

FDA regulation of human cells and tissues: Donor cell collection topics

ASFA

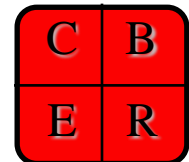
June 2, 2011

CAPT Ellen F. Lazarus

Director, Division of Human Tissues

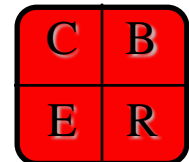
Office of Cellular, Tissue, and Gene Therapies

CBER, FDA



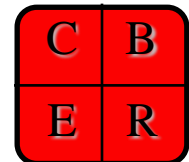
Overview

- Regulatory approach to human cells for clinical use
- Licensure of unrelated allogeneic HPC-C and regulatory status of HPC-A
- Cell recovery establishments – registration data snapshot
- Educational resources



Products regulated in OCTGT

- Cellular therapy products
- Tumor vaccines and immunotherapy
- Gene therapies
- Tissues and tissue-based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Donor infectious disease screening tests

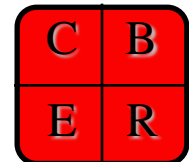


Regulation of Cellular and Tissue-Based Products

- A tiered regulatory framework with the level of regulation proportional to the degree of risk
- Provides greater flexibility; intended to encourage innovation in the field of cellular therapies
- Risk determines level of regulation

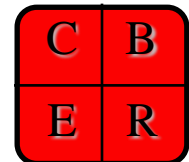
Lower Risk – Premarket approval not required – prevent introduction, transmission, and spread of communicable diseases

Higher Risk – Preapproval required - demonstrate safety and efficacy



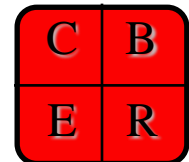
Premarket Review Pathways

- **Biologics Regulations**
 - IND Investigational New Drug
 - BLA Biologics License Application
- **Device Regulations**
 - IDE Investigational Device Exemption
 - PMA Premarketing Application
 - HDE Humanitarian Device Exemption
- **Combination products**
 - Pathway determined by primary mode of action – Request for designation (RFD) process through Office of Combination Products
 - Previous intercenter agreements and precedents



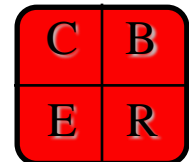
HCT/Ps

- Human Cells, Tissues, and Cellular and Tissue-based Products: Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient
- HCT/Ps do not undergo premarket review and approval if they meet all criteria for regulation solely under section 361 of the PHS Act
 - 21 CFR Part 1271.10(a)



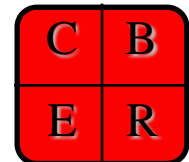
What is Included?

- Musculoskeletal tissue (e.g., bone, ligament, tendon)
- Skin
- Ocular tissue (e.g., cornea, sclera)
- Human heart valves
- Human dura mater
- Reproductive cells and tissue (e.g., semen, oocytes, embryos)
- Hematopoietic stem/progenitor cells from peripheral blood and cord blood
- Cellular therapies (e.g., chondrocytes, islet cells)
- Tissue/device and other combination therapies



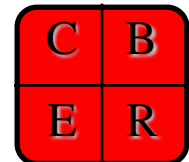
What is Not Included?

- Vascularized organs and blood vessels recovered with an organ
- Minimally manipulated bone marrow (homologous use)
- Tissues intended for educational or non-clinical research use
- Xenografts
- Blood products
- Secreted or extracted products; e.g., human milk, collagen, cell factors
- Ancillary products
- *In vitro* diagnostic products



HCT/P Regulations

- **Definition of key terms and Scope**
 - Subpart A 21 CFR 1271.1 - 1271.20
- **Registration and Listing**
 - Subpart B 21 CFR 1271.21-1271.37
- **Current Good Tissue Practice**
 - Subpart C Donor Eligibility 21 CFR 1271.45-1271.90
 - Subpart D 21 CFR 1271.145-1271.320*
- **Additional Requirements**
 - *applicable only to non-reproductive “361” HCT/Ps*
 - Subpart E 21 CFR 1271.330-1271.370
- **Inspection and Enforcement**
 - *applicable only to “361” HCT/Ps*
 - Subpart F 21 CFR 1271.390-1271.440



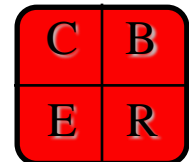
*Only 1271.150(c) and 1271.155 are implemented for reproductive HCT/Ps.

