



Human Cells, Tissues, and Cellular and Tissue Based Products – Selected Regulatory Issues for Tissue Banking in the Hospital

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Tissue is not blood...

...even though it may be obtained from a blood source, or may be managed in the hospital by the blood bank.

- Different set of regulations
 - 21 CFR 1271 (HCT/P collected on or after 5/25/05)
 - Some HCT/P also regulated as biological products or devices
- Different registration and reporting mechanisms
- Different inspection and enforcement provisions
- Different office jurisdiction

What is the objective of the tiered regulatory approach?

- Prevent the use of contaminated tissues that could spread infectious disease
Section 361
(US Public Health Safety Act)
- Prevent the improper handling or processing that might contaminate tissues
- Ensure that clinical safety and efficacy is demonstrated for cellular therapeutics
Section 351
(US Public Health Safety Act)

Who regulates cellular and tissue products ?

Government Agency	Products
Food and Drug Administration	<ul style="list-style-type: none">•Blood and Blood Products•Cellular Therapeutics•Tissues•Tissue Engineered Products•Xenografts•Gene Therapies
Health Resource Services Administration	<ul style="list-style-type: none">•Bone Marrow for homologous use (min manip)•Whole Vascularized Organs

The “Tissue Rules”

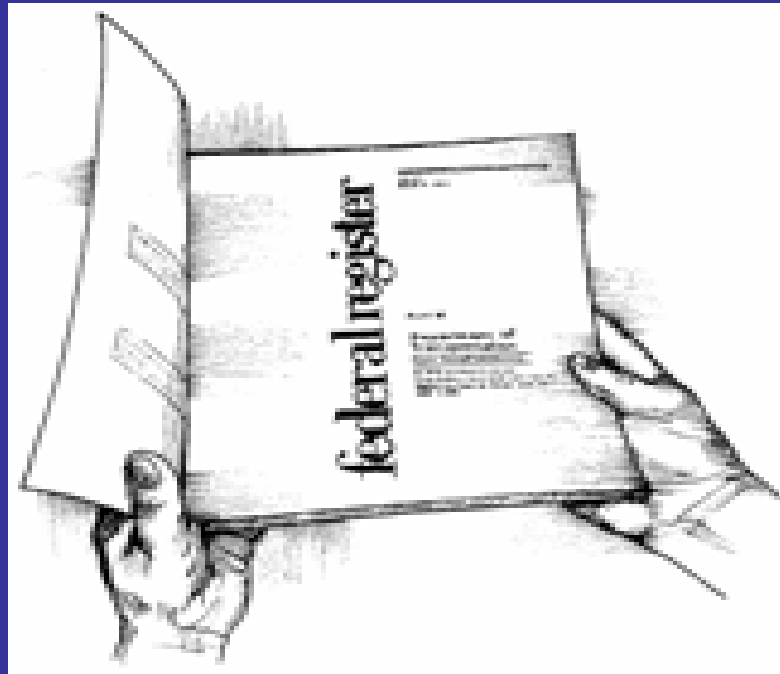
effective May 25, 2005

Tissue Rule	Issues Addressed
Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules, requirements for registering and listing products
Donor Eligibility	Requirements for donor screening and testing for “relevant communicable disease agents and diseases”
Current Good Tissue Practice (CGTP)	Manufacturing to ensure that HCT/Ps do not contain communicable disease agents, are not contaminated, and do not become contaminated

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

- Musculoskeletal tissue and skin
- Ocular tissue
- Cellular therapy products, e.g., chondrocytes, pancreatic islet cells
- Hematopoietic stem/progenitor cells (peripheral blood and cord blood)
- Reproductive tissue
- Combination tissue/device; tissue/drug
- Human heart valve allografts
- Dura mater
- Vascular tissue

Selected HCT/P regulatory topics relevant to tissue banking in the hospital



Registration

Do I have to register if...

- we only store HCT/P used for nonclinical scientific research?
 - No [21 CFR 1271.15(a)]
- surgeons at our hospital remove and re-implant tissue from the same individual, during the same surgical procedure?
 - No [21 CFR 1271.15(b)]
- we receive and store HCT/P only for use in our facility?
 - No [21 CFR 1271.15(d)]

Do I have to register if...

