



Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products

Division of Human Tissues Update

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CBER, FDA

AABB Annual Meeting
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Human Cells, Tissues, and Cellular and Tissue-Based Products

- Musculoskeletal tissue and skin
- Ocular tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapy products, including islet cells, autologous chondrocytes
- Reproductive tissue
- Combination tissue/device; tissue/drug
- Human heart valve allografts
- Human dura mater

HCT/P update

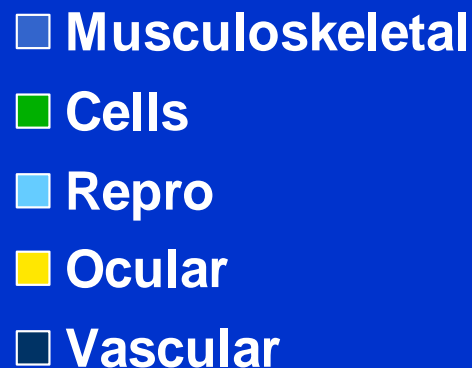
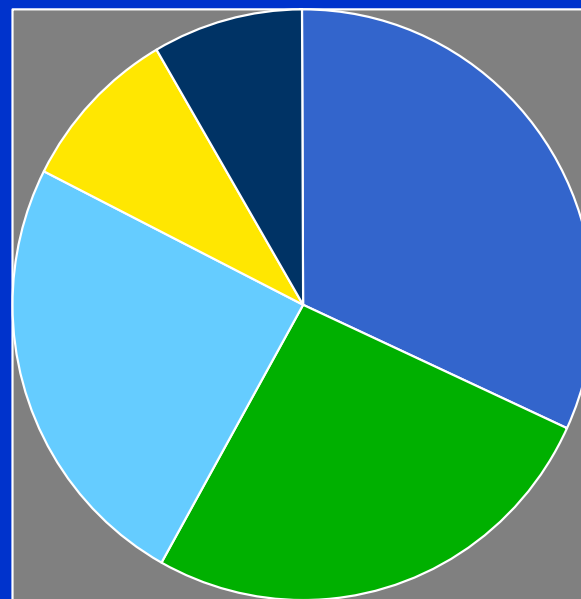
- Registration
- Donor Eligibility
- CGTPs
- Exemptions and Alternatives
- Adverse Reactions
- HCT/P Deviations
- Inspection
- Compliance; Import Alert
- Human Tissue Task Force

Division of Human Tissue

- DHT Director - Ruth Solomon, MD
- Human Tissue and Reproductive Branch Chief - Martha Wells, MPH, RAC
- Staff
 - Ellen Lazarus, MD
 - Melissa Greenwald, MD
 - Laura St. Martin, MD, MPH
 - Jackie Neidinger, BA, CTBT
 - Rose Wiseman

Registration

- Electronic Human Cell and Tissue Establishment Registration System (eHCTERs)
www.fda.gov/cber/tissue/tisreg.htm
 - Registration form
 - Electronic submission instructions
 - Public Query Application
 - Contact information for questions
 - List of registered establishments
- 1,960 total establishments
- 603 (30%) PBSC or cord blood, including registries and testing labs
 - 136 (24% of the registered cell establishments) non-US



Annual Registration

- Required every year in December
 - Make changes if needed
 - Sign and date
 - Mail/fax or complete on web
www.fda.gov/cber/tisreg.htm
- This year – in November
 - If you registered by mail/fax annual forms will be mailed
 - If you registered electronically, you will only be reminded by email

Failure to Register

- If you do not register or renew your registration annually, you will receive a letter telling you to do so in April
- If you still do not register, we will e-mail the responsible person listed in the registration database; OCBQ will contact district offices
- A Failure to Register Notice has been posted on CBER's website

www.fda.gov/cber/tissue/failreg.htm

Registration update and changes

- Update of registration required annually, in December
- Changes to listing are required within 6 months
- Change of ownership or location required within 5 days
- Inactivation - check box #2(d)
- Electronic registration is encouraged

Donor Eligibility

- Final Guidance being prepared for publication
- Donor Screening Tests for Testing HCT/P Donors – information at www.fda.gov/cber/tissue/prod.htm
 - Licensed donor screening tests - includes sample type; whether licensed for cadaveric samples
 - Cleared NAT for Chlamydia trachomatis and Neisseria gonorrhoea

CGTPs

- Draft guidance in progress
- CGTP Rule reminder: 1271.150(c)(1)
Manufacturing Arrangements
 - (iii) Before entering into a contract, agreement, or other arrangement with another establishment to perform a step in manufacture for you, you must ensure that the establishment complies with applicable CGTP requirements. [Note: CGTP includes DE requirements]

Manufacturing arrangements (cont.)