“361” HCT/Ps

Regulated solely under 21 CFR Part 1271 and Section 361 of the PHS Act

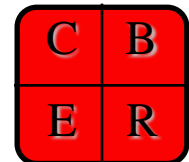
Examples

- musculoskeletal tissue, skin, cornea
- reproductive cells
- minimally manipulated HPC-A and HPC-C for homologous use in the donor/patient or in a first- or second-degree blood relative

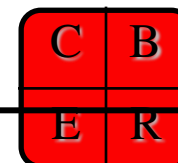


“351” HCT/Ps

- Do not meet one or more criteria in 21 CFR 1271.10(a); applicable regulations include but not limited to those listed in 21 CFR 1271.20
- Require pre-market review and approval
- Pre-license/approval inspection
- Routine FDA inspections
- Examples
 - HPC-C for unrelated allogeneic use; cell expansion; gene therapy products; tumor vaccines

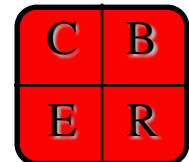


HCT/P	HCT/P regulated as biologic product/drug/device
Section 361 of PHS Act	FDCA and/or Section 351 Section 361
No pre-market review—no application to FDA required	Pre-market review and approval
Meet all criteria in 1271.10(a) <ul style="list-style-type: none"> •Minimally manipulated •For homologous use •Not combined with another article •No systemic effect, not dependent on metabolic activity of living cells (with exceptions) 	Do not meet one or more criteria in 1271.10(a)
Distribution may begin without inspection; compliance determined at routine FDA inspections	Pre-license/pre-approval inspection Routine FDA inspections



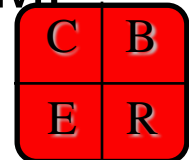
CGTP and CGMP (1)

- CGTP govern methods used in, and facilities and controls used for, manufacture of HCT/Ps
 - Section 361 PHSA: prevention of introduction, transmission, spread of communicable disease
 - HCT/P manufacturing includes donor screening and testing, recovery, processing, microbial testing, storage, and distribution



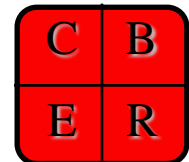
CGTP and CGMP (2)

- CGMP in 21 CFR Parts 210 and 211 govern methods used in, and facilities and controls used for, manufacture of a drug including biological drug product
 - Food Drug and Cosmetic Act (FDCA): safety, purity, potency
- If a regulation in 21 CFR Part 1271 is in conflict with a biologic drug product requirement in 21 CFR Parts 210, 211, 600, or 610, the regulations more specifically applicable to the product will supersede the more general
 - Most CGTP are subsumed under broader CGMP requirements



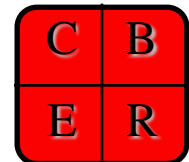
HPC licensure approach (1)

- HCT/P regulations
 - Proposed a tiered approach in 1997
 - Implemented by promulgating 3 final rules, all of which were effective as of 5/25/05
- Unrelated allogeneic hematopoietic stem/progenitor cells including cord blood (HPC-C) and PBSC (HPC-A) meet criteria for regulation as biological products under the PHS Act



HPC licensure approach (2)

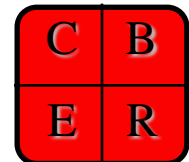
- 1998 FR notice: Request for Proposed Standards
 - Requested submission of comments and data
 - Establishment controls
 - CMC controls-processing & product standards
 - For minimally manipulated unrelated allogeneic HPC-C and HPC-A intended for hematopoietic reconstitution
 - If adequate information submitted to show safety and efficacy, FDA intends to issue guidance containing controls and standards for licensure



HPC licensure approach (3)

Meetings and publications

- 2003 BRMAC: Cord blood scientific issues
 - FDA and invited speakers presented clinical outcome data
 - Committee discussed safety & efficacy issues
 - Subsequently, CBER recommended that the cord blood data submitted to the docket and published literature support development of criteria for licensure (no data on PBSCs)
- 5/05 – All tissue rules implemented
- 1/07 - Published cord blood draft guidance
- 3/07 - CTGTAC meeting
- 10/09 – Published cord blood final guidance and companion draft IND guidance



