility determination
    - Statement that the communicable disease testing was performed by a lab certified to perform such testing on human specimens under the CLIA has met equivalent requirements
    - Listing and interpretation of the results of all communicable disease tests performed
    - Name and address of the establishment that made the donor-eligibility determination
    - In the case of an HCT/P from a donor who is ineligible, a statement noting the reason(s) for the determination of ineligibility

Import Alert: March 2006

- Import requirement exception
  - FDA does not intend to review any entries of mobilized peripheral blood and umbilical cord blood HCT/Ps at the time of entry to verify compliance
  - Entry should be facilitated as promptly as possible
  - Permit products to travel to the consignee under quarantine

Import for Processing and Further Manufacture

- HCT/Ps imported for further processing for distribution in the US or for export are subject to Section 361 regulation.
- Requirements
  - Labeling
  - Shipped in quarantine
  - Records may not be complete at the time of import, and that lack of completeness should not delay entry

Nonclinical Scientific or Educational Use

- HCT/Ps imported by establishments that use them **solely** for nonclinical scientific or educational use are not subject to these import regulations
- However several other US agencies may have jurisdiction
  - CDC
  - USDA
  - Animal and Plant Health Inspection Service (APHIS)
  - Customs
- Recommended labeling
  - Description of the biological specimens
  - A statement regarding the intended use of the specimen
  - Results of any infectious disease testing

Problem Area

- FDA intention to require licensure of cord blood units and mobilized peripheral blood
  - A substantial fraction of US HSC transplants use grafts from non-US sources
  - Will non-US cord blood banks and mobilized peripheral blood suppliers apply for FDA licensure?
  - Will this regulation reduce the availability of HSC grafts in the US?

Summary

- Import and export regulation of cell therapy products is based on the FDA's risk based approach which separates cell therapy products into two risk tiers
- Lower tier HCT/Ps are regulated under PHS Act Section 361 (21 CRF 1271)
- Higher tier HCT/Ps are governed by both Section 351 and 361 requirements
- Section 351 requirements are identical to standard therapeutic biological products
- Section 351 products are regulated differently based on whether they are IND stage or commercially marketed
- In all cases compliance with 21 CRF 1271 (Section 361) is required
- Ensure that summary of records is included in all shipments (21 CFR 1271.55)
- Non-US tissue establishments must comply with all applicable regulations if they are exporting HCT/Ps to the US

Thank You

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