- If during the course of this contract, agreement, or other arrangement, you become aware of information suggesting that the establishment may no longer be in compliance with such requirements, you must take reasonable steps to ensure that the establishment complies with those requirements.
- If you determine that the establishment is not in compliance with those requirements, you must terminate your contract, agreement, or other arrangement with the establishment. [Note: See CGTP preamble - comments 28-30]

Exemptions and Alternatives

- OCTGT SOPP 9151 6/13/06
 - DHT coordinates
 - Database
 - Consults others outside of division
 - Draft letter presented to Tissue Policy Team
 - Center Director sign-off

Adverse Reactions

- Guidance for Industry:
MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to HCT/Ps
- www.fda.gov/cber/gdlns/advhctp.htm

HCT/P Adverse Reaction

21 CFR 1271.3(y)

- A noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response

HCT/P Adverse Reaction Reporting

21 CFR 1271.350(a)

- Required for AR involving “361” non-reproductive HCT/Ps recovered on or after 5/25/05
- Must be investigated
- Must report AR that involve a communicable disease if the reaction is fatal, life-threatening, results in permanent impairment of body function or damage to body structure, or necessitates surgical or medical intervention

Adverse Reaction Reporting When, How, Where

- Submit report on a Form FDA-3500A within 15 calendar days of initial receipt of the information
- www.fda.gov/medwatch
- Electronically or by mail
- Submit follow-up reports within 15 calendar days of receipt of new information or as requested by FDA

Adverse Reaction Reports

CBER Tissue Safety Team

- SOPP 8508 describes procedures for handling AR reports - coordination by 5 offices in CBER
 - www.fda.gov/cber/regsopp/8508.htm
- MedWatch reports involving HCT/Ps come to CBER
- Entered into 2 databases: AERS and AEPP
- Follow-up infectious adverse reactions
- All information entered into AEPP database
- Review by OCTGT, OBE, OCBQ
- Seek more information from reporter and manufacturer
- Develop categories for classifying “conclusions”

Adverse Reaction Reports

Statistics for November '05 to July '06

- Total = 152
- Product Type
 - Tissues 108 (71%)
 - Cells 44 (29%)
- Tissue Type
 - Bone 39 (36%)
 - Eye 26 (24%)
 - Skin 23 (21%)
 - Soft Tissue 9 (8%)
 - Cardiac 8 (7%)
- Reports from
 - Manufacturers 54%
 - Healthcare workers 46%
- Infectious/Non-infectious 80%/20%

HCT/P Deviation

21 CFR 1271.3(dd)

- An event that represents a deviation from applicable regulations, standards or established specifications that relate to prevention of communicable disease transmission or contamination, or
- An unexpected or unforeseeable event that may be related to transmission or potential transmission of a communicable disease or may lead to HCT/P contamination

HCT/P Deviation Reporting

21 CFR 1271.350(b)

- Required for “361” non-reproductive HCT/Ps recovered on or after 5/25/05
- Related to a distributed HCT/P
- Must be investigated
- Must report those that occurred in your facility or in a facility that performed a manufacturing step for you under contract, agreement or other arrangement
- Only related to “core” CGTPs (1271.150(b))

Deviation reporting

When, How, Where

- As soon as possible, not to exceed 45 days after discovery
- Form FDA-3486 and instructions
 - www.fda.gov/cber/biodev/biodev.htm
- Electronically or by mail
- HCT/P Deviation Codes
 - www.fda.gov/cber/biodev/devcode.htm