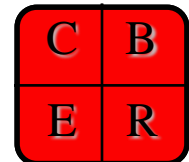
Cord Blood Guidance Documents

- Final Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (HPC-C Licensure Guidance) - 10/20/09

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf>

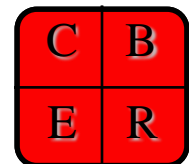
- Draft Guidance for Industry and FDA Staff: IND Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (Draft HPC-C IND Guidance) – 10/20/09

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187146.pdf>



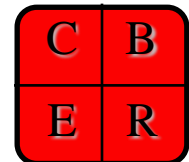
Implementation of IND and BLA requirements for certain HPC-C

- Phased-in implementation period for IND and BLA requirements ends October 20, 2011 (2 years after date of guidance publication)
- Sponsors encouraged to send in IND and BLA applications as soon as possible to allow sufficient time for review, comment, and resubmission as needed to complete all actions by the end of this 2 year period
 - Contact OCTGT to schedule a pre-BLA meeting to obtain advice about licensure submission process



Regulatory status of other HPCs

- Bone marrow excluded from definition of HCT/Ps unless more than minimally manipulated, combined with another article*, or for nonhomologous use
 - IND and BLA requirements for FDA-regulated (“351 HCT/P”) bone marrow in effect
- HPC-A from unrelated allogeneic donors (or not meeting all other criteria in 1271.10(a))
 - “351 HCT/P”
 - Still in period of delayed enforcement of IND and BLA requirements (homologous use)
 - IND and BLA requirements in effect for HPC-A that is more than minimally manipulated, combined with another article*, or for nonhomologous use

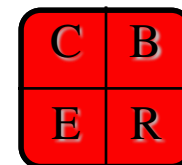


*Except for water, crystalloids, or sterilizing, preserving, or storage agents that do not raise new safety concerns (21 CFR 1271.10(a)(3))

Summary: FDA Regulation of HPC-A and HPC-C from autologous and allogeneic donors

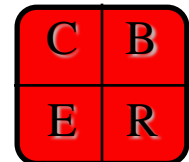
Cell Source	Applicable FDA Regulations
Autologous	21 CFR Part 1271; donor eligibility determination not required (1271.90(a))*
Related allogeneic (1 st or 2 nd degree blood relative)	21 CFR Part 1271*
Unrelated allogeneic	<ul style="list-style-type: none"> • 21 CFR Part 1271 subparts A-D • “351 HCT/Ps” • Period of delayed enforcement of IND and BLA requirements for HPC-C ending October 20, 2011

*Autologous and related allogeneic HPCs and other cell therapy products must meet all criteria in 21 CFR 1271.10(a) to be regulated solely under section 361 of the PHS Act and the regulations in this part.



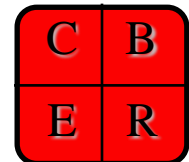
Cell product recovery (1)

- Recovery is a HCT/P manufacturing step
- HCT/P establishment registration (Form 3356)
- Apheresis centers performing recovery of source material for manufacture of investigational or licensed cell therapy products are expected to register, comply with applicable CGTPs, and follow sponsor's procedures and specifications under the IND or approved BLA
 - 21 CFR 1271.215 Recover each HCT/P in a way that does not cause contamination or cross-contamination, or otherwise increase risk of introduction, transmission, spread of communicable disease through use of the HCT/P