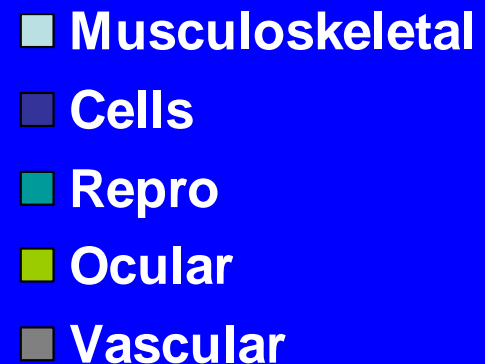
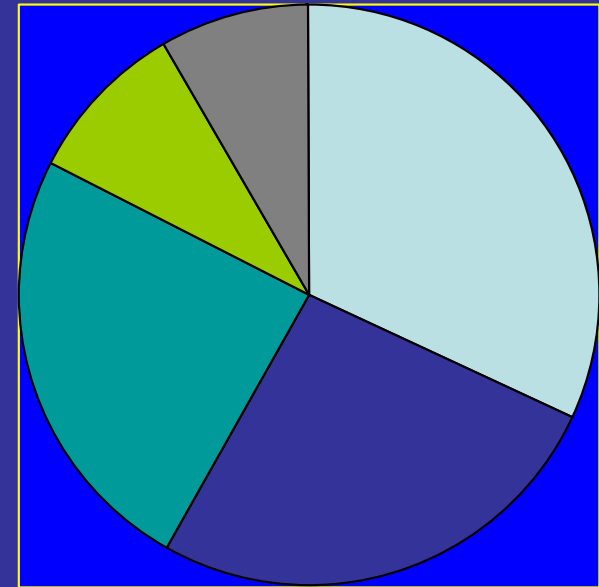
- my hospital routinely sends tissue in our inventory to another hospital?
 - Yes. You would be engaged in distribution, which is considered a part of manufacturing [21 CFR 1271.3(e)].
 - You do not have to register if the other hospital is part of your same corporate entity.
- we store autologous calvarium sections (bone flaps) for possible future re-implantation?
 - No, as long as no further manufacturing occurs [21 CFR 1271.3(e)]. The answer is the same even if you send the autologous tissue to another facility for storage.

Do I have to register if...

- we send autologous tissue to another hospital when the patient is transferred?
 - No, you would not be considered to be a distributor as long as this were an infrequent practice.

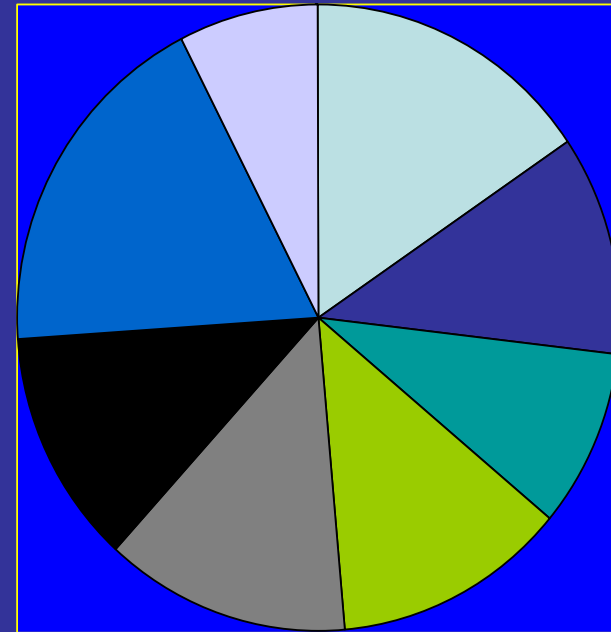
Registered establishments

- 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



Registered establishment manufacturing activities

- Many registered establishments perform more than one manufacturing activity
- Relatively even distribution of manufacturing activities
- Storage and distribution largest categories (18 % and 16% respectively)



Adverse reactions

What is an 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 an adverse reaction involving “361” non-reproductive HCT/Ps recovered on or after 5/25/05
- Must be investigated
- Must report an adverse reaction that involves 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 Reactions

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

Enforcement policy

What is a recall?

21 CFR 7.3

- **Recall** means a firm's removal or correction of a product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure.
 - Recall does not include a market withdrawal
 - **Correction** includes patient monitoring, without removal of the product [21 CFR 7.3(h)]
- The **recalling firm** is the firm that initiates a recall, or in the case of a FDA-requested recall, the firm that has the primary responsibility for the manufacture and marketing of the product.

What is a market withdrawal?

- Market withdrawal means a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA or which involves no violation [21 CFR 7.3(j)].
- FDA determines when a firm's action is a recall and when it is a withdrawal.

What should I do when one of our tissue suppliers notifies us of a recall or market withdrawal?

- Follow the tissue supplier's instructions for quarantine and return of unused tissue.
- Provide the tissue supplier with information about the disposition of all affected tissue.
- The tissue supplier may recommend that you (the transplant facility) identify which patient(s) received affected tissue and notify their transplant physician(s) of the recall.
- Communicate any recipient adverse reaction information that becomes available to you to the tissue supplier.

Contact Information

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