HCT/P Deviation Codes

DE	Donor Eligibility
DS	Donor Screening
DT	Donor Testing
EC	Environmental control
SR	Supplies and reagents
RE	Recovery
PC	Processing
LC	Labeling control
ST	Storage
SD	Receipt, Pre-distribution Shipment, Distribution

HCT/P Deviations – FY 2006

Donor Eligibility	22
Donor Screening/Donor Testing	10/19
Environmental Control	1
Supplies and Reagents	2
Recovery	2
Processing/Storage	11/1
Receipt, Pre-Distribution, Distribution	32
Not reportable	101
Total	201

HCT/P Establishment Inspections

Fiscal Year Oct-Sept	# Inspections	# FDA-483s Issued
'06 (to July 30)	285	77 (27%)
'05	270	49 (18%)
'04	285	48 (17%)
'03	227	60 (26%)
'02	163	53 (33%)
'01	132	50 (39%)

HCT/P Inspections FY 2006

(October 1, 2005 to July 30, 2006)

Type of Establishment	# Inspections	# FDA-483s Issued
Reproductive cells/tissues	57	16 (27%)
Cord Blood and Peripheral Blood Stem Cell	30	10 (30%)
All other (MS, Ocular)	198	51 (28%)
Total	285	77 (27%)

Compliance Information

www.fda.gov/cber/tissue/inspect.htm

- Compliance Program 7341.002 (covers tissue recovered after 5/25/05)
 - July 1, 2005 through September 30, 2009
- Compliance Program 7341.002A (covers tissue recovered before 5/25/05)
- Note Attachments—box entitled “During the inspection,…”

Import Alert # 57-19

issued 3/10/06

- This document is for reviewing entries of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps) regulated solely under section 361 of the PHS Act and 21 CFR 1271
- Note: HCT/Ps should be permitted to travel to the consignee under quarantine while FDA is determining admissibility, due to the perishable nature of most HCT/Ps

Import Alert # 57-19

- Import Requirement Exceptions For Hematopoietic Stem Cells (and Reproductive HCT/Ps): FDA should act promptly to facilitate release of HSC (peripheral or cord blood) and reproductive HCT/Ps. The import requirements in 21 CFR 1271.420 ... generally do not apply to hematopoietic stem cells. FDA does not intend to review any entries of these HCT/Ps at the time of entry to verify compliance. Consequently, entry should be facilitated as promptly as possible. Should these products come up for review, permit them to travel to the consignee under quarantine.

Top 10 FDA-483 Citations

- Failure to [prepare] [validate] [follow] written procedures for prevention of [infectious disease contamination] [cross-contamination] during processing.
- Failure to [prepare] [follow] written procedures for all significant steps for [obtaining] [reviewing] [assessing] the relevant medical records of a donor.
- Procedures for all steps performed in the [testing] [screening] [determining] of donor eligibility of HCT/Ps were not [established] [maintained] [defined] [documented] [implemented] [followed] [reviewed] [revised].

Top Ten continued

- Procedures appropriate to meet core CGTP requirements for all steps that you perform in the manufacture of HCT/Ps were not [established] [maintained] [defined] [documented] [implemented] [followed] [reviewed] [revised].
- Failure to [prepare] [follow] written procedures for designating and identifying quarantined tissue.
- Human tissue intended for transplantation was not accompanied by a summary or copies of the donor's relevant medical records.

Top Ten continued

- Failure to maintain records which are [accurate] [indelible] [legible].
- Records fail to [identify the person performing the work] [include the dates of the various entries] [be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular tissue involved].
- Records fail to include documentation of receipt and/or distribution of human tissue.
- Records fail to include documentation of destruction or other disposition of human tissue.

Human Tissue Task Force

- Multidisciplinary FDA task force (CBER and Office of Regulatory Affairs - ORA)
- Assess the effectiveness of the implementation of tissue rules -1 yr ago
- Are additional steps needed to assure tissue safety and availability?
- Review of recent findings at recovery establishments
- Identify problems; propose changes to existing policies if necessary; identify resources needed
- Continue to work with professional organizations to support their ongoing efforts

Contact Information

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