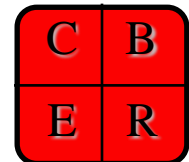
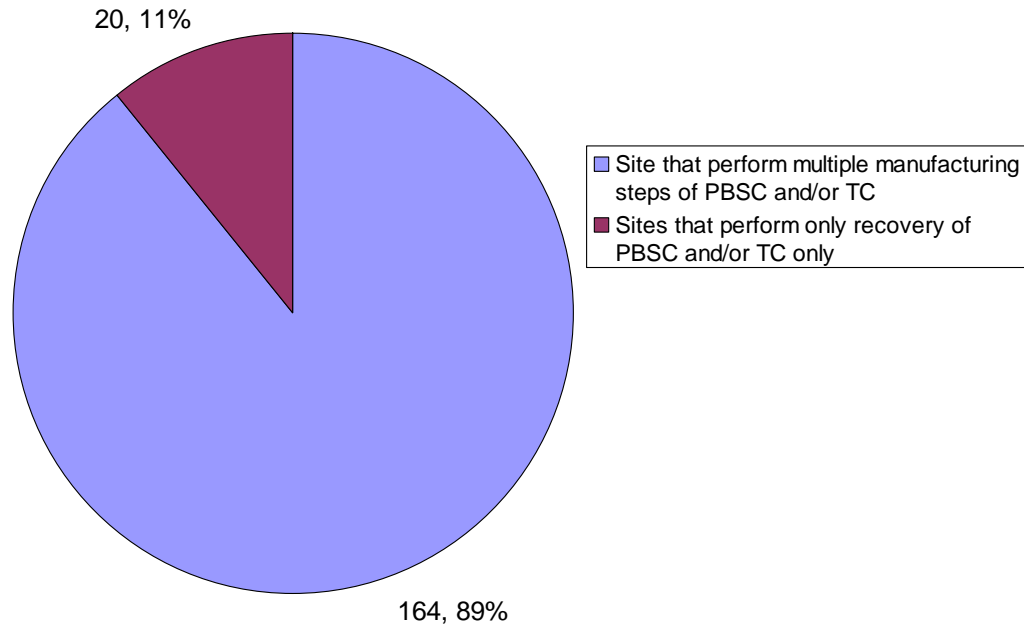
Cell product recovery (2)

- Apheresis staff activities to assure safety and quality of the licensed cell product include
 - Training
 - Conformance with sponsor's policies and protocols
 - Device manufacturer instructions
 - Aseptic technique; sterile equipment and reagents
 - Labeling
 - Product identity
 - Applicable donor eligibility labeling requirements
 - Product handling and shipping
- Apheresis staff perform vital role in donor adverse event recognition, management, and reporting to sponsor and/or device manufacturer as indicated

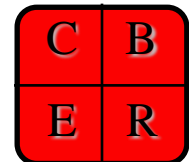
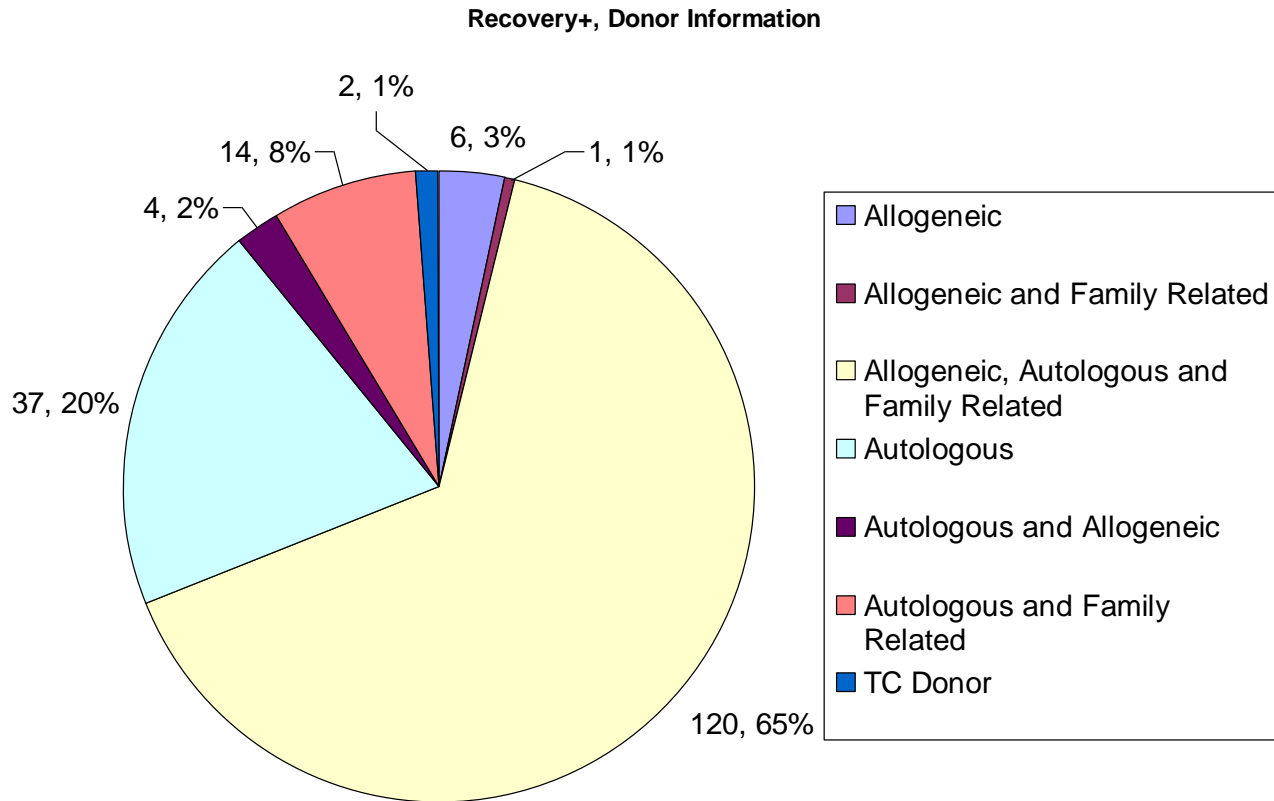


Recovery establishment Registration data (1)

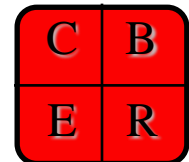
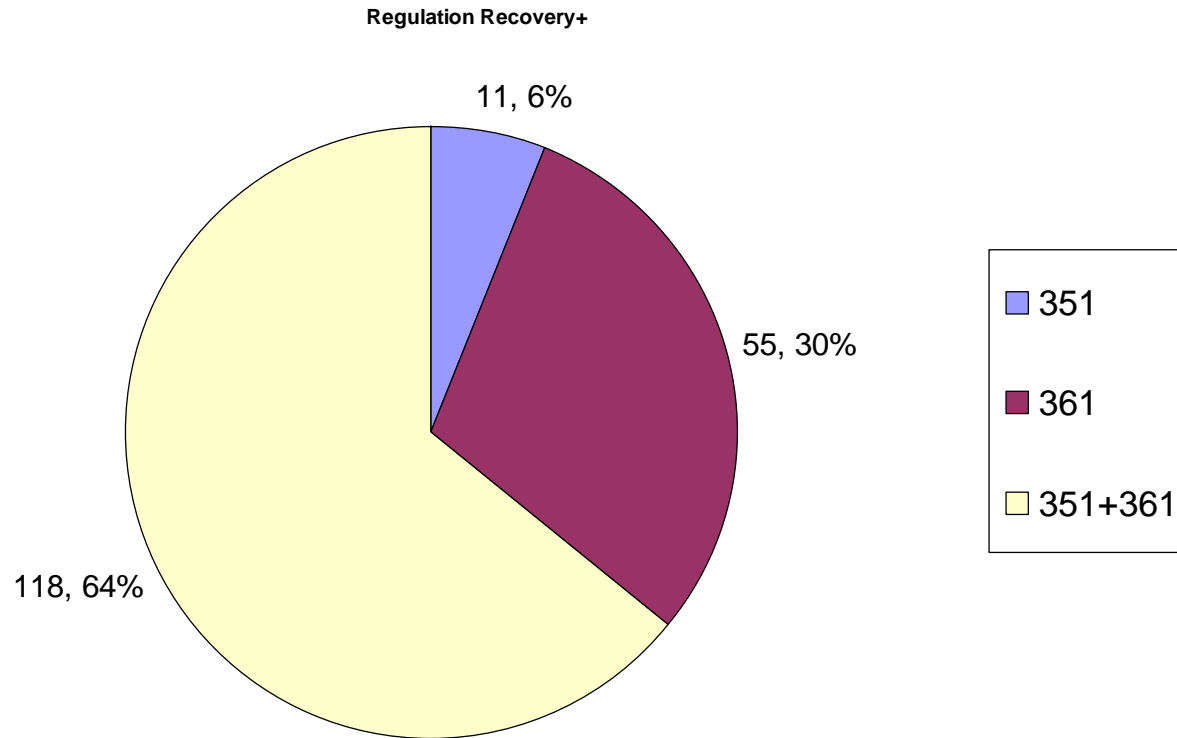
Apheresis Cells- U.S. sites only



Registration data (2)

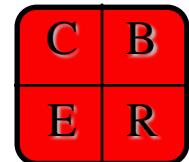
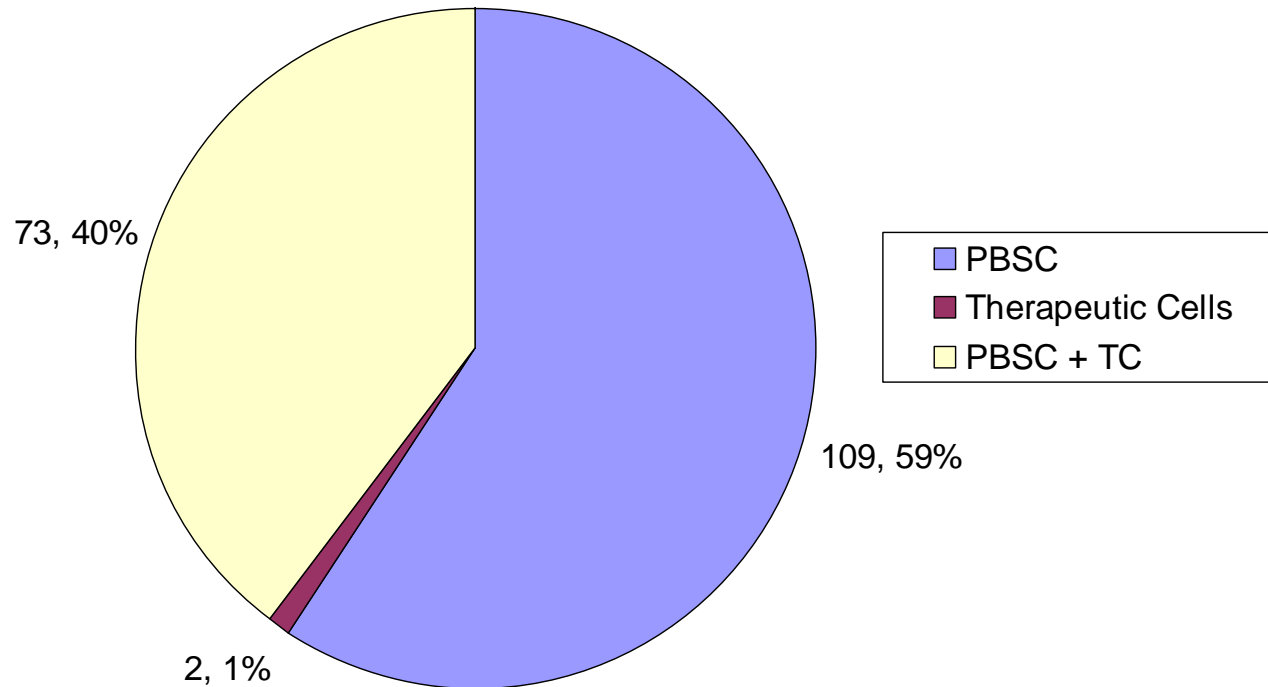


Registration data (3)



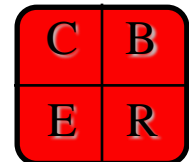
Registration data (4)

Cell Types



Educational resources

- OCTGT Learn – web page for industry education:
www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- NHLBI PACT workshop: Cell Therapy for Pediatric Diseases, September 14-15, 2011, NIH Lister Hill Auditorium
www.pactgroup.net



Information and Contacts

- Contact CBER
<http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm106001.htm>
 - Consumer questions about products: ocod@fda.hhs.gov
 - Manufacturers assistance: Industry.Biologics@fda.hhs.gov
 - Phone: 800-835-4709 or 301-827-1800
- CBER Tissue Webpage
 - Regulations, guidance and other documents
 - Registration and listing information<http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm>
- Regulatory Questions (submissions and related meetings):
Contact the Regulatory Management Staff in OCTGT at
CBEROCTGTRMS@fda.hhs.gov or Patrick.Riggins@fda.hhs.gov
or by calling (301) 827-6536
- Ellen.Lazarus@fda.hhs.